Amsterdam, 26 February 2026
EMA/51225/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Palsonify

International non-proprietary name: Paltusotine

Procedure No. EMEA/H/C/006636/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Administrative/regulatory information and recommendations on the procedure 10
1.1. Information on the product 10
1.2. Scientific advice 11
1.3. Eligibility to the centralised procedure 12
1.4. Legal basis and dossier content 12
1.5. Information on paediatrics 12
1.6. Information on orphan market exclusivity 12
1.6.1. Similarity with authorised orphan medicinal products 13
1.7. Applicant's request for consideration 13
1.7.1. New active substance status 13
1.8. Patient experience data 13
1.9. Steps taken for the assessment of the product 14
1.10. CHMP outcome 15
1.10.1. Considerations related to paediatrics 15
1.10.2. Considerations related to orphan market exclusivity 15
1.10.3. Opinion 15
1.10.4. Conditions or restrictions regarding supply and use 15
1.10.5. Other conditions and requirements of the marketing authorisation 15
1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product 16
1.10.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States 16

2. Introduction 16
2.1. Therapeutic context 16
2.2. Aspects of development 20
2.3. Description of the product 20
2.4. Inspection issues 21
2.4.1. Good manufacturing practice (GMP) inspection 21
2.4.2. Good laboratory practice (GLP) inspection 21
2.4.3. Good clinical practice (GCP) inspection(s) 21

3. Quality aspects 21
3.1. Introduction 21
3.2. Active substance 21
3.2.1. General information 21
3.2.2. Manufacture, process controls and process development 22
3.2.3. Specification 23
3.2.4. Stability 23
3.3. Finished medicinal product 23
3.3.1. Description of the product and pharmaceutical development 23
3.3.2. Manufacture of the product and process controls 25
3.3.3. Product specification 25
3.3.4. Stability of the product 26

3.3.5. Adventitious agents 26
3.4. Discussion and conclusions on quality aspects 27
3.4.1. Recommendation(s) for future quality development 27

4. Non-clinical aspects 27
4.1. Introduction 27
4.2. Analytical methods 27
4.3. Pharmacology 28
4.3.1. Pharmacodynamics 28
4.3.2. Pharmacokinetics 30
4.4. Toxicology 32
4.4.1. Single-dose toxicity 32
4.4.2. Repeat-dose toxicity 32
4.4.3. Genotoxicity 33
4.4.4. Carcinogenicity 34
4.4.5. Developmental and reproductive toxicity 35
4.4.6. Toxicokinetics and exposure margins 36
4.4.7. Local tolerance 36
4.4.8. Other toxicity studies 36
4.4.9. Ecotoxicity/environmental risk assessment 37
4.5. Overall discussion and conclusions on non-clinical aspects 38
4.5.1. Discussion 38
4.5.2. Conclusions 40

5. Clinical aspects 40
5.1. Introduction 40
5.1.1. Good Clinical Practice (GCP) aspects 40
5.1.2. Tabular overview of clinical trials 40
5.2. Clinical pharmacology 42
5.2.1. Methods 42
5.2.2. Pharmacokinetics 43
5.2.3. Pharmacodynamics 53
5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD) 57
5.2.5. Dose selection and therapeutic window 60
5.2.6. Overall discussion and conclusions on clinical pharmacology 61
5.3. Clinical efficacy 66
5.3.1. Dose response studies 66
5.3.2. Main studies 83
5.3.3. Clinical studies in special populations 168
5.3.4. Supportive studies 169
5.3.5. Analysis performed across trials (pooled analyses and meta-analysis) 169
5.3.6. Healthcare professional engagement 173
5.3.7. Overall discussion and conclusions on clinical efficacy 173
5.4. Clinical safety 191
5.4.1. Safety data collection 192
5.4.2. Patient exposure 192
5.4.3. Adverse events 194

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events 202
5.4.5. Discontinuation due to adverse events 204
5.4.6. Safety in special populations 204
5.4.7. Immunological events 206
5.4.8. Safety related to drug-drug interactions and other interactions 206
5.4.9. Vital signs and laboratory findings 206
5.4.10. Post-marketing experience 208
5.4.11. Overall discussion and conclusions on clinical safety 208

6. Risk management plan 215
6.1. Safety specification 215
6.1.1. Proposed safety specification 215
6.1.2. Discussion on proposed safety specification 216
6.2. Pharmacovigilance plan 216
6.2.1. Proposed pharmacovigilance plan. 216
6.2.2. Discussion on the pharmacovigilance plan 217
6.3. Plans for post-authorisation efficacy studies 218
6.4. Risk minimisation measures 218
6.4.1. Proposed risk minimisation measures 218
6.4.2. Discussion on the risk minimisation measures 218
6.5. RMP summary and RMP annexes overall conclusion 218
6.6. Overall conclusion on the Risk Management Plan 219

7. Pharmacovigilance 219
7.1. Pharmacovigilance system 219
7.2. Periodic safety update reports (PSURs) submission requirements 219

8. Product information 219
8.1. Summary of product characteristics (SmPC) 219
8.1.1. SmPC section 4.1 justification 219
8.1.2. SmPC section 5.1 justification 219
8.2. Labelling 219
8.2.1. User consultation 219
8.2.2. Labelling exemptions 220
8.3. Additional monitoring 220

9. Benefit-risk assessment 220
9.1. Therapeutic context 220
9.1.1. Disease or condition, therapeutic indication 220
9.1.2. Available therapies and unmet medical need 221
9.2. Main clinical studies 222
9.3. Favourable effects 223
9.3.1. Uncertainties and limitations about favourable effects 226
9.4. Unfavourable effects 227
9.4.1. Uncertainties and limitations about unfavourable effects 228
9.5. Effects table 229
9.6. Benefit-risk assessment and discussion 231

9.6.1. Importance of favourable and unfavourable effects 231
9.6.2. Balance of benefits and risks 234
9.6.3. Additional considerations on the benefit-risk balance 234
9.7. Benefit-risk conclusions 235
9.7.1. CHMP conclusions 235
10. Appendix 235

List of abbreviations

Abbreviation	Definition
2MSA	dimesylate salt form of paltusotine
AcroQoL	Acromegaly Quality of Life
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ANCOVA	analysis of covariance
ASD	Acromegaly Symptoms Diary
API	Active pharmaceutical ingredient
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
BCRP	breast cancer resistant protein
BCS	Biopharmaceutics Classification System
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CBA	Critical bioavailability attribute
CE	Conformité Européenne (European Conformity)
CFR	Code of Federal Regulations
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	total body clearance from plasma
CMA	Critical material attribute
C_{max}	maximum (peak) plasma drug concentration
COMP	Committee for Orphan Medicinal Products
CPCA	Carcinogenicity potential characterisation approach
CQA	Critical quality attribute
C_{trough}	steady-state trough concentration
CYP	cytochrome P450
CSR	clinical study report
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DSC	Differential scanning calorimetry
EAS	Efficacy Analysis Set
EC	European Commission
EC_{50}	half-maximal response
ECG	Electrocardiogram

eGFR	estimated glomerular filtration rate
eCDFs	empirical cumulative distribution functions
EOR	End of Randomized Controlled Phase
EOT	End of Treatment (for RC Phase or OLE Phase)
EQ-5D-5L	EuroQol-5 Dimensions 5-Level
EQ VAS	EuroQol Visual Analogue Scale
E-R	exposure-response
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
FPM	Finished Product Manufacturer
FTIS	Fourrier transform infrared spectroscopy
GC	Gas chromatography
GCP	Good Clinical Practice
GMP	Good manufacturing practice
GH	growth hormone
H2	histamine type-2
HbA1c	hemoglobin A1c
HCP	healthcare professional
HDPE	High density polyethylene
HMG	hot melt granulation
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IGF-1	insulin-like growth factor-1
IND	Investigational New Drug
IQR	interquartile range
IR	immediate release
IR	Infrared
IRT	interactive response technology
ITT	intent-to-treat
IV	Intravenous
KF	Karl Fischer titration
LA-SRL	long-acting somatostatin receptor ligand
LAR	long-acting release
LFT	liver function test
LLDP	Linear low-density polyethylene
LS	least squares
MAA	Marketing authorisation Application
MAH	Marketing authorisation holder

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MWPC	meaningful within patient change
NDA	New Drug Application
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
OLE Phase	Open-label Extension Phase
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic(s)
PDE	Permitted Daily Exposure
P-gp	P-glycoprotein
PGI-S	Patient Global Impression of Severity
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PP	Polypropylene
PPI	proton pump inhibitor
PPM	Parts per million
PT	preferred term
QD	once daily
QP	Qualified person
QTPP	Quality target product profile
RC Phase	Randomized Controlled Phase
RH	Relative humidity
RPM	Revolutions per minute
RWP	Randomized Withdrawal Phase
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDD	spray-dried dispersion
SE	standard error
SKK	Sanwa Kagaku Kenkyusho Co., Ltd
SmPC	Summary of product characteristics
SOC	system organ class
SRL	somatostatin receptor ligand
SSA	somatostatin analogue
SST2	somatostatin receptor type 2
SST5	somatostatin receptor type 5

$t_{½}$	apparent terminal elimination half-life
$t_{½eff}$	effective half-life
TAMC	Total aerobic microbial count
TGA	Thermogravimetric analysis
t_{max}	time to achieve maximum plasma concentration
TEAE	treatment-emergent adverse event
TPQ	treatment preference questionnaire
TQT	thorough QT
TSQM9	treatment satisfaction questionnaire for medication
TTC	Threshold of toxicological concern
TYMC	Total combined yeasts/moulds count
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase 1A1
UGT1A9	uridine 5'-diphospho-glucuronosyltransferase 1A9
UHPLC	Ultra-high performance liquid chromatography
ULN	upper limit of normal
US	United States
UV-Vis	Ultraviolet-visual spectroscopy
V_z	apparent volume of distribution during terminal phase after intravenous administration
WRO	Written Responses Only
XRPD	X-ray powder diffraction

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Palsonify
Active substance	Paltusotine hydrochloride
INN or common name	Paltusotine
Applicant	Crinetics Pharmaceutical Europe GmbH Barbara Strozzilaan 201 1083 HN Amsterdam Netherlands
EMA product number	EMEA/H/C/006636
ATC code and pharmacotherapeutic group	H01CB06 Pituitary and hypothalamic hormones and analogues
Pharmaceutical form(s) and strength (s)	Film-coated tablet, 20 mg and 30 mg
Packaging	bottle (HDPE)
Package size(s)	60 tablets
Route of administration	Oral use
Device or diagnostic	Not applicable
Orphan designation	Yes (EU/3/25/3035)
Orphan indication status confirmed	Yes
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Palsonify is indicated for the medical treatment of adult patients with acromegaly
New active substance status	Granted

1.2. Scientific advice

Table 1 ***Scientific advice and protocol assistance***

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
23 July 2020	Non-clinical and clinical	EMEA/H/SA/4492/1/2020/SME/III	The Scientific advice pertained to the following non-clinical and clinical aspects: The adequacy of the planed non-clinical development strategy: general strategy, immunotoxicity. The proposed DDI studies, the approach to collect QT/QTc data and the need to conduct dedicated studies in patients with renal impairment; Phase 3 study plans, including study design, patient population, choice of control, study duration, primary and secondary endpoints, sample size and statistical analysis methods; overall clinical evidence plans to support MAA for treatment of acromegaly.
11 November 2021	Quality	EMA/SA/0000069283	The Scientific advice pertained to the following quality aspects: Designation of starting materials for drug substance manufacture, tests and acceptance criteria for control and release of the starting materials, risk assessment and control strategy for potential genotoxic impurities in the drug substance; number of primary stability batches for MAA per strength
25 May 2023	Clinical and Quality	EMA/SA/0000134586	The Scientific advice pertained to the following quality and clinical aspects: Starting materials: acceptability, control and release criteria; risk assessment and control strategy for potential genotoxic impurities in the drug substance; number of primary stability batches for MAA per strength Need for clinical studies to support the 30 mg tablet strength

22 February 2024	Non-clinical and clinical	EMA/SA/0000162419	The follow-up Scientific advice pertained to the following non-clinical and clinical aspects: Adequacy of non-clinical tests for immunotoxicity and approach to environmental risk assessment Acceptability of the characterisation of arrhythmogenic potential and for not performing a thorough QT study

1.3. Eligibility to the centralised procedure

The applicant Crinetics Pharmaceutical Europe GmbH submitted on 4 March 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Palsonify (paltusotine), through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2024.

The applicant applied for the following indication: treatment and long-term maintenance therapy of adult patients with acromegaly.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) (EMA/PE/0000223523) on the granting of a product-specific waiver.

1.6. Information on orphan market exclusivity

Paltusotine was designated as an orphan medicinal product (EU/3/25/3035) on 26 February 2025 in the following condition: "treatment of acromegaly".

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Palsonify as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/palsonify

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products, from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Applicant's request for consideration

1.7.1. New active substance status

The applicant requested the active substance paltusotine contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.1.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that paltusotine hydrochloride is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. Patient experience data

Table 2 Patient experience data relevant to the application

Patient experience data submitted with this application				***Section where discussed (if applicable)***
☐	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		X	Patient-reported outcomes (PRO)	5.3.1, 5.3.2.
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	X	CHMP early dialogue with patient organisations		8.7.2
	☐	Third party interventions from patients and patient groups		

Patient experience data submitted with this application			Section where discussed (if applicable)
	☐	Other (e.g. medical literature, summaries/analysis from patient engagement activities - please specify)	

1.9. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Nicolas Beix
Co-rapporteur:	Paolo Gasparini

The rapporteur and Co-rapporteur appointed by the PRAC were:

PRAC rapporteur:	Liana Martirosyan
PRAC Co-rapporteur:	Zoubida Amimour

The application was received by the EMA on	4 March 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	16 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	19 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	30 June 2025
The Quality Biologics working party agreed on the Assessment Overview during their meeting on	15 July 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 October 2025
A routine GCP inspection was conducted at te sponsor site located in the United States, as well as two investigator sites, located in Belgium and Brazil, between 11 Aug - 03 Oc 2025. The outcome of the inspection carried out was issued on	13 November 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	11 December 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	26 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues	11 February 2026

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Palsonify on	26 February 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	26 February 2026

1.10. CHMP outcome

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.10.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.10.2.1. Similarity with authorised orphan medicinal products

Not applicable.

1.10.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Palsonify is favourable in the following indication(s):

Palsonify is indicated for the medical treatment of adult patients with acromegaly.

1.10.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.10.5. Other conditions and requirements of the marketing authorisation

1.10.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.10.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.10.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Disease definition and important clinical characteristics

Acromegaly is a serious, chronic, rare disease caused by excess secretion of GH by a pituitary adenoma which in more than 90% of the cases is benign and leads to increased production of insulin-like growth factor-1 (IGF-1) from the liver and other organs.

Clinical symptoms include signs and symptoms attributed to tumour mass effects compressing the surrounding structures (e.g., headaches and vision loss), and by the chronic overproduction of both GH and IGF-1 leading to disordered growth (progressive skeletal and soft tissue overgrowth, mainly at the extremities and head, organ enlargement) and metabolic complications including insulin resistance, increased blood glucose levels, hyperinsulinemia, diabetes, and dyslipidaemia.

Symptoms of acromegaly include abnormal growth of hands and feet; alteration of facial features; and thickening of tissue leading to arthritis, diabetes, hypertension, joint pain, fatigue, headache, hyperhidrosis, asthenia, paraesthesia, soft tissue oedema, sleep apnoea, and excessive snoring.

If left untreated, acromegaly has a mortality rate that is nearly **2-fold** higher than the general population, mainly due to cardiovascular complications and a significant decreased quality of life (QoL). Based on its clinical presentation, acromegaly is regarded as a serious and chronically debilitating condition with high impact on patient QoL.

Number of people affected or at risk

The prevalence estimate for each EU member state was used to calculate an estimate of the number of

cases for 2023, using 2023 population estimates. Where no prevalence data was available, the highest reported prevalence (1.367 per 10,000, Iceland) was used to provide the maximum number of cases.

Based on an estimated 50,257 cases, the EU prevalence of acromegaly has been calculated as **1.11 cases** per 10,000 (upper estimate).

Diagnostic criteria and methods used in clinical practice

The diagnosis of acromegaly is confirmed based on elevated serum insulin-like growth factor 1 (IGF-1) and lack of growth hormone suppression after glucose administration.

In adults, the diagnosis of acromegaly should be considered in patients presenting with acral enlargement or suggestive facial features as well as in those presenting with a constellation of symptoms, signs, or conditions associated with acromegaly, including frequent headache, excessive perspiration, hypertension, sleep apnoea, oligomenorrhea, arthralgias, carpal tunnel syndrome, and type 2 diabetes mellitus.

Randomly sampled serum GH levels, measured by immunoassays, are generally not recommended for the diagnosis of acromegaly but have been associated with biochemical outcomes of both surgical and medical treatments. Serum GH levels, measured every 30 minutes for 2 hours after the administration of an oral glucose load (75 g), can be helpful in establishing the diagnosis of acromegaly.

In the last consensus on criteria for acromegaly diagnosis and remission (*14th Acromegaly consensus: Giustina et al 2024*), in a patient with typical acromegaly features, insulin-like growth factor (IGF)-I > 1.3 times the upper limit of normal for age confirms the diagnosis. Random growth hormone (GH) measured after overnight fasting may be useful for informing prognosis but is not required for diagnosis.

Once the diagnosis of acromegaly has been confirmed based on the results of endocrine testing, a pituitary magnetic resonance imaging (MRI) examination should be obtained to detect a pituitary adenoma, which is the cause of acromegaly in most cases.

Current Therapeutic Options

The current major treatment goals for acromegaly are to normalize IGF-1 levels for age and sex and to decrease GH levels below 1 ng/mL to reduce mortality, reverse or attenuate signs and symptoms, control tumour mass, and maintain pituitary function.

The optimal treatment should provide robust efficacy in controlling IGF-1 levels and consistently minimising acromegaly symptoms, while having an acceptable safety profile. The ultimate objective is to improve patient QoL and satisfaction. Unmet needs include optimizing biochemical and symptom control, reducing treatment burden and enhancing QoL. Of note, recurring symptoms and compromised QoL can be also seen in patients that are biochemically controlled.

The existing therapeutic strategy includes surgery (first-line therapy) and/or medical treatment and/or radiotherapy.

Transphenoidal surgery is generally regarded as first line therapy for patients with acromegaly; however, surgical effectiveness varies depending on various factors, such as the size and extension of the anatomic mass, and the preoperative levels of GH. Surgery is most successful in patients with blood GH levels below 40 µg/L before the operation and with pituitary tumours no larger than 10 mm in diameter (microadenomas). Most patients with a macroadenoma require post-surgical medical treatment to achieve disease control (i.e. normalization of GH and IGF-1). Overall, after surgery, the hormone levels normalise only in 40-70% of the patients (*Kumar et al 2009, Melmed 2009, Platta et al 2010*).

Radiotherapy is generally reserved for patients with tumour remaining after surgery, for patients who are not good candidates for surgery because of other health problems, and for patients who do not

respond adequately to surgery and medication. Radiation therapy lowers GH levels by about 50% over 2 to 5 years (*Wass et al, 2001*). Radiation therapy causes a gradual loss of production of other pituitary hormones with time which can result in the undesirable effect of panhypopituitarism. Loss of vision and brain injury can be complications from radiation treatments.

Current medical treatment

According to clinical practice guidelines and expert consensus, medical therapy is recommended for the treatment of acromegaly in patients who have persistent or recurrent disease despite surgery, or who are waiting for radiotherapy, or who are not candidates for surgery or radiotherapy because of poor health.

Current medical treatment options for the management of acromegaly include somatostatin receptor ligands (SRLs), GH-receptor antagonists and dopamine agonists.

Table 3 Current medical therapies for acromegaly in Europe

Medical treatment		**Indication**
Somatostatine analogues	octreotide acetate (Sandostatine LAR pre-filled syringe IM)	Treatment of acromegaly, in: · Patients who are adequately controlled on sc treatment with Sandostatin, · Patients in whom surgery, radiotherapy are anappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective.
	octreotide acetate (Sandostatine solution for subcutaneous injection)	Treatment of acromegaly: When the circulating levels of growth hormone (GH) and IGF-1 remain abnormal after surgery and/or radiotherapy or when surgery and/or radiotherapy is inappropriate
	lanreotide acetate (Somatuline LAR pre-filled syringe IM or powder and solvent for solution for injection)	Treatment of acromegaly: When the circulating levels of growth hormone (GH) and IGF-1 is abnormal after surgery and/or radiotherapy or when surgery and/or radiotherapy is inappropriate
	pasireotide pamoate (Signifor 10 mg, 20 mg, 30 mg, 40 mg and 60 mg) powder and solvent for suspension for injection)	Treatment of acromegaly: Adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.
	octreotide acetate 20 mg (Mycapssa 20 mg) gastro-resistant hard capsules	Mycapssa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues.
GH receptor antagonist	pegvisomant (Somavert, powder and solvent for solution for subcutaneous injection)	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin

		analogues did not normalize IGF-1 concentrations or was not tolerated.
Dopamine agonists	bromocriptine (Parlodel 2.5 mg, tablets)	· Prolactinomas: - basic treatment of prolactinomas: micro or macroadenomas, - In particular, preparation to surgery in case of macroadenoma in which Parlodel can favour surgery in reducing the tumoral volume especially in case of extra-fossa extension. - In case of precocious or late failure of surgery: recurrence of a hyperprolactinemia
	cabergoline (Dostinex 0.5 mg, tablets)	· Idiopathic hyperprolactinemia · Hyperprolactinemia due to the presence of a microadenoma or a hypopituitary macroadenoma and clinical symptoms: - in women: galactorrhoea, oligo or amenorrhoea, infertility - in men: gynaecomastia, impotence

Of note, the Marketing of Authorisation of Mycapssa has been withdrawn since the 26 February 2025. The dopamine agonists (bromocriptine and cabergoline) and prolactin inhibitors (lisuride if tumour secretes prolactin) are used off-label in association with other medical treatment of acromegaly.

On 30 June 2025, Oczyesa (octreotide hydrochloride) 20 mg prolonged-release solution for injection in pre-filled pen has been authorized in Europe in the following indication: "maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues".

The treatment strategy depends on the details of the condition, such as presence of micro-/ macroadenoma, responsiveness to treatment, and GH or IGF-1 levels (see *Giustina et al 2014*).

Somatostatin analogues are used as first line pharmacological treatments in patients not cured by surgery/radiotherapy or requiring additional treatment pre- or postoperatively. For patients not cured by surgery or for whom surgery is contra-indicated, somatostatin receptor ligands (SRLs) are established as first–line medical treatment with potential for further improvements and lead to limited disease control with biochemical response rate of 30-55%, continued symptoms, and increased mortality.

In case of partial response with SRLs, adjunctive therapies can be considered in association to SRLs such as dopamine agonists (cabergoline, bromocriptine) which are used off-label and pegvisomant. In case of no response, pegvisomant can be considered in monotherapy.

Currently approved octreotide-based therapies have significant limitations related to their administration, including complex handling, inconvenient dosing, and a low, or very low, bioavailability, resulting in low or variable plasma exposure.

While SRL depot injections octreotide and lanreotide are currently the first-line medical therapy for patients with persistent disease after surgery or for those who are not candidates for surgical treatment, they are associated with substantial treatment burden and technical challenges, limit patients' abilities to manage treatment of their disease, and have a significant negative impact on patient quality of life for the duration of their use in this chronic disease.

There remains an unmet need for a targeted therapy that reduces the overall treatment burden and combines rapid, consistent, and durable disease control to treat a wide range of the acromegaly patient population that requires medical treatment.

2.2. Aspects of development

The clinical development program includes **11 phase 1** clinical studies in healthy volunteers and 1 phase 1 clinical study in participants with hepatic impairment. A phase 2/3 study **PA9001** in participants with acromegaly in Japan is being conducted as well.

The efficacy of paltusotine was evaluated in **two completed phase 2 studies** (study **CRN00808-03** and study **CRN00808-02**) and 1 on-going OLE phase 2 study in participants with acromegaly (study **CRN00808-05**).
- **Study CRN00808-03** included participants with acromegaly who were treated with SRL-based treatment regimens.
- **Study CRN00808-02** enrolled participants who were switched from long-acting octreotide/lanreotide monotherapy to once-daily paltusotine oral capsules.
- Both studies included the option of participants continuing in the on-going OLE study (CRN00808-05). During Study **CRN00808-05**, paltusotine participants were transitioned from **once-daily paltusotine oral capsules to once-daily paltusotine oral tablets**, the intended commercial formulation of paltusotine.

The paltusotine clinical registration program includes 2 pivotal, global, randomized, double-blind, placebo-controlled clinical phase 3 studies (**CRN00808-08** and **CRN00808-09**) with on-going OLE phases:
- **Study CRN00808-08** was designed to evaluate the efficacy and safety of paltusotine versus placebo as treatment (as assessed by IGF-1 levels) for biochemically uncontrolled acromegaly in participants not being treated medically at study randomization.
- **Study CRN00808-09** was designed to evaluate the efficacy and safety of paltusotine versus placebo as maintenance therapy (as assessed by IGF-1 levels) in participants with acromegaly whose IGF-1 was controlled at screening on long-acting octreotide or lanreotide monotherapy.
The population studied in the phase 3 studies included participants with medically naïve and previously medically treated acromegaly, including those who were biochemically controlled on SRLs and those who washed out from SRLs, and is representative of the broad patient population with acromegaly.

2.3. Description of the product

Paltusotine hydrochloride is a novel orally administered nonpeptide somatostatin receptor 2 (SST2) agonist.

It has been developed to reduce serum GH and IGF-1 levels in healthy volunteers and acromegaly patients. Phase 3 studies in acromegaly patients are still on-going in different countries around the world, including in the European Union (EU).
Proposed indication: medical treatment and long-term maintenance therapy of adult patients with acromegaly.
***Proposed posology*:** The recommended initial dose is 40 mg paltusotine by oral route once a day, administered as 2 × 20 mg tablets. During initiation, paltusotine may be temporarily reduced to 20 mg if needed, based on tolerability.

After at least one week, based on insulin growth factor-1 (IGF-1) levels or clinical signs and symptoms, titrate to a dose of 60 mg daily, administered as 2 × 30 mg tablets.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

The Committee for Medicinal Products for Human Use (CHMP) has adopted a request for a routine GCP inspection to be carried out for the following clinical trial CRN00808-09, in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and article 15 of Directive 2001/20/EC.

No critical findings were identified that could have impacted negatively the data quality. The conclusion was that the data submitted was reliable and could support the benefit/risk assessment.

3. Quality aspects

3.1. Introduction

The finished product is presented as a film coated tablet containing 20 mg or 30 mg of paltusotine as active substance (as paltusotine hydrochloride).

Other ingredients are:

Tablet core: copovidone, cellulose, microcrystalline, crospovidone, silica, colloidal anhydrous, magnesium stearate, mannitol (E 421);

Film-coating (Palsonify 20 mg film-coated tablets): hypromellose, titanium dioxide (E 171), triacetin (E 1518), iron oxide, yellow (E 172), iron oxide, red (E 172);

Film-coating (Palsonify 30 mg film-coated tablets): hypromellose, titanium dioxide (E 171), triacetin (E 1518), iron oxide, yellow (E 172).

The product is available in heat induction sealed, white high-density polyethylene (HDPE) bottles closed with white child resistant polypropylene (PP) closure. Each bottle contains a silica gel desiccant.

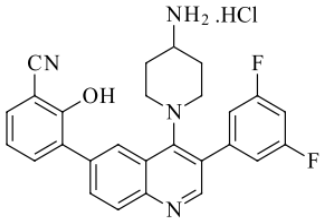
3.2. Active substance

3.2.1. General information

Full information on the active substance is included in the dossier.

The chemical name of paltusotine hydrochloride is 3-[4-(4-aminopiperidin-1-yl)-3-(3,5-difluorophenyl)quinolin-6-yl]-2-hydroxybenzonitrile hydrochloride corresponding to the molecular

formula $C_{27}H_{22}F_2N_4O.HCl$ It has a relative molecular mass of 492.95 (hydrochloride salt) or 456.49 (free base) and the following structure:



The active substance structure was elucidated using elemental analysis, chloride content, FTIR spectroscopy, mass spectrometry, NMR spectroscopy and UV-Vis spectroscopy tests. Physicochemical characterisation was performed by determining melting point, thermal analysis (DSC and TGA), dissociation constant (pKa), partition coefficient (Log P) and hygroscopicity. Polymorphic screening demonstrated that form A is consistently produced by the manufacturing process, and it was determined that no potential isomerism is possible as the active substance is achiral.

The active substance is a light yellow to reddish-brown crystalline solid which reversibly picks up moisture. It is slightly soluble in pH 1 acidic media but practically insoluble as pH increases.

3.2.2. Manufacture, process controls and process development

Evidence of GMP compliance has been provided in the QP declaration.

Manufacture of paltusotine hydrochloride is a convergent process consisting of several steps using four starting materials, defined according to a previous scientific advice procedure, with acceptable specifications.

Adequate information on the source, impurity profiles and routes of synthesis of the starting materials as appropriate, was provided. Information on the fate and origin of impurities, results from spiking and purging studies and process knowledge support the control strategy and intermediate specifications. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regard to their origin and characterised. Mutagenic impurities were assessed and controlled according to ICH M7. A risk assessment indicated no risk of nitrosamine impurities.

Residual solvents are controlled in the active substance specification according to ICH Q3C. Class 1 and 2A elements are below 30% of the ICH Q3D option 1 limits and thus not included in the specification. Palladium, used as a catalyst in the process, is controlled to NMT 20 ppm in the active substance.

The applicant explained the history of development of manufacturing process and discussed the impact on comparability. All changes made during process development are justified and resulted in an active substance of improved quality. The in-process data, combined with the batch data, indicate that the process is capable of operating within defined parameters to generate active substance of the required quality routinely.

The active substance is packaged in tied linear low-density polyethylene (LLDPE) bags which comply with Commission Regulation (EU) 10/2011, as amended. The LLDPE bags containing drug substance are placed inside a second LLDPE bag which is stored in an aluminium bag inside a high-density polyethylene (HDPE) drum.

3.2.3. Specification

The active substance specification includes tests for appearance (visual), identification (IR, UHPLC), assay (UHPLC), related substances (UHPLC), residual solvents (GC), palladium content (ICP-MS), boron content (ICP-MS), water content (KF), residue on ignition (Ph. Eur.), and chloride content (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Mutagenic impurities are controlled according to ICH M7.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data 11 production batches of the active substance are provided, 8 from the proposed commercial manufacturer and 3 from a previous manufacturer. The results are within the specifications and consistent from batch to batch.

3.2.4. Stability

Stability data from a representative number of batches stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The analytical methods used were the same as for release and the parameters tested are according to the release specification (table 1), with the omission of tests for identity, residual solvents, elemental impurities and residue on ignition.

All results of the stability studies provided met the specified limits and no significant trends were observed.

Photostability testing following ICH guideline Q1B was performed on 2 batches indicating that paltusotine is photosensitive and thus requires secondary packaging.

A forced degradation study was carried out under thermal, acidic, basic and oxidative conditions, thereby demonstrating that the analytical methods are stability indicating. The active substance degrades under oxidative conditions and is moderately sensitive to temperature.

The provided stability data support the proposed retest period of 36 months stored at or below 25 °C in the proposed container closure system.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

This medicine is supplied in two different strengths:

20 mg is presented as immediate release, oval, biconvex film-coated tablets coated with a pink-coloured water-soluble film. It is debossed with "PAL" on one side and "20" on the other side.

30 mg is presented as immediate release, oval, biconvex film-coated tablets with a yellow-coloured water-soluble film. It is debossed with "PAL" on one side and "30" on the other side.

The tablets are dose proportional, have the same % and w/w composition and are readily distinguished by size, colour and debossing.

A Quality Target Product Profile (QTPP) was developed in accordance with ICH Q8 (R2) to guide pharmaceutical development of paltusotine tablets.

Separate risk assessments were performed to identify the spray-dried dispersion (SDD) intermediate manufacturing process risks, drug product manufacturing process risks, and drug product biopharmaceutical risks. These risk assessments provide the framework for identifying finished product and SDD critical quality attributes (CQAs), critical material attributes (CMAs), critical bioavailability attributes (CBAs) and manufacturing process critical process parameters (CPPs). CQAs were presented and justified.

The active substance is a BCS Class IV compound, with low solubility and low permeability. It is formulated as an amorphous spray-dried dispersion (SDD), which enhances solubility such that it behaves as a highly soluble compound. Since the first step of the manufacturing process involves dissolution of the active substance, its physicochemical properties such as particle size and crystalline form are of limited importance.

Compatibility of the SDD with the other excipients has been demonstrated. Information about the functionality-related characteristics of the excipients is provided and justified. This would allow to ensure that these parameters will remain to be adequately controlled in case of any future changes in excipient suppliers. The functionality-related characteristics of pharmacopeial excipients (crospovidone, microcrystalline cellulose, mannitol, colloidal silicon dioxide and magnesium stearate) cover such parameters as particle size distribution, specific surface area and loss on drying. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

As paltusotine.HCl is a BCS class IV substance, the initial biopharmaceutics risk classification for the finished product was determined to be medium. Potential CBAs (pCBAs) were selected from finished product failure modes that could impact bioavailability, including formulation variables, CQAs, CMAs, and CPPs. The risk of impact on bioavailability (absorption rate and extent) for each pCBAs was evaluated through failure mode and effects analysis (FMEA).

Control strategies are in place for the two potential failure modes related to potential CBAs with high severity scores, crystallization of the active substance (pCBA: crystalline content, measured by XRPD at release and on stability) and disintegration of the tablet (pCBAs: tablet hardness, tablet disintegrant level).

Early phase clinical trials were conducted with hot melt granulation capsules, whereas the proposed commercial formulation was used in phase 3 studies. The two formulations were successfully bridged by bioavailability studies.

A dissolution test has been developed for routine quality control. The method is considered to be clinically relevant based on the similarity of the dissolution profiles (f2>50) between bioequivalent 20 mg and 30 mg tablets. Discriminatory power was investigated on batches manufactured with meaningful changes in composition or material attributes of individual components. Some discrimination was generally seen at early timepoints for all modifications. However, the initially

proposed specification limit was not accepted by CHMP as it was too wide to allow detection of non-compliant batches, resulting in a major objection. In response, the applicant agreed to tighten the limit for the 20 mg tablet which was considered acceptable. The limit for the 30 mg tablet was also amended. Further tightening was not possible given the limited manufacturing experience, although the applicant also tightened the acceptance limits for hardness which was considered sufficient to resolve the major objection. The CHMP recommends re-evaluating the specification for the 30 mg tablet upon completion of the first 10 commercial batches and to update the dossier as appropriate.

Manufacturing process development has been adequately described including identification of CPPs and an appropriate control strategy.

The primary packaging is a heat induction sealed, white HDPE bottle closed with white child resistant PP closure. Each bottle contains a silica gel desiccant. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product, sufficient evidence of GMP compliance has been provided.

Representative batch formulae for paltusotine SDD intermediate and paltusotine film-coated tablets were provided. The SDD manufacturing process consists of dissolution of the components in methanol, spray drying and secondary drying.

The finished product manufacturing process consists of six main steps: blending of intra-granular excipients with the SDD, roller compaction, blending with extra-granular excipients, compression, film-coating and packaging. Process controls were listed for each step.

The manufacturing process is a standard process in alignment with the guideline on process validation for finished products. Process validation will be performed in accordance with cGMP's prior to commercial distribution of the drug product. The validation protocols are provided and acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

3.3.3. Product specification

The finished product release and shelf-life specifications are consist of tests for appearance (visual), identification (UHPLC, UV), assay (UHPLC), impurities (UHPLC), water content (KF), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), crystallinity (XRPD) and microbial contamination (Ph. Eur.).

The acceptance criteria are the same at release and shelf-life except for assay, for 3 specifically identified impurities and total impurities, where wider limits are proposed at shelf-life in line with stability data. The levels of impurities have been assessed for mutagenic potential and determined to be non-mutagenic. Also, crystallinity by XRPD and TAMC, TYMC and specified microorganism are tested annually during stability. Different acceptance criteria are applied to the 20 mg and 30 mg strength paltusotine tablets as previously explained.

A risk assessment on the potential presence of elemental impurities in the finished product was provided and complies with ICH Q3D. The results of the risk assessment show that none of the evaluated elemental impurities exceed 30% of the established PDEs.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant identified risks based on the presence of 3 active substance impurities containing secondary amine moieties, and the use of excipients known to contain trace nitrite and assigned acceptable intakes based on the CPCA. Test data for two of the potential nitrosamine impurities was provided. However, the analytical method was not validated. Furthermore, test data for the third potential impurity was not available, resulting in a major objection. In response, the applicant provided the requested batch data, including data on aged samples to show that levels remain acceptable throughout shelf-life. The analytical method was shown to be validated and sufficiently sensitive. Therefore, it is considered acceptable to omit controls for nitrosamine impurities from the specification and the major objection is resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

The batch analysis data (14 batches for 20 mg tablets and 7 batches for 30 mg tablets) were provided, including the analytical results of four registration/primary stability batches of paltusotine tablets (for each strength of tablets). The analytical results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.3.4. Stability of the product

Stability data from four commercial scale batches per strength of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal products are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested according to the stability specification listed in table 10.

Tablets of each strength were stored in the commercial bulk packaging (two polyethylene bags sealed with a twist tie and a desiccant pack placed between the polyethylene bags). Bulk storage of up to 12 months is supported by the provided stability data. No significant changes or trends were observed.

Tablets were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Palsonify is not photosensitive.

Based on available stability data, the proposed shelf-life of 30 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

3.3.5. Adventitious agents

No materials of human and animal origin are used in the manufacturing process.

3.4. Discussion and conclusions on quality aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Two major objections were raised concerning the acceptance criteria for the dissolution method and the control strategy for potential nitrosamine impurities. Both were resolved by provision of additional data. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, the dissolution limit for the 30 mg tablet could still potentially be tightened following manufacture of additional commercial scale batches. This point is put forward and agreed as a recommendation for future quality development.

The quality of this product is acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.4.1. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To re-evaluate the specification for the 30 mg tablet upon completion of the first 10 commercial batches and to update the dossier as appropriate.

4. Non-clinical aspects

4.1. Introduction

The non-clinical program was developed according to ICH M3(R2). The rat and dog were selected as the species for non-clinical toxicity studies based on similarity in the metabolic profiles compared to humans. Both species are also pharmacologically relevant. The pivotal toxicity studies were performed up to 26 weeks in rats and up to 39 weeks in dogs with appropriate recovery periods. The standard genotoxicity battery recommended in ICH S2 was performed. The carcinogenic potential was assessed in 6-month rasH2 mouse and 2-year rat carcinogenicity studies. DART program is composed with a GLP fertility and early embryonic development study in rats, embryo-foetal development studies in rats and rabbits and a pre- and postnatal study in rats. GLP *in vitro* and *in vivo* studies were conducted to assess the phototoxic potential of paltusotine. Additional identified impurities associated with the paltusotine drug substance and/or drug product were evaluated for potential genotoxicity by QSAR prediction methodologies or Ames in accordance with ICH M7(R2). All pivotal studies were GLP compliant. A full ERA was provided.

4.2. Analytical methods

LC-MS/MS technics were conducted in two different laboratories located in China and the United States using different analytical procedures. Differences in the pre-treatment procedure (liquid-liquid extraction or protein precipitation) and in the analytical range and limit of sensitivity (2.50 to 2500 ng/mL or 10 to 10,000 ng/mL) were observed in laboratories in the US and China, respectively. The methods were validated and although the lower and upper limits of quantification differed, the reliability of quantitative data did not appear to be significantly affected.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Paltusotine is a bias agonist of SST2 receptor with a CHO K1 human cells EC_{50}= 0.25nM. This value is compared to peptide agonists: octreotide and native somatostatin-14 (SS14) respectively EC_{50}=0.058nM and EC_{50}=0.14nM. Paltusotine EC_{50} is slightly higher than octreotide and SS14 EC_{50} which demonstrated a lower or same effect. This trend is the same for CHO K1 cells in other species (rabbit, rat, dog and monkey). Paltusotine is a biased agonist and preferentially affect G-protein signalling and inhibition of cAMP accumulation over other pathways (internalization and desensitization via β-arrestin). Paltusotine, octreotide and SS14 were tested on these receptors and Paltusotine demonstrated the less internalization and desensitization of them. Internalization and desensitization are led to tachyphylaxis and this study demonstrated that paltusotine did not induce tachyphylaxis compared to octreotide and SS14. This may lead to a reduction in adverse events of β-arrestin. The reversibility liaison of paltusotine on its receptors has not been measured in the pharmacology studies but non-clinical and clinical studies did not suggest non-reversible liaison and effects.

The suppression effect on GH after a single oral administration of paltusotine was measured on rat. A challenge model was used for measuring acute effects of somatostatin analogues on GH secretion. GH levels were evaluated when paltusotine was orally administered at doses of 3, 10, and/or 30 mg/kg to male or female rats at 1 and/or 3 hours. Single administration of paltusotine produced significant plasma GH suppression in a dose dependant manner (ranged from 15% to 79% at 3 mg/kg, 32% to 89% at 10 mg/kg, and 85% to 97% at 30 mg/kg).

The IGF-1 level was measured on rat chronic model. The ability of orally administered paltusotine (at 10 mg/kg/day and 30 mg/kg/day) to reduce IGF-1 in rats over 14-days was assessed and compared to continuous administration of 240 µg/kg/day of octreotide delivered via a surgically implanted subcutaneous mini-osmotic pump. A better decrease for octreotide was observed at D1 and a little better for 30 mg/mL paltusotine at D14 (16% vs 12%). These results showed no difference with these 2 drugs at D14. In parallel of IGF-1 level, non-fasting blood glucose and body weight was measured. There were no treatment effects on non-fasting blood glucose levels all along the study and groups. Compared to vehicle, decreased body weight gain was observed in paltusotine and octreotide-treated rats. Octreotide induced a more important change in body weight than paltusotine (25.4-26.8% vs 16.2%) but less than vehicle control which is not normal (30.3%). 10 mg/kg/day was an effective dose in the rat (Cmax and AUC0-24 = 127 ng/mL and 975 ng×h/mL). Another study on dog was realized to measure IGF-1 levels at 6, 30, and 150 mg/kg/day once daily for 7 days. All doses of paltusotine suppressed IGF-1 on average up to 42% on Day 7 compared to baseline (0%). No dose response was evident, suggesting that the lower dose of 6 mg/kg/day was effective (Cmax and AUC0-24 = 729 ng/mL and 3700 ng×h/mL for male and 1610 ng/mL and 9040 ng×h/mL for female).

4.3.1.2. Secondary pharmacodynamics

CHO-K1 cells expressed hSST receptors and paltusotine was tested on 5 receptors to visualize cAMP reduction. Paltusotine is highly selective for SST2 (EC_{50}=0.25nM) and was no selective for other SST receptors (1100 to >10,000nM). Paltusotine was then compared to octreotide and SS14, peptide somatostatin agonists. SS14 was selective with any receptors and EC50 on these 5 SST receptors was comprised between 0.065 and 0.85nM. Octreotide is more selective on SST2 with EC50=0.058nM but

the difference of selectivity with other SST receptors is less important than paltusotine. In fact, EC50 of SST1, 3, 4 and 5 are respectively >10,000, 7.9, 470 and 2.5 nM. Paltusotine has less risk to touch other SST receptors than octreotide or SS14. Paltusotine was demonstrated to be >4000-fold more selective for SST2 relative to the other SST receptors whereas octreotide was only 43-fold more. Paltusotine was tested on a selectivity panel of 87 assays. Paltusotine was not selective with most of these targets. The only exception was the serotonin transporter in which paltusotine at 10 µM showed 88% inhibition (Ki = 0.097 µM). Most serotonin transporters are associated with CNS and the enteric nervous system. Paltusotine do not penetrate CNS in rats and has a >2000-fold selectivity over EC50 for hSST2, the interaction with the serotonin transporter did not seem to be possible at therapeutic exposure.

4.3.1.3. Safety pharmacology

SST2 and SST5 receptors are largely found in pancreas. These receptors are respectively responsible of glucagon production and insulin inhibition and can have an impact on glycaemia. An oral glucose tolerance test was realized on rat by paltusotine oral gavage at 10 and 100mg/kg. At several time, paltusotine had no effect on oral glucose tolerance. The CNS safety was evaluated by functional observational battery on rat after an oral gavage at 25, 75 and 500mg/kg at several time. No significant CNS effects on qualitative and quantitative functional observational battery evaluations at any time point and dose. At the higher dose, unbound Cmax is 21-fold higher than clinical unbound Cmax. Several studies on cardiovascular system have been conducted. Two *in vitro* studies have been realized and demonstrated no hERG inhibition, neither ion channels inhibition (> 700-fold clinical concentration). Two non GLP cardiovascular telemetry study in beagle dogs were conducted to finally selected the higher and pertinent dose for GLP pivotal studies and are negative. Based on these studies a maximum dose of 10 mg/kg was selected for the GLP cardiovascular study. A GLP cardiovascular telemetry study in beagle dogs was conducted. Each dog (n=5) was administered vehicle (100% propylene glycol) or paltusotine at 0.5, 2, 5, and 10 mg/kg with a 7-day washout period between dosing days and cardiovascular parameters were collected continuously from approximately 2 hours predose through approximately 24 hours post dose following each dose administration. As non GLP studies, HR decrease at all doses, and this decrease was statistically significant at all doses except 5mg/kg. A slight increase for blood pressure and MAP, and no continuous effects on ECG parameters were observed. QT interval and QTc presented statistically significant change compared to vehicle at some hours. There is no dose dependant effect on these parameters. At 10 mg/kg, the unbound plasma Cmax of paltusotine was 16 ng/mL which is approximately 5.5-fold higher than the unbound steady state clinical Cmax of 2.96 ng/mL at a 60 mg dose. In these 3 cardiovascular telemetry studies in beagle dogs, HR, BP and MAP are modified by paltusotine. These effects are transitory and last few hours in 24h monitoring and need to be followed on longer studies in animals and in human. In the clinical part, bradycardia and cardiac conduct abnormalities were found too. A GLP respiratory study have been conducted on rat by oral gavage at 0, 25, 75 and 500mg/kg. At the highest dose, statistically significant increase in respiratory rate and minute volume was demonstrated at 2 and 6 hours and at 75mg/kg at 6 hours. At 24 hours, there is no change on these parameters which demonstrate the reversibility of these events. At 500 mg/kg, the unbound plasma Cmax of paltusotine was 62 ng/mL, which is approximately 21-fold higher than the unbound clinical Cmax of 2.96 ng/mL a 60 mg dose.

4.3.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted, and this was found to be acceptable.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

In vitro, the permeability of paltusotine in colorectal adenocarcinoma 2 cells was moderate. Absorption studies showed that paltusotine was a P-gp and BCRP substrate. As a concentration-dependent decrease in efflux was observed, a minimal impact on the absorption of paltusotine at the proposed therapeutic doses is expected.

In vivo absorption was extensively studied mostly exclusively by oral route; only one study was performed by IV route. After IV administration of 2.5 mg/kg of paltusotine to rats, dogs, and monkeys, the mean Vss were 1.5, 3.4, and 2.3 L/kg, respectively, which ranged from 2 to 5 times of total body water in all species.

Absolute bioavailability was determined in three experiments conducted in three species i.e. rat, dog and monkey, which revealed a poor absorption of paltusotine after oral administration, 8.8, 48 ± 7.4 and 10 ± 1.6 respectively. Many studies using different formulations, salts, feeding conditions each time were secondly performed to optimize the absorption of paltusotine. All were carried out using oral gavage. $AUC_{0\text{-last}}$, parameter that clearly illustrates the impregnation of the body by the drug, obtained in the different experimental conditions were compiled. The small number of animals used each time, and the large intra- and inter-assay variability did not allow for quantitate evaluation of relative bioavailability. And, even if many data are presented, they are difficult to compare since the experimental conditions are always different in terms of formulation (presence of ethanol, propylene glycol, vitamin E, HCl,), salt (di HCl, HCl, dimesylate), food regimen (fasted, not fasted, food ad libitum), dose, etc. However, some findings could be drawn from these data: some formulations seemed to promote absorption; although less well absorbed HCl salt seemed more stable; food intake clearly decreased the absorption of paltusotine. For lower concentration and after a single paltusotine dose, it may be considered that when dose increased, $AUC_{0\text{-last}}$ increased. For higher doses, no dose-concentration correlation was clearly established with concentration that increased in a less than dose proportional manner. For lower doses, a linear $AUC_{0\text{-last}}$ – dose relation was roughly obtained with a large intra- and inter-assay variability at each point and a poor correlation. Moreover, inconsistent values may be observed possibly due to emesis episodes, unsuitable formulation, poor solubilization of paltusotine (dosing formulations with concentrations 25 mg/mL and higher considered suspensions), etc. The same observations are made when analysing the AUC 0-last data obtained after the first dose in repeated dose studies. A very careful attention should be paid to the experimental conditions carried out in safety animal studies after oral administration given the large inter-assay variability in terms of absorbed dose and resulting AUC. The risk would be to overestimate the actual dose present in the animal after oral administration and not to reach toxic concentrations. This is particularly true for high doses where no dose-concentration relationship has been shown. Note that the solubilization of paltusotine that is given by oral gavage as solution at low dose and suspension at high dose might contribute to the malabsorption of high doses. The low absorption of paltusotine is justified by different vehicles and formulations requirement to enhance absorption, the Biopharmaceutics Classification System (class IV: low permeability and solubility) and vomiting animals.

Considering the short half-life, a very large accumulation of paltusotine was not expected. But, regarding the T½ of paltusotine 3.6 and 12 hours measured in rat and dog respectively after oral administration, a larger accumulation was expected in dog. In line, the mean ratio was 1.3 in rats, 2.5 in dogs.

Exposures reached at highest doses in 26-week rat and 39-week dog studies were 6.9- and 25-fold higher, respectively, than the anticipated steady state clinical AUC exposure at 60 mg.

Toxicokinetic analysis in rats and dogs showed peak and total systemic exposures of paltusotine increased in a dose-dependent manner over the dose range. Conversely, AUC values did not show time-dependency: in both 13- and 26-weeks toxicity studies in rats and in 13- and 39-weeks studies in dogs, exposure values decrease from day 1 to the last day of treatment.

4.3.2.2. Distribution

In vitro studies were performed to investigate the binding of paltusotine to plasma proteins and to determine its partitioning into whole blood and red blood cells. Paltusotine was highly protein bound (98 to 99%) in animals and humans and had a blood to plasma ratio of around 1.1, which was comparable to the blood to plasma ratio observed in the clinical study after oral administration of paltusotine to humans, suggesting minimal accumulation of paltusotine into red blood cells. In addition, *in vivo* studies were performed to investigate distribution of paltusotine into tissues of Sprague Dawley (non-pigmented) and Long Evans (LE, pigmented) rats following oral administration of [^{14}C]paltusotine (QWBA study). This study was performed only in male, therefore no distribution study in female reproductive organs is available. Paltusotine was widely distributed to tissues and was generally similar in the two strains. Little to no radioactivity was detected in the lens of the eye, and the central nervous system, which was confirmed by a dedicated study. Minimal brain to plasma ratio of paltusotine (<0.05) was observed in rats. QWBA study demonstrated a preferential binding to melanin containing tissues, namely the meninges, uveal tract, and the pigmented skin. In a rat foetal transfer study, a placental transfer was observed after paltusotine treatment, which is confirmed in pre- and postnatal study in rats.

4.3.2.3. Metabolism

Exploratory metabolite profiling and identification of paltusotine was conducted *in vitro* using microsomes, hepatocytes and HμREL cells from humans and animal species. Metabolism was also studied *in vivo*, in plasma, bile (rat only), and urine samples collected from rats, dogs, and humans orally administered with paltusotine. This was followed by radiolabelled ADME studies in rats. Paltusotine is mainly metabolized to the glucuronide conjugate (M632/1, also known as CRN06377), the oxidative metabolite M472/1, and its glucuronide conjugate (M648/1). A carbamoyl glucuronide (M676/1, also known as CRN06554) was also identified as a minor metabolite. This indicated that glucuronidation and oxidation were the main metabolic pathways of paltusotine. Glucuronidation studies in human liver microsomes suggested that UGT1A1 was the main contributor in the formation of CRN06377 with minor contribution from UGT1A9. The oxidative metabolite M472/1 was CYP enzyme mediated and was primarily formed by CYP3A4/5 with minor contribution from CYP2D6. In mass balance study performed in humans, no metabolites were detected in plasma in humans. paltusotine was the only circulating radioactive component in humans and the most abundant component in rats. The human study also indicated that in human excreta, CRN06377 was the major metabolite, implying that paltusotine was primarily eliminated via glucuronidation. CRN06377 was also the major metabolite in urine and bile in the rat ADME studies. A similar metabolic profile was observed in vitro, when paltusotine was incubated with dog hepatocytes and HμREL cells. Glucuronidation to CRN06377 was the primary metabolic pathway in all species investigated. In rats, glucuronide metabolites were also observed in the plasma, unlike findings in human plasma. They are not expected to have any pharmacological activity. Therefore, glucuronidation to CRN06377 was the primary metabolic pathway in all species investigated. Rat and dogs were demonstrated to be metabolically relevant.

4.3.2.4. Excretion

Elimination was studied in rats (male and females) and in bile duct cannulated male rats. Faeces was the predominant route of paltusotine excretion in rats, as in humans. There were no sex differences. Toxicokinetic parameters measured in PPND study (see DART part of this AR) supported the excretion of paltusotine in maternal milk with milk-to-plasma ratio at 4hours postdose on LD20 ranging from 2.36- to 3.77-fold. Exposure levels measured in rat offspring on that day (Cmax and AUC_{0-8}) were 0.1-0.8% of those measured in dams.

4.3.2.5. Pharmacokinetic drug interactions

See clinical assessment.

4.4. Toxicology

4.4.1. Single-dose toxicity

Paltusotine (di-HCl) was well-tolerated after single oral dose up to 1000 mg/kg in rats and up to 150 mg/kg in dogs.

4.4.2. Repeat-dose toxicity

Exploratory repeat-dose toxicity studies (non-GLP) with paltusotine were conducted in the rat and dog for up to 14 days to ensure an appropriate dose selection in pivotal GLP studies. All exploratory studies, except 14-days in dogs were performed with di-HCl salt form of paltusotine. All pivotal rat and dog studies were performed with HCl salt form and the 14-day exploratory study in dogs. In rats, an optimization of the dose formulation was conducted. Simple formulations containing citrate buffer and/or cosolvent (e.g. PG) were used in preliminary rat toxicity studies using the di-HCl salt form of paltusotine. The formulation containing a cosolvent (PG) and a non-ionic surfactant (vitamin E D-α-tocopherol polyethylene glycol succinate [TPGS]) in 0.1N HCl was able to achieve dose-dependent increases in systemic exposures at higher doses, therefore this formulation was selected for pivotal studies in rats. TK analysis was performed in rat toxicity studies and an additional investigative PK study in rats (14 days, see in PK part of this report) were performed following the lack of toxicity in the pivotal 28-day GLP study in rats in order to obtain a higher rat exposure. PK profile in rats showed a saturation of AUC was achieved at 250 mg/kg in male rats and at 500 mg/kg in female rats. For the dog, changes to the formulation did not improve systemic exposure compared to 100% PG (2 ml/kg) and, thus, PG was used in both exploratory and pivotal GLP studies. PK profile in dogs suggested a point of saturation at 75 mg/kg/day. Paltusotine was well tolerated in exploratory studies in rats, MTD was determined in rats and in dogs at the maximum tested dose which correspond to be the point of exposure saturation. MTD in rats was determined at 250 mg/kg/day up to 14-day treatment. Test article-related changes were limited to reduced body weight gain in all paltusotine-treated groups resulting in decreased body weights relative to control throughout the dosing period. In dogs, after 7-day treatment the MTD was determined to be below 150 mg/kg/day based on an increased incidence and frequency of emesis, as well as decreased body weight, therefore the dose of 75 mg/kg/day was used in the first pivotal study, a 28-day study. However, no toxicity was observed at the maximum tested dose, and an additional investigative dog study was performed (14-day study) demonstrating that the point of exposure saturation was 75 mg/kg/day.

Pivotal repeat-dose toxicity studies have been conducted in the rat (up to 6 months) and dog (up to 9 months). 500 mg/kg/day and 75 mg/kg/day doses were selected as the highest dose in rats and in dogs respectively. This was considered acceptable given that these two doses are demonstrated to be the point of exposure saturation.

In rats, paltusotine caused non-dose dependent and non-adverse decreases in body weight and body weight gain at all doses tested (25, 75 and 500 mg/kg/day). This effect could be considered as a pharmacologically driven effect. This effect reversed after cessation of treatment. The decreases of body weights were also observed with SST2 agonist (octreotide, pasireotide, lanreotide). No organ specific toxicity was observed during the rat studies. A higher incidence of progressive cardiomyopathy was observed in 13-week study at 500 mg/kg/day at final necropsy, not observed at recovery necropsy, and not observed after 26-week of treatment. A higher incidence of ovary atrophy was also observed at the high dose at the final necropsy and was not considered treatment related by the Applicant. In reproduction toxicity studies, treatment-related changes were observed on female reproductive parameters and reported in SmPC sections 4.6 and 5.3. In the 26-week rat study, NOAEL was set up at 500 mg/kg/day. This was considered acceptable. The exposure at the NOAEL of 500 mg/kg/day in rats was 6.9-fold higher than the anticipated steady state clinical exposures at the recommended therapeutic dose of 60 mg.

In dogs, similar effects were observed. Clinical observations included emesis, abnormal stool (characterized by soft, loose, watery, and/or mucoid stools), loss of appetite/decreased food consumption and accompanied decreased body weight. The loss of appetite/decreased food consumption and consequential decreased body weight were readily resolved by offering the standard pellet diet mixed with canned food. Emesis was dose-dependent but sporadic and generally resolved over repeated dosing. Abnormal stool resolved upon cessation of dosing. These GI effects could be considered as a pharmacologically driven effect and were observed with SST2 agonist (octreotide, pasireotide, lanreotide). In the 39-week dog study, NOAEL was set up at 75 mg/kg/day, which correspond to 25-fold clinical exposure expected at the maximum recommended dose. It was considered acceptable. In 13-week dog study, thymus findings were observed at final necropsy (small thymus correlated to thymus depletion at all dose groups), and thymus depletion in one male at the high dose of 75 mg/kg/day at recovery necropsy. These thymic findings were noted observed after longer time exposure, therefore the Applicant's justification that these findings could be related to stress was accepted.

4.4.3. Genotoxicity

In screening non-GLP genotoxicity studies, di-HCl paltusotine was negative for mutagenicity in a standard plate bacterial mutation assay and negative for induction of micronuclei in an *in vitro* micronucleus assay with and without S9 activation. Then, a GLP compliant standard battery was performed with HCl paltusotine. Although an important cytotoxicity effect was observed, the test could be considered negative. No mutagenicity potential was detected for paltusotine.

An *in vitro* micronucleus GLP study was performed with HCl paltusotine in CHO cells. In the definitive assay, paltusotine was tested at 5, 12, 16, 20 µg/ml with and without metabolic activation for 3h treatment and at 1, 2, 6, 10 µg/ml without metabolic activation for 24h treatment. In the S9-activated 3-hour treatment series and the non-activated 24-hour treatment series, no significant increases in the percentage of cells with micronuclei were observed at any concentration. In the non-activated 3-hour treatment series, a concentration-related response (2.55% MN cells) was identified by the statistical Cochran-Armitage test because at 16 µg/ml the percentage of micronuclei was slightly above the 99% control limits of the historical negative control data (0.61-1.95% MN cells). The Applicant did not consider this result as biological relevant as no statistically significant increases in the percentage of cells with micronuclei at the higher dose of 20 µg/ml was observed. However, the response at 20 µg/ml (1.75%

of MN cells) was slightly above the 95% control limits of the historical negative control data (0.8-1.67% MN cells). The 24h treatment without metabolic activation was tested at lower concentrations (up to 10 µg/ml) and therefore, the equivocal result observed after 3h treatment could not be ruled out. The *in vitro* MN test was considered as equivocal. An *in vivo* micronucleus GLP test was conducted in SD rat. Paltusotine (HCl) was administrated for 3 days at 250, 500, 2000 mg/kg/day by oral gavage. Paltusotine did not induce cytotoxicity in bone marrow and no statistically significant increases in micronucleus formation at 7-fold the clinical exposure range at the MHRD. Therefore, no genotoxic potential was identified with paltusotine at the clinical exposure range in the standard genotoxicity battery. This was reflected in the SmPC.

4.4.4. Carcinogenicity

The carcinogenicity potential of paltusotine was assessed in oral 26-week transgenic mice study and in oral 2-year rat study.

A dose-range finding study in transgenic mice was preliminary performed (2 phases: 5-day and 28-day treatment). After 5-day treatment, the MTD was determined to be above the highest tested dose of 1000 mg/kg/day and NOAEL after 4-week treatment was set up at the highest tested dose of 500 mg/kg. In the pivotal study, transgenic mice were administrated orally with 25, 75 and 300 mg/kg/day paltusotine for 26 weeks. Exposures in male mice increased in dose-dependent manner. However, in female mice, exposures in 75 mg/kg/day group measured at D180 were far higher than expected, this could be explained by one individual animal and in 300 mg/kg/day at D180, female exposures were largely decreased but similar to male exposure. The PK profile is not completely understood. The food effect and the physicochemical property of paltusotine may explain the inconsistency observed in PK parameters. There was no carcinogenic effect related to paltusotine administration up to the maximum tested dose of 300 mg/kg/day which corresponded to 2.8-fold clinical exposure at the MHRD. The neoplastic changes observed in the study were not considered test article related, since the incidence of these findings were in the historical range and not dose-dependent effect.

Paltusotine was administrated by oral gavage in rats at 25, 75 and 500 mg/kg/day. The dose selection was based on the point of saturation observed in shorter rat studies, which was acceptable. Toxicokinetic animals were treated for 26 weeks only. The PK profile appeared coherent in this study. Due to low survival of water and vehicle control animals, the study was terminated early during Week 91 for males and Week 89 for females. However, at least 28 animals/sex in each group survived to Week 80, which provided enough animals to adequately evaluate carcinogenicity. Clinical observations were limited to orange discoloration of the faeces in animals administered 500 mg/kg/day. Mass observations noted were considered normal background observations in studies. Test-related lower body weight trends were observed at all dose levels correlated to a lower food consumption, as in the shorter rat studies (not considered adverse). Most of the neoplasms identified as the cause of death/moribund condition were considered representative of common, spontaneously occurring, age-related neoplasms that occur in laboratory rats. Paltusotine decreased incidences of pituitary and mammary neoplasms in males and/or females administered from 25 mg/kg/day was potentially attributable to the pharmacological mechanism of action of paltusotine via a direct effect of hormonal modulation and/or acting on the gastrointestinal tract. Paltusotine increased incidences of minimal to moderate cystic glandular hyperplasia in the uterus and/or minimal to slight epithelial hyperplasia in the cervix occurred for females administered from 25 mg/kg/day, relative to water and vehicle controls. These increases were potentially attributable to hormone modulating effects of CRN00808 and/or secondary to the decreased incidence of pituitary neoplasms. A statistical analysis of neoplastic lesion incidence data suggested the possibility of a test article-related increase in combined cervix/uterus stromal neoplasms. The combined incidence of these neoplasms was 3, 0, 2, 4, and 0 for water controls, vehicle controls, and females administered 25, 75, and 500 mg/kg/day, respectively. The absence of these neoplasms in females administered 500

mg/kg/day and the similar (3 vs 4) incidence for water controls and females administered 75 mg/kg/day suggested the statistical finding was not indicative of a biological effect. Additionally, the incidences of these neoplasms were within the historical control range for this strain of rats from 104-week carcinogenicity. During non-neoplastic finding analysis, paltusotine increased incidence and/or severity of brain mineralization, relative to control animals, was observed for males administered ≥75 mg/kg/day and females administered 500 mg/kg/day. This finding was reviewed by a neuropathologist expert. The parenchymal mineralization of the brain, mainly the thalamus, was confirmed to represent a spontaneous background change and not evidence of paltusotine-related neurotoxicity. The justification was acceptable. In addition, paltusotine was demonstrated to have a low blood brain barrier passage and dedicated safety pharmacology study in rats at same concentrations did not demonstrate functional impact. To conclude, administration of paltusotine for 2-year in rats caused some evidence of hormonal modulation (as in fertility study, see DART program). Paltusotine was considered not to have carcinogenic potential up to 500 mg/kg/day, which correspond to 33-fold the clinical exposure at the MHRD.

4.4.5. Developmental and reproductive toxicity

A full package of developmental and reproductive toxicology studies is available in rats and rabbits. In the fertility study conducted in rats treated at doses up to 500 mg/kg/day, there were no treatment-related effect on mating and fertility indices, sperm parameters and male reproductive organ weights. However, treatment-related decreases in mean numbers of corpora lutea and implantations with subsequent increased preimplantation loss and decreased numbers of total and live embryos were observed at ovarian and uterine examination of females treated at 500 mg/kg/day. These findings were not reported at doses up to 75 mg/kg/day (5-fold human exposure). In addition, there was an increase in oestrous cycle length at ≥75 mg/kg/day.

Embryofoetal development toxicity studies were conducted in rats and rabbits. In maternal animals, expected pharmacological decreases in body weight and body weight gain were observed. In rats, these effects were non-dose dependent and consisted in decreases in body weight gain up to 14-20% compared to controls during treatment duration that were overall not considered as adverse. In rabbits, these effects were more marked and treatment was less tolerated. At the high dose level of 75 mg/kg/day, this led to abortion of three dams on GD 25-27 (each with 9-10 implantation sites detected at necropsy) because of body weight loss and little to no food consumed between GD 7-24/27. Foetal examinations did not reveal treatment-related malformations or embryofoetal lethality in either rat or rabbit at doses up to 500 mg/kg/day and 75 mg/kg/day, respectively, corresponding to 11.5-fold (rat) and 5.8-fold (rabbit) human exposure. The developmental NOAEL was determined at 500 mg/kg/day in rats since no other effect on embryofoetal development was reported. In rabbits, a decrease in foetal body weights was observed at 75 mg/kg/day leading to a developmental NOAEL of 25 mg/kg/day (2.9-fold human exposure).

In the pre- and postnatal development toxicity study, reductions in mean maternal body weight gain (impacting on body weight) and food consumption were observed at ≥75 mg/kg/day and considered non-adverse. Effects on body weight of F1 offspring were also noted at 500 mg/kg/day during the preweaning period. Based on combined sex values, the difference was statistically significant at each testing occasion from PND7. On PND21, the body weight was decreased by 10.5% compared to controls. During the postweaning period at this dose level, there was still a decrease in body weight gain and body weight in both sexes with final body weight decreased by 10.1% (males PND113) and 7.0% (females, PND92) compared to controls. There were decreases in mean body weight at 75 mg/kg/day during the preweaning and postweaning periods that were considered test article related but non-adverse. There were no effects on sexual maturation, neurobehavioral or reproductive function in the F1 generation rats. Toxicokinetic parameters supported the excretion of paltusotine in maternal milk with milk-to-

plasma ratio at 4hours post-dose on LD20 ranging from 2.36- to 3.77-fold. Exposure levels measured in rat offspring on that day (Cmax and AUC0-8) were 0.1-0.8% of those measured in dams. Based on the decreased pup weight observed during the development period at 500 mg/kg/day, the preweaning and postweaning developmental NOAELs were established at 75 mg/kg/day corresponding to 6.1-fold human exposure levels considering exposure levels measured at this dose in the rat EFD study.

4.4.6. Toxicokinetics and exposure margins

Margins of exposures (animal/human) are based on Cmax and $AUC_{0\text{-}24h}$ measured in healthy volunteers, as PK profile in healthy volunteers and in patients were similar, this could be acceptable. However, the resulting animal/human margins of exposure should be taken in consideration with caution, given the large variability of paltusotine bioavailability.

4.4.7. Local tolerance

Dedicated local tolerance studies have not been performed with paltusotine. Local tolerance data were part of repeat-dose toxicology studies. GI effects were noticed in dogs (diarrhoea, emesis) and were considered as pharmacologically driven given SST2 receptor was present in GI tractus.

4.4.8. Other toxicity studies

The Applicant has justified that no dedicated immunotoxicity study was performed, since no immune adverse effects are expected from the pharmacological properties. In addition, no immunotoxicity findings were observed in the non-clinical or clinical program. This was considered acceptable. A low immuno-toxicological potential of paltusotine was predicted.

No metabolites were detected in plasma in humans. Therefore, no need the animal characterization of human metabolites. In human excreta, only glucuronide metabolites were detected and were also detected in rats (plasma or excreta).

Seventy-nine starting materials, intermediates or process impurities were tested according to ICH M7 guideline. Two QSAR models were conducted and accompanied with an expert opinion and when needed, assessments were performed in miniaturized and/or standard Ames test. The presented data was acceptable. In addition, to set the specifications of 808-Imp 3 (2-Pyrrolidone) at 1%, 808-Imp 4 (Chloro Impurity) at 0.3%, 808-Imp 9 (Dimer Impurity) at 0.3%, 808-Imp 10 (Amine Impurity) at 0.5% and 808-Imp-G at 0.3%, two 28-day rat study were conducted with paltusotine with spiked impurities levels. No toxicity was observed and the NOEL was set at the highest tested dose, which was acceptable. Therefore, in study 424-0157-TX, 808-Imp 3 (2-Pyrrolidone) present at 2.3% in the tested batch was considered qualified at 0.037 mg/kg/day (considering the human equivalent dose at the NOAEL), 808-Imp 4 (Chloro Impurity) present at 0.47% in the tested batch was considered qualified at 0.0075 mg/kg/day (considering the human equivalent dose at the NOAEL), 808-Imp 10 (Amine Impurity) present at 0.54% in the tested batch was considered qualified at 0.0087 mg/kg/day (considering the human equivalent dose at the NOAEL), 808-Imp-G present at 0.49% in the tested batch was considered qualified at 0.0079 mg/kg/day. In study 424-0163-TX, 808-Imp 9 (Dimer Impurity) present at 1% in the tested batch was considered qualified at 0.019 mg/kg/day. Therefore, the proposed specifications were considered acceptable with a maximum daily dose at 60 mg.

The phototoxic potential was assessed according to ICH S10 guideline. Paltusotine absorbs at 238 nm (UV light). Considering that the MEC is above the threshold in UV wavelengths (> 1000 mol-1 cm-1 at wavelengths between 203 nm to 350 nm), an *in vitro* 3T3 NRU was conducted. The results indicated a

phototoxic potential since the photoirritancy factor (PIF> 5) and the mean photoeffect (MPE> 0.15) were above the recommended threshold. To further characterize effects of real administration of paltusotine on eyes and skin, an *in vivo* study was conducted in pigmented rats. As paltusotine showed bonding to melanin, the used species was considered acceptable. Rats were administered at 0, 10, 75 and 2 groups at 250 mg/kg/day for 3 days at around Tmax (one 250 mg/day/day with UV-vis light exposure and one without). There were no paltusotine-related ocular or cutaneous findings indicative of phototoxicity. Initially, corneal dystrophy was observed but no dose-dependency was observed (2 animals at 10 mg/kg/dose, bilateral, 1 animal at 75 mg/kg/day, bilateral, and none at 250 mg/kg). This effect is justified as common background and not test-related effect. This effect was further investigated by an extended histopathology analysis (5 additional serial sections of eye of each rat). This effect was not confirmed (incidence of cornea inflammation is similar in each group including group and 1 case of fibrodysplasia is observed one in left cornea and one in right cornea at 10 mg/kg/day). Therefore, this effect could indeed be considered as not test-related. Initially, inferior focal retinal retinopathy was observed in two animals unilaterally at the high dose 250 mg/kg/day. This effect was not considered as phototoxicity as the product absorbs at 238 nm (in UV spectrum) and the UVs wavelengths would be stopped by cornea and lens and not reach the retina. Additional histopathology analysis (amendment 1) showed minimal degeneration of retina with minimal inflammation in 0/10 eyes in control group, 2/10 eyes at 10 mg/kg/day, in 3/10 eyes at 75 mg/kg/day and 4/10 at 250 mg/kg/day. Although the severity of this effect was not worsened with the dose, the number of affected animals was dose-dependent. The incidence of this effect was higher that the presented historical control values (max 15/120 examined eyes). Therefore, the applicant's conclusion that this effect could not be considered as test-related was not endorsed. The retina distribution was not studied in QWBA distribution study. Exposures measured in this 3-day administration study at the highest dose of 250 mg/kg (at D3, Cmax = 2650-5550) were lower than those observed after 91 days of administration at the highest dose of 500 mg/kg/day in the 26-week study (at D91 Cmax= 5970/7830 ng/ml) and similar than those observed after 182 days of administration (Cmax = 3005 ng/ml). Ophthalmologic examinations and eye histopathology analysis revealed no test-related effect. In the same way, no test-related effect was observed in dogs at higher exposures for a longer time (up to 39-week). Therefore, the link between paltusotine administration and the adverse effect observed in retina in phototoxicity study after 3-day administration was questioned. Currently, investigative ocular monitoring is set up in 4 clinical trials (see clinical part). No additional non-clinical study was requested. The non-clinical findings are reported in the RMP. The relevance of the retina degeneration in human is not known and is currently studied in the on-going clinical trials (see clinical safety part).

4.4.9. Ecotoxicity/environmental risk assessment

As an ionizable compound, paltusotine Log Kow was experimentally determined according to OECD guideline 107 and was <4.5. Therefore, the definitive PBT/vPvB assessment was not requested.

The initially calculated value of PEC surface water was above the trigger value of 0.01 µg/L, studies for Phase II, Tier A environmental fate and effects testing and analysis following the 2006 EMA Guideline were submitted and during the on-going Phase II, Tier A studies, a further review of the recent epidemiological data of acromegaly in the EU revealed the erroneous calculations. The newly determined prevalence value of 1.1/1000 was endorsed by the COMP (EMA/OD/0000234998, 23/01/2025). The updated calculation of $PEC_{surface\ water}$ was below the threshold value, therefore no ERA Phase II was needed.

In Phase II no environmental risk was characterized for surface water, groundwater and micro-organisms. However, some properties of paltusotine may be of concern in the long term (even if PBT/vPvB evaluation was not requested), resulting from a poor biodegradation and the formation of non-

extractable residues in sediments, putatively bioavailable for sediment dwelling organisms. No questions were raised as the Phase II was not needed based on the updated calculation of PEC_{SW}.

In addition, the Applicant considered that paltusotine is not an endocrine active substance; however, as highlighted in DART part of this AR, the adverse effects observed at ovarian/uterine examination and oestrous cycle length in high dosed females of the fertility study may be related to the pharmacological activity of paltusotine considering the data obtained with somatostatin analogues. In addition, the literature reports e.g. that somatostatin, acting primarily through sstr2, is an inhibitor of electrical excitability of GnRH neurons in adult female and male mice, and inhibits the LH surge after intracerebroventricular injection in rats. The influence of GH on reproduction is documented (*Chang et al., 2022*).

Table 4 Summary of main study results: Phase I

Substance (INN/Invented Name):	Paltusotine/Palsonify		
CAS-number (if available):	2361216-83-1 (hydrochloride salt) 2172870-89-0 (free base)		
PBT screening	***Test protocol***	***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow} (log D)	OECD107	2.46 at pH 5 3.40 at pH 7 3.49 at pH 9	Potential PBT: N

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Paltusotine to the environment or the PBT/vPvB assessment.

The Applicant commits to perform the following studies as follow-up measures: the ERA will be updated, and a fish full lifecycle test will be conducted (*OCDE 240 guideline*).

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Paltusotine has demonstrated its efficacy through pharmacology studies. Paltusotine is a biased, highly selective SST2 agonist that decreases levels of GH, IGF-1 and cAMP. Paltusotine was not selective on a panel of 87 assays, no off-targets were identified. Safety studies showed no impact on oral glucose tolerance and CNS. Some events occurred on cardiac and respiratory system (variation of heart rate, blood pressure, interval QT, minute volume and respiratory rate) but at minimal 5-fold higher clinical dose. These events were transient, dose-independent and have been observed in clinical studies.

Paltusotine was demonstrated to be poorly metabolized and circulated mainly in the blood as unchanged, was mostly eliminated in the form of glucuronide conjugates via the bile, had the same metabolic pathways in animals and humans, and accumulated moderately after repeat dose. The small number of animals used each time, and the large intra- and inter-assay variability did not allow for quantitate evaluation of relative bioavailability. Even if many data were presented, they were difficult to compare since the experimental conditions were always different in terms of formulation (presence of ethanol, propylene glycol, vitamin E, HCl,), salt (di HCl, HCl, dimesylate), food regimen (fasted, not fasted, food ad libitum), dose etc.

Exposures reached at highest doses in 26-week rat and 39-week dog studies were 6.9- and 25-fold higher, respectively, than the anticipated steady state clinical AUC exposure at 60 mg. Toxicokinetic analysis in rats and dogs showed peak and total systemic exposures of paltusotine increased in a dose-

dependent manner over the dose range. Conversely, AUC values did not show time-dependency: in both 13- and 26-weeks toxicity studies in rats and in 13- and 39-weeks studies in dogs, exposure values decrease from day 1 to the last day of treatment. The non-clinical safety program was conducted according to ICH guideline M3, which was acceptable. The toxicity profile determined in rats and in dogs revealed no specific organs toxicity. Non-adverse decreases in body weight and body weight gain at all doses tested were observed in rats and in dogs in addition to the clinical observation of emesis and abnormal stool observed in dogs. These findings were considered non-adverse and could be explained by paltusotine pharmacological activity. NOAEL in rats and in dogs were determined at the highest tested dose 500 mg/kg/day in rats and 75 mg/kg/day in dogs which correspond to 6.5- and 25-fold the clinical exposure. The multiple of exposure in rats measured in 26-week study at D182 were lower than expected. Rat exposures treated at 500 mg/kg/day were not coherent between studies, the apparent variability could be inherent to the physicochemical properties of paltusotine, characterised by low solubility and permeability. To conclude, animal/human margins of exposure calculated in the whole dossier were taken in consideration with caution, given the large variability of paltusotine bioavailability (see animal PK part of AR).

A standard genotoxicity battery was conducted according to ICH guideline S2. The AMES test did not detect a mutagenicity potential. *In vitro* micronucleus test was considered as equivocal. The *in vivo* micronucleus test was negative. Paltusotine was considered to be a non-genotoxic compound.

No carcinogenicity potential was detected in 26-week study in transgenic mice (up to 2.8-fold the exposure at the MHRD) and in 2-year study in rats (up to 33-fold the exposure at the MHRD).

The package of developmental and reproductive toxicity studies in rats and rabbits was in line with the regulatory requirement applicable to the current marketing authorization. In rats, there were no treatment-related effects on fertility indices, male reproductive organs and sperm parameters at up to 500 mg/kg/day (16.7-fold human exposure), whereas decreased numbers of corpora lutea and implantations with increased preimplantation loss contributed to a decrease in the number of foetuses. These conclusions are reported in SmPC sections 4.6 and 5.3. In embryofoetal development studies no treatment-related malformations or embryofoetal lethality were shown in rats and rabbits at dose levels inducing exposure levels up to 11.5-fold and 5.8-fold, respectively, human exposure. In rabbits, abortions related to drug-induced body weight loss and markedly decreased food intake during the dose period were seen at the high dose level. The developmental NOAEL was 2.9-fold human exposure based on decreased foetal weight in that species. In the pre- and postnatal development toxicity study, there were no effects on sexual maturation, neurobehavioral or reproductive function in the F1 generation rats. The developmental NOAEL was determined on the basis of a decrease in F1 body weight during the pre- and postweaning periods at 500 mg/kg/day (6.1-fold human exposure levels). Toxicokinetic parameters measured on LD20 showed excretion of paltusotine in maternal milk, as well as systemic exposure of F1 pups (0.1-0.8% of maternal exposure, lowest exposure could be also due to decreased maternal milk intake from PND 14/15 in rats). The absence of any juvenile animal study was acceptable to support marketing of a product which would only be used in adult patients.

The specified and identified impurities in drug substance and drug product above the qualification thresholds as per ICH Q3A and ICH Q3B, respectively, were qualified in two 28-day repeat-dose toxicity studies in rats. The impurities tested are the following: N-isopropyl, O-isopropyl, 808-Imp 9 (study 424-0163-TX) and 808-Imp 4, 808-Imp-G, 808-Imp-I, 808-Imp 3, 808-Imp 5, 808-Imp 6, 808-Imp 10 (study 424-0157-TX).

No phototoxic potential was determined for paltusotine. However, retina degeneration was observed in the *in vivo* phototoxicity study. Although the link between paltusotine administration and this adverse effect is not clear, the Applicant has set up an ophthalmologic monitoring assessment in clinical trials of

6- month duration or longer to assess any potential clinical relevance in humans. No further animal study was requested as clinical experience is available (see clinical safety part).

The available data do not allow to conclude definitively on the potential risk of paltusotine to the environment. However, the CHMP has agreed that the ERA will be updated, when a fish full lifecycle test will be conducted (*OCDE 240 guideline*) and its results will be submitted in the post-approval setting.

4.5.2. Conclusions

From a non-clinical point of view, the application is approvable with the proposed ERA post-approval measure.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for GCP inspection has been adopted for the following clinical study CRN00808-09. The inspection covered two investigational sites and the site of the sponsor. The Integrated Inspection Report was provided on 13 November 2025.

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier (see section 2.4.3).

5.1.2. Tabular overview of clinical trials

Table 5 Overview of Clinical Pharmacology and Biopharmaceutic Clinical Studies and Studies in Participants with Acromegaly

Study	Objective(s)	Assessment
Phase 1 Studies in Healthy Participants		
CRN00808-01[a]	PK, safety, tolerability, and PD of single doses of paltusotine oral solution and oral capsules and of multiple doses of oral capsules; food effect on paltusotine PK of HMG capsule; and effect of paltusotine HMG capsule on the PK of midazolam	Single ascending doses (oral solution)
		Midazolam drug interaction
		Pharmacodynamic activity
		HMG capsule: single and multiple ascending doses, relative bioavailability (vs oral solution), dose proportionality, food effect

Study	Objective(s)	Assessment
CRN00808-04[a]	Effect of meal timing on paltusotine PK of HMG capsule	Food effect on HMG capsule
CRN00808-06[a]	Mass balance, route of elimination, and metabolic profile of [^{14}C]paltusotine and absolute bioavailability of paltusotine oral solution	ADME
		Absolute bioavailability
CRN00808-07[a]	Performance of the SDD tablet and 2MSA tablet formulations, relative bioavailability between the SDD and 2MSA tablets, effect of meal timing, and effect of PPI on paltusotine PK	PK and dose proportionality of SDD tablet
		PPI interaction with SDD tablet
		Relative bioavailability (vs capsule) and food effect on SDD tablet
		Characterization of 2MSA tablet
CRN00808-10	Effect of hepatic insufficiency on the safety, tolerability, and PK of paltusotine SDD tablets	Hepatic impairment participants and healthy participants PK
CRN00808-13[a]	Relative bioavailability of paltusotine SDD tablets at the same dose (60 mg) using tablets of 2 different strengths (3×20 mg tablets [reference product] vs 2×30 mg tablets [test product])	Relative bioavailability of 20 mg vs 30 mg SDD tablets
CRN00808-14	Safety, tolerability, and PK of single doses of paltusotine oral solution up to 240 mg	Single supratherapeutic doses PK
CRN00808-15	Potential drug interactions of paltusotine SDD tablets with carbamazepine, cyclosporine, metformin, and midazolam	Single and multiple-dose PK of SDD tablets
		Carbamazepine effect on paltusotine PK
		Cyclosporine effect on paltusotine PK
		Paltusotine effect on midazolam PK
		Paltusotine effect on metformin PK
		Paltusotine effect on cyclosporine PK
CRN00808-18	PK and safety of single dose followed by multiple doses of paltusotine SDD tablets in healthy Chinese participants	PK of SDD tablet
CRN00808-20	Relative bioavailability of single dose paltusotine 1×60 mg 35% drug load SDD tablet vs 3×20 mg 15% drug load SDD tablets	PK of SDD tablet
PA0001[b]	PK and safety of paltusotine SDD tablets in healthy Japanese vs Caucasian participants	PK of SDD tablet
PA0002[b]	PK, PD, and safety of paltusotine SDD tablets in healthy Japanese participants	PK of SDD tablet
		Pharmacodynamic activity
Phase 2 Studies in Participants with Acromegaly		
CRN00808-02	Safety, PK, and efficacy of paltusotine HMG capsules in participants with acromegaly who are responders to octreotide LAR or lanreotide depot	Sparse sampling PK
CRN00808-03	Safety, PK, and efficacy of paltusotine HMG capsules in participants with acromegaly treated with somatostatin analogue-based treatments	Sparse sampling PK

Study	Objective(s)	Assessment
CRN00808-05	Safety and efficacy of paltusotine HMG capsules and SDD tablets in participants with acromegaly (open-label extension)	Sparse sampling PK
Phase 3 Studies in Participants with Acromegaly		
CRN00808-08	Safety and efficacy of paltusotine SDD tablets in non-pharmacologically treated participants with acromegaly	Sparse sampling PK
CRN00808-09	Safety and efficacy of paltusotine SDD tablets in participants with acromegaly treated with longacting somatostatin receptor ligands	Sparse sampling PK

5.2. Clinical pharmacology

The clinical pharmacology program for Paltusotine encompasses 17 completed clinical studies, 12 performed in healthy volunteers (see below), 3 Phase 2 in patients with acromegaly (**CRN00808-02**, **CRN00808-03**, **CRN00808-05**) and two pivotal Phase 3 studies (**CRN00808-08** and **CRN00808-09**):

- One SAD/MAD, DDI, food effect study (**CRN00808-01**)
- One mass balance and metabolism study (**CRN00808-06**)
- Five biopharmaceutical studies investigating rBA, food or pH effect (**CRN00808-01**, **CRN00808-04**, **CRN00808-07**, **CRN00808-13**, **CRN00808-20**)
- Four studies investigating intrinsic factors (**CRN00808-10**, **CRN00808-18**, **PA0001**, **PA0002**)
- Two DDI studies (**CRN00808-01**, **CRN00808-15**)
- A QT/QTc study (**CRN00808-14**).

5.2.1. Methods

Bioanalysis

Six validated bioanalytical methods were used during clinical development to quantify paltusotine in human plasma by LC-MS/MS techniques. The methods are considered adequate and comply with the acceptance criteria of the bioanalytical method validation *of EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2* or of *ICHM10 on bioanalytical method validation and study sample analysis*.

Pharmacokinetic analysis

For single or multiple-dose studies, PK parameters evaluated in plasma include Cmax, Cmin, Tmax, AUCs (AUC0-t, AUC0-24, AUCtau, AUC0-∞), CL, CL/F, V, Vd/F and Vz/F, AUC%extra, AR (accumulation ratio), λz, T1/2.

For the mass balance study, additional PK parameters as Ae_u, fe_u, Ae_f, fe_f and CL_R were calculated.

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix WinNonlin v8.1 or later.

Pharmacodynamic Methods

In a phase III study conducted outside Japan, subjects took SDD tablets one hour before meals after overnight fasting. In this study, when paltusotine was administered immediately after a meal, it was confirmed that the exposure was significantly reduced for both capsules and SDD tablets, and the exposure was reduced even when the capsule was given 2 hours after a meal. Based on the above, the timing of administration of paltusotine was decided to be 1 hour before breakfast and 3 hours after breakfast.

The effects of paltusotine **40 mg QD** on serum IGF-1 concentration were evaluated under 2 dosing conditions: administration of paltusotine at 3 hours after a standard meal vs 1 hour before a standard meal.

Pharmacodynamic blood samples were collected for the determination of IGF-1 in serum at specified timepoints as follows: Day -1 (prior to dosing start), Days 1 to 6 pre-dose and at 12 hours post-dose; and on Day 7 pre-dose and at 12, 24, 96, and 168 hours post-dose.

Paltusotine can reduce blood levels of GH and IGF-1 via selective action on SST2. However, serum GH is difficult to detect in healthy adults because it has a short half-life and is secreted cyclically, primarily at night. There is also a method of temporarily increasing the serum GH concentration and evaluating it, but from ethical considerations, only IGF-1 was to be measured in this study.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Overall, the clinical pharmacokinetics of paltusotine has been described and substantiated adequately with the submitted clinical package.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

A population PK analysis was developed (crn00808-pop-pk-rpt) from which predicted exposure metrics were used as input for two exposure-response (ER) analysis (crn00808-er-rpt).

The population dataset was based on paltusotine PK data from 13 clinical studies (rich data from 11 Phase 1 studies in healthy volunteers, and sparse data essentially Ctrough from the 2 pivotal phase 3 studies **CRN00808-08** and **CRN00808-09** in patients with acromegaly using the proposed SDD tablets) that evaluated the oral solution or commercial SDD tablet formulations of paltusotine. Data from capsule formulations (not of interest, except for ER analysis) and data from doses less than 20 mg or greater than 160 mg (outside the clinically relevant dose range of 20-60 mg) were excluded from the analysis.

Covariates of interest were baseline demographic covariates (age, body weight, gender, race/ethnicity, renal function (eGFR) and UGT1A1 polymorphisms) and extrinsic factors as the formulation, mealtime, meal type and concomitant PPI.

NLME methodology was used to develop the paltusotine Pop-PK model. The first-order conditional estimation (FOCE) method was used as the default. Various disposition (2-, 3-, and 4-compartment) and absorption models (e.g. mixed order absorption) were assessed. PK parameters were assumed to follow

a log-normal distribution. A full model approach was implemented by simultaneously incorporating all covariate–parameter relationships of interest. Following construction and successful estimation of the full model, a backward elimination process was performed, where covariates were deleted singly from the full model based on change in OFV. Standard diagnostic plots were generated, and the final model was qualified using visual predictive check, quantitative predictive checks, and bootstrapping.

5.2.2.2.2. Physiology based pharmacokinetic model

Physiologically based pharmacokinetic (PBPK) modelling was performed to inform on DDI and to evaluate the effect of renal impairment on Paltusotine PK (crn00808-pbpk-rpt-crin-1d).

5.2.2.3. Absorption

Healthy volunteers

Following single dose of paltusotine with the SSD tablet (1h post-dose fasting) from 20 mg to a 60 mg dose, geometric mean Cmax and AUC24h ranged from 80.7 to 235 ng/mL and 651 to 2350 ng.h/mL (**CRN00808-07**). Tmax was generally achieved 1 to 4h regardless of post-dose duration.

Following multiple doses of paltusotine with the SDD tablet at a 60 mg QD dose geometric mean, Cmax was 290 ng/mL and AUC of 2890 ng.h/mL.

Patients

Following multiple doses of paltusotine QD (SDD tablet) from 20 mg to 60 mg, geometric mean **Ctrough** ranged from 51.3 to 79.8 ng/mL (**CRN00808-08**).

Following multiple doses of paltusotine QD (SDD tablet) at doses of 40 mg or 60 mg, dose normalized concentrations collected 2h post-dose at steady-state was 4.51 ng/mL/mg dose (**CRN00808-05**).

Based on *in vitro* investigations, paltusotine is a substrate of P-gp and BCRP.

Absolute bioavailability

An average absolute bioavailability of paltusotine (oral solution) was estimated at 70% with individual values ranging from 59% to 82%. For the SDD tablet, absolute bioavailability of paltusotine was estimated at 51%.

BCS classification

Based on *in vitro* investigations on solubility and permeability, paltusotine (HCl.SSD) can be classified as a BCS class 3 compound (high solubility/low permeability).

Influence of food

A food effect on paltusotine PK was demonstrated. With a high fat-meal both Cmax and AUC24h decreased by 81% and 85%, respectively (**CRN00808-07**). With a low fat-meal both paltusotine Cmax and AUCt decreased by approximately 72% and 68%, respectively (**CRN00808-07**).

Influence of gastric modifiers

A dose dependent decreases of paltusotine exposure (AUC and Cmax) by 20% and 40% was observed following a 20 mg or a 60 mg dose (**CRN00808-07**).

5.2.2.4. Bioequivalence

Relative bioavailability/Bioequivalence

Several oral formulations of paltusotine were developed and evaluated during the clinical development program:

- An aqueous solution containing paltusotine.HCl which was optimized to provide appropriate solubility (**Form 1**). This solution contained 65 w/w% Ora-sweet flavoring syrup, 25 w/w% propylene glycol and 10 w/w% D-α-tocopherol polyethylene glycol succinate
- An IR capsule containing a powder blend of paltusotine.HCl manufactured by hot melt granulation (HMG) (**Form 2**). The final blend was filled into Swedish orange gelatine capsules and supplied at 5, 10 and 20 mg strengths.
- An IR uncoated tablet containing paltusotine dimesylate salt (paltusotine.2MSA) manufactured by direct compression (**Form 3**). One strength was developed at 10 mg.
- An IR film-coated tablet containing paltusotine.HCl formulated as an amorphous spary-dried dispersion (SDD) with stabilizing polymer copovidone (**Form 4**). The SDD composition is 15:85 paltusotine:copovidone for a nominal SDD drug load of 15%. Two strengths were developed at 20 mg and 30 mg.
- A **Form 5** was also developed and consisted of **Form 4** with a 35% SDD drug load and used solely in the rBA study **CRN00808-20**.

Form 4 is the proposed commercial formulation and have been used in the Phase 3 pivotal studies (**CRN00808-08/09**).

Bridging between Form 1 vs Form 2

Between Form 1 (R) and Form 2 (T), Form 2 has a rBA of 0.689 (**CRN00808-01**).

Bridging between Form 2 vs Form 4

Between Form 2 (R) and Form 4 (T), Form 4 has a rBA of 0.825 (**CRN00808-07**).

Bridging between Form 4 20 mg vs 30 mg

Both strengths are BE, with GMR (CI90%) for Cmax and AUCt of 100% (84.4-118.5) and 98.8% (84.2-115.9), respectively (**CRN00808-13**).

5.2.2.5. Distribution

Paltusotine has a >99% and >98% protein binding on albumin and AAG, respectively, a B/P close to 1 and has a high distribution in tissue with a Vz/F estimated at 406 L.

5.2.2.6. Metabolism

Metabolite profiling was performed, and 4 metabolites were identified in total excreta and none in plasma (figure 1).

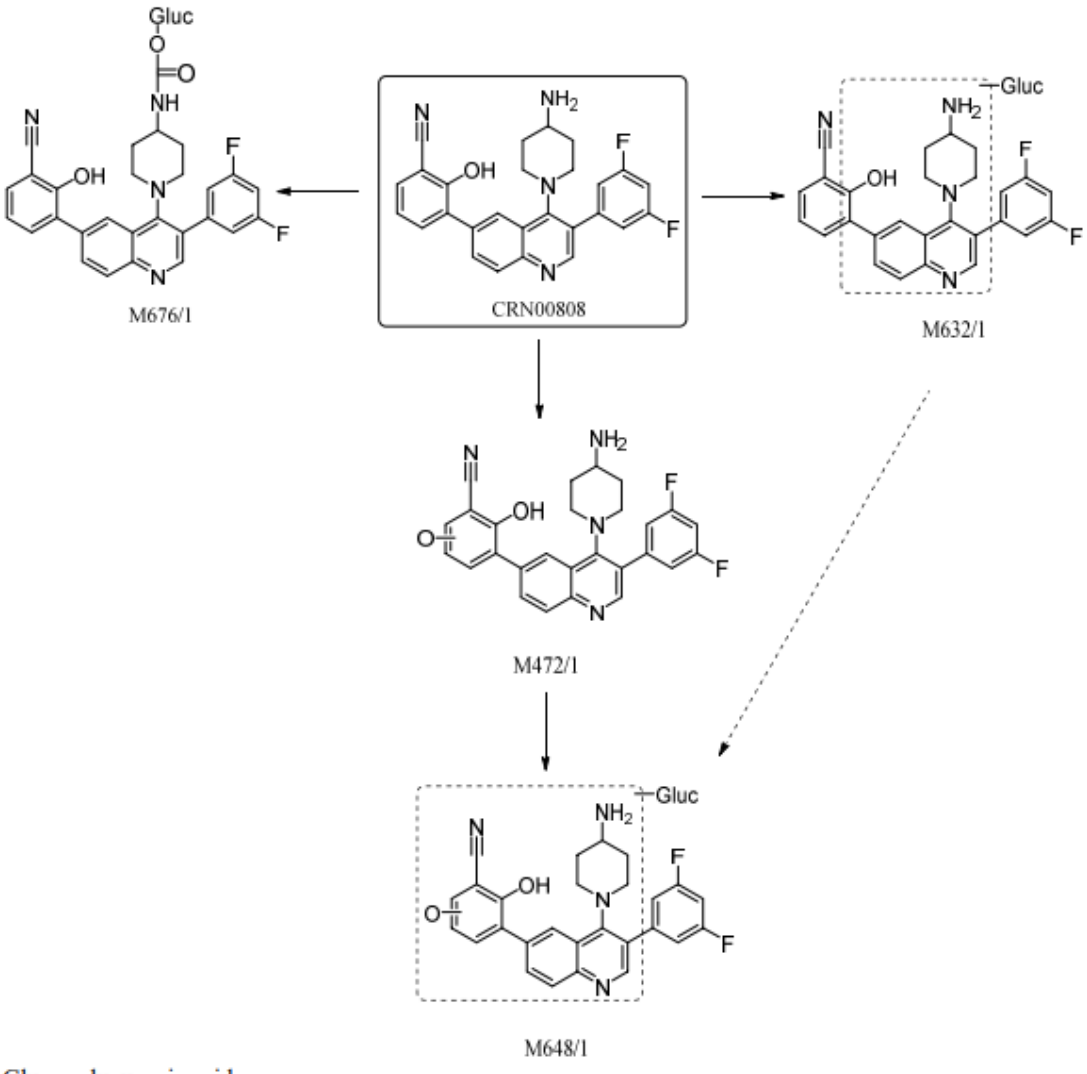
In plasma pooled sample (AUC48h), the unchanged parent paltusotine accounted for 100% of TRA.

In faeces, paltusotine was the main component excreted with 39.7% of the dose, followed by M632/1 (20.4%), M472/1 (7.92%). M648/1 and M676/1 accounted for less than 5% of TRA. 9.5% of the dose excreted in faeces was not identified, thus more than 83% of the dose excreted in faeces was identified.

In urine, unchanged paltusotine was detected at a low level (1.33%). M632/1 accounted for 1.44% of the dose and other metabolites less than 0.5%. More than 84% of the dose excreted in urine was identified.

Paltusotine is extensively metabolized mainly through glucuronidation via UGT1A1 and to a lesser extent by 1A9, and oxidation via CYP3A4 mainly and to a lesser extent CYP2D6.

Figure 1 Proposed metabolic scheme for Paltusotine in human subjects



Gluc = glucuronic acid

5.2.2.7. Elimination

Across the clinical studies in healthy volunteers, after a single dose of paltusotine from 20 to 120 mg geometric mean half-life ranged from 22 to 30 hours. Based on the PPK analysis, CL/F was estimated

at 11 L/h.

In the ADME study **CRN00808-06** following a 20 mg dose of paltusotine as an oral solution, mean T1/2 was 26h, CL/F was 8.4 L/h. Paltusotine is highly metabolized and cleared mainly by metabolism and faecal excretion.

- Mass balance

The excretion and biotransformation of [^{14}C]-paltusotine was investigated in 6 healthy subjects following a single oral dose of 20 mg paltusotine (solution) incorporating approximately 80 µCi [^{14}C]-paltusotine.

The arithmetic mean (±SD) cumulative recovery from faeces and urine was 94 % (± 1.1) of the administered radioactive dose with recovery ranging from 92 to 95 %.

Faecal excretion was the predominant route of elimination, with arithmetic mean recovery of TRA of 90% (± 2.2) and 3.9 (± 1.2) in urine. Unchanged paltusotine was recovered at 1.33% and 39.7 % in urine and faeces respectively. Most of the administered radioactivity (90%) was recovered in the first 120 h post-dose.

5.2.2.8. Dose proportionality and time dependency

Dose proportionality was demonstrated after a single paltusotine dose between 20 to 120 mg in healthy volunteers. Steady-state is expected to be reached by 7 days. At a 60 mg dose the accumulation ratio for Cmax and AUCt was 1.31 and 1.55 respectively.

5.2.2.9. Pharmacokinetics in the target population

Five clinical studies investigated paltusotine PK in patients with acromegaly following phase 2 (studies **CRN00808-02/03/05**) or phase 3 studies (studies **CRN00808-08/09**).

In study **CRN00808-08** (pivotal study, naïve or uncontrolled participants), participants received a starting dose of paltusotine 20 mg QD (or matching placebo) as tablet (**Form 4, 20 mg strength only**), and their dose could be titrated up to 60 mg QD through Week 24 based on biochemical status (IGF-1 level) and tolerability. Down-titration was allowed based on tolerability.

Table 6 Summary of pre-dose concentration at steady-state per dosing cohort (CRN00808-08)

		Visit		
		Week 12	**Week 20**	**Week 22**
Paltusotine Dose (mg)		**Concentration (ng/mL)**		
20	n	0	1	1
	Mean	-	39.5	51.5
	SD	-	NE	NE
	Geometric mean	-	39.5	51.5
	Geometric %CV	-	NE	NE
40	n	21	14	14
	Mean	57.7	58.9	86.0

		Visit		
		Week 12	**Week 20**	**Week 22**
	SD	40.4	34.78	50.54
	Geometric mean	43.8	51.8	74.5
	Geometric %CV	105.4	54.0	58.9
60	n	31	35	36
	Mean	93.2	88.9	113.4
	SD	56.17	59.37	108.44
	Geometric mean	76.4	69.4	79.8
	Geometric % CV	79.0	114.3	131. 6

Plasma concentrations reported as less than the limit of quantitation (LLOQ) or 2.0 ng/mL were imputed to LLOQ/2 for summaries of concentrations.
SD=standard deviation; CV=coefficient of variation

In study **CRN00808-09** (pivotal study, non-naïve or controlled participants), participants who switched from long-acting therapy to paltusotine, received a 40 mg dose (**Form 4, only the 20 mg strength**) and could be titrated up to 60 mg or to 20 mg, if the 40 mg dose was not tolerable.

Table 7 Summary of pre-dose concentration at steady-state per dosing cohort (CRN00808-09)

		Visit		
		Week 24	**Week 32**	**Week 34**
Paltusotine Dose (mg)		**Concentration (ng/mL)**		
40	N	14	14	14
	Mean	59.6	50.0	74.5
	SD	26.2	27.2	67.7
	Geometric mean	54.9	44.7	58.1
	Geometric %CV	44.4	50.0	75.9
60	N	15	15	15
	Mean	86.2	77.8	97.2
	SD	47.1	38.5	120.6
	Geometric mean	62.1	57.2	57.0
	Geometric %CV	188	180	214

SD=standard deviation

Population Pharmacokinetic analysis (Pop-PK)

A Pop-PK analysis (Pop-PK, CRNT-Proj1-23-0005) aiming to characterize the PK of paltusotine and identify / quantify sources of variability was developed. Model-based steady state exposure metrics were predicted at in the target population and used for subsequent E-R analysis for efficacy and safety.

Overall, 5560 observations from 316 subjects were included. All post-dose BLQ (n= 118, 3.2% of total observations <5%) were excluded from the analysis. This was found to be acceptable. Two outliers (|CWRES|>6) were identified and removed later resulting in a total of 315 subjects with 5558 paltusotine concentrations available.

The full model estimated clinically meaningful effects for the tablet formulation, mealtime, concomitant proton pump inhibitor (PPI) use, and sex, with each significantly impacting paltusotine bioavailability. The effects of meal type, race, body weight, UGT1A1 metabolizer status, eGFR, and cholecystectomy status were not clinically or statistically significant.

The final model consisted of a linear 3-compartment disposition model with first-order absorption (Ka), a relative BA for the tablet formulation (Ftab) and separate absorption lag times for oral solution and tablet formulations. IIV was estimated for CL, V2, Ka, tlags, and Ftab, IOV was included on Ftab and Ka and the model used a proportional residual error. Population estimates of paltusotine CL/F and Vss/F were approximately 24.2 L/h (9.41 /0.389 [38.8% being Ftab of the SDD tablet given with a meal at 1 h meal postdose, equivalent to absolute BA of 27.2% (0.389×70% the absolute AB of the oral solution) and 598 L (232.5 L/0.389). Ka was estimated at 0.317 h-1 and tlag was slightly longer for the SDD tablet relative to the oral solution (approximately 12 min vs 8 min). The proportional RUV was reasonable estimated at 21.1%.

Table 8 Population PK parameter estimates of the final PPK model

Parameter	Description	Estimate	RSE (%)	95% CI	Shrinkage (%)	CV (%)
tvCL	Apparent Clearance (L/hr)	9.41	6.28	[8.25 ; 10.6]	-	-
tvKa	Absorption Rate (hr-1)	0.317	10.4	[0.253 ; 0.381]	-	-
tvV2	Apparent Volume, central (L)	28.7	14.4	[20.6 ; 36.8]	-	-
tvV3	Apparent Volume, peripheral 1 (L)	71.8	16.0	[49.3 ; 94.3]	-	-
tvQ3	Apparent Distribution Rate 1 (L/hr)	1.84	30.9	[0.729 ; 2.96]	-	-
tvV4	Apparent Volume, peripheral 2 (L)	132	10.2	[106 ; 158]	-	-
tvQ4	Apparent Distribution Rate 2 (L/hr)	17.6	8.85	[14.5 ; 20.6]	-	-
TLG1	Oral Solution Lag Time (hr)	0.134	8.96	[0.110 ; 0.157]	-	-
TLG2	Tablet Lag Time (hr)	0.200	3.00	[0.188 ; 0.213]	-	-
$\theta_{F,tablet}$	Bioavailability, tablet	0.779	7.57	[0.664 ; 0.894]	-	-
θ_{MEALT}	Meal time effect on bioavailability	0.294	13.9	[0.214 ; 0.374]	-	-
$\theta_{F,PPI}$	PPI effect on bioavailability	-0.308	20.8	[-0.433 ; -0.182]	-	-
$\theta_{F_TAB_SEX}$	Sex effect on bioavailability	0.238	29.0	[0.103 ; 0.372]	-	-
omega1	BSV CL	0.268	6.34	[0.235 ; 0.302]	13.8	27.3
omega2	BSV V2	0.758	5.01	[0.684 ; 0.833]	22.7	88.1
omega7	BSV Ka	0.0650	155	[-0.132 ; 0.263]	86.1	6.50
omega8	BSV Ftab	0.344	8.72	[0.286 ; 0.402]	27.9	35.4
omega9	BSV tlag	0.316	10.1	[0.252 ; 0.379]	35.5	32.4
omegaftab_occ	IOV Ftab	0.381	7.09	[0.327 ; 0.434]	-	39.5
omegaka_occ	IOV Ka	0.407	12.0	[0.311 ; 0.502]	-	42.4
sigma_prop	Proportional RUV %	21.1	3.32	[19.7 ; 22.5]	-	-
Epsilon shrinkage	-	-	-	-	15.3	-

BSV=between subject variability, CI=confidence interval, CL=clearance, CV=coefficient of variation, IOV=inter-occasion variability, Ka=first-order absorption rate constant, Q3=inter-compartmental clearance between central and peripheral 1, Q4=inter-compartmental clearance between central and peripheral 2, RSE=relative standard error, RUV=residual unexplained variability, tlag= absorption lag time, V2=central volume, V3=volume of peripheral compartment 1, V4=volume of peripheral compartment 2

5.2.2.10. Special populations

Renal impairment

No formal dedicated PK study was performed to investigate the effect of renal impairment on paltusotine PK given the minor contribution of the renal route for paltusotine elimination (only 3.9% of TRA recovered

in urine with 1.33% as unchanged paltusotine). This was further supported by results from the PBPK modelling approach. Relative to the healthy control group, the GMR of predicted steady state AUC0-t and Cmax across all groups of renal impairment and dose levels increased by <16%, indicating a minimal impact of renal impairment.

Subjects included in the Pop-PK analysis were characterized with regard to renal status using the eGFR metric (calculated using CKD-EPI method) with a mean eGFR of 99 mL/min/1.73m^2, median 100 mL/min/1.73m^2, min max 52-144 mL/min/1.73m^2 in the target patients with acromegaly. However, the exact numbers and proportions of subjects in each category of renal impairment was unknown. The effect of renal function was investigated as a continuous covariate within the Pop-PK analysis and was not identified to have a significant effect on the PK of paltusotine.

Hepatic impairment

A formal PK study (**CRN00808-10**), investigating the effect of mild, moderate and severe hepatic impairment on paltusotine PK was performed. Results of this analysis indicated that following a 20 mg single dose, hepatic impairment had no effect on paltusotine PK.

Data of interest from mild/moderate and severe hepatic impairment arms (n= 22 subjects, 418 PK samples from Study CRN00808-10) was excluded from the Pop-PK analysis. No conclusion regarding the effect of hepatic impairment on the PK of paltusotine could be drawn from the population approach.

Gender

No formal dedicated PK study was performed has been performed. This was accepted.

The effect of gender was investigated using the Pop-PK analysis. Even though female participants showed higher paltusotine oral bioavailability, this results in a moderate 22% higher AUCss relative to males, with a 95CI of GMR of [1.18-1.26], indicating no significant clinical impact on paltusotine PK exposures.

Ethnicity

A formal PK study (**CRN00808-18**) investigating the PK of single and multiple doses of 40 mg of paltusotine in Chinese healthy subjects was performed. After a single oral dose of 40 mg paltusotine in Chinese healthy volunteers, Tmax was reached at 1.5h, with a geometric mean Cmax of 238 ng/mL and AUC24h of 1700 ng.h/mL. At steady state, Tmax was reached at 1.5h, with a geometric mean Cmax of 311 ng/mL and AUC24h of 2950 ng.h/mL. Accumulation ratio for Cmax and AUC were 1.42 and 1.84 respectively.

A formal PK study (**PA0001**) investigating the PK of single ascending dose of paltusotine (20 to 80 mg) in healthy adult Japanese subjects was performed. At the paltusotine 40 mg dose level, Cmax and AUC0-inf were higher and tmax was shorter in the Japanese participants relative to the Caucasian participants. The GMRs of Cmax, AUC0-last, and AUC0-inf for Caucasian to Japanese participants in the paltusotine 40 mg group were 38.2%, 50.7%, and 51.7%, respectively.

In the Pop-PK analysis, the analysed dataset included a majority of White subjects (n= 195 of 316, 62%), while n= 75 were Asian (23.7%) and n= 45 were neither Asian nor White (14.2%, classified as other race). Race effect was investigated as a categorical covariate (Asian or other race versus White) and did not have a meaningful effect on the exposure of paltusotine.

Weight

No formal PK study with regard to weight has been performed.

The BW effect was investigated within the Pop-PK analysis. The mean BW of the 119 patients with acromegaly analyzed was 83 kg (median = 81 kg, min = 45 kg, max = 138 kg). Compared to a reference BW of 70 kg, patients with a BW of 55 kg (5th percentile) is expected to have a marginal increase of

AUCss by approximately 4% (<5%); and similarly, patients with a BW of 106 (5th percentile) kg is expected to have minimal decrease on AUCss by 4.7%, with 95% CI of GMR at [1.01- 1.08] and [0.92-0.99], respectively, both within the range of [0.8-1.25] indicating no clinically meaningful impact on PKs of paltusotine.

Age

No formal investigations in elderly have been performed. The effect of age (as a continuous covariate) on the PKs of paltusotine was investigated within the Pop-PK analysis (290 participants aged 18-65 years and 25 elderly participants, including 20 aged 65-74 years, 5 aged 75-84 years and none above 85 years) and was not considered clinically meaningful.

Paediatric population

No clinical / PK data are available in children below 18 years. The safety and efficacy of paltusotine in the paediatric population have not been established.

5.2.2.11. Pharmacokinetic interaction studies

Based on *in vitro* investigation, a clinically significant interaction of paltusotine mediated by CYP3A4 and CYP2D6 inhibition, P-gp, BCRP inhibition could not be excluded. Although *in vitro* paltusotine inhibited MATE1/2K inhibition, the DDI study conducted with metformin refuted the *in vitro* findings.

To assess paltusotine DDIs, clinicals studies were conducted and a PBPK model was used predict the interaction magnitude. No major deficiencies in the conducted clinical DDI studies were observed. The PBPK model tends to under-predict Cmax following single doses of 40 and 60 mg by 20% to approximately 40 % (range 19% - 39%) which was consistent with the observed 32% underprediction of Cmax,ss following multiple administration, without major misperception of exposure (AUC0-inf). Overall, the model predictions of paltusotine PK were considered acceptable, except for predictions of paltusotine interactions with strong CYP3A4 inhibitors. See the clinical pharmacology discussion.

<u>Paltusotine as victim drug</u>

Clinically relevant interactions are expected to be limited due to the relatively mild contribution of CYP3A4 (fm CYP3A4 14.3%) in the paltusotine metabolism.

The metabolism of paltusotine is mainly mediated by glucuronidation (fm UGTs = 0.38) and mostly by UGT1A1 (fm ~ 0.29). Based on a worst-case scenario, it is not expected that a paltusotine drug increase following UGT1A1 should significantly affect UGT1A1 drug substrate as these are, mostly, not NTI drugs.

In a clinical study conducted in healthy patients (Study CRN00808-15), paltusotine co-administration with carbamazepine, a strong UGAT1A1, CYP3A4, and P-gp inducer, led to a clinically significant decrease in paltusotine exposure by 70% (90% CI AUC GMR [0.26-0.35]) and a decrease in Cmax by 64% (90% CI Cmax GMR [0.45-0.70]). Therefore, in case of concomitant treatment with UGT1A1 inducer, the paltusotine dose should be increased.

Cyclosporine increased paltusotine exposure by almost two-fold (GMR AUC = 1.89 90% CI AUC GMR [1.65-2.17]) and led to a two-fold increase in Cmax (90% CI Cmax GMR [1.66-2.41]) in healthy subjects (study CRN00808-07 cohort 3). The SmPC was aligned accordingly.

<u>Paltusotine as perpetrator</u>

The drug-drug interactions study results conducted in healthy subjects (study CRN00808-07 cohort 4) showed paltusotine did not significantly inhibit CYP3A4 with an increase in midazolam exposure by 13% (90% CI in AUC GMR [1.03-1.25]).

Paltusotine decreased metformin exposure by 22% (90% CI AUC GMR [0.67-0.90]) and Cmax by 39% (90% CI Cmax GMR [0.54-0.70]) (study CRN00808-07 cohort 2), which was not consistent with paltusotine inhibition of MATE 1/2K observed *in vitro*.

When co-administered with paltusotine 40 mg in healthy subjects (Study CRN00808-07 cohort 3), the reduced exposure in cyclosporine by 35 % (90% CI AUC GMR [0.56-0.75]) and reduced Cmax by 53% (90% CI Cmax GMR [0.42-0.54]) was also observed with somatostatin analogues.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Similar to the natural hormone somatostatin (SST), paltusotine demonstrates potent suppression of GH and IGF-1 secretion in healthy volunteers and in patients with acromegaly. As an agonist, paltusotine exerts its pharmacological activity via highly selective binding to SST2 and exhibits little or no affinity for other SST receptor subtypes or other receptors.

Paltusotine potently inhibited cyclic adenosine monophosphate (cAMP) accumulation via human SST2 activation with an average drug (agonist) concentration that results in EC50 of 0.25 nM. The paltusotine selectivity over other human SST receptors was >4000-fold, potentially reducing the risk of off-target activity.

Table 9 Selectivity of paltusotine toward SST receptor subtypes

Compound	Human SST EC_{50} (nM)				
	SST1	**SST2**	**SST3**	**SST4**	**SST5**
Paltusotine	>10000	0.25	3300	1100	>10000
SS14	0.83	0.14	0.16	0.20	0.065

EC_{50}=Effective concentration resulting in 50% inhibition of cAMP, SS14=native somatostatin-14, SST=somatostatin

Paltusotine was evaluated for its ability to cause internalization and desensitization of receptors.

In studies with hemagglutinin-tagged human SST2, paltusotine was less potent at internalization (EC50=19 nM) and exhibited a larger bias ratio (approximately 10-fold higher than native somatostatin), which may translate to a low propensity for tachyphylaxis.

For comparison, paltusotine is more specific to SSRT2 than the other SRLs.

The primary PD effect of paltusotine has been evaluated in 2 phase 1 healthy participants in study CRN00808-01 (IGF-1 and GH) and study PA0002 (IGF-1 only) which demonstrated that paltusotine PD activity is consistent with literature that describes the pharmacological activity of SST agonists. Indeed, paltusotine demonstrated suppression of stimulated GH secretion and rapid and sustained decline in serum IGF-1 concentrations, resulting in target engagement for paltusotine.

Proof of concept in healthy participants informed the 3 phase 2 and 2 placebo-controlled phase 3 studies of paltusotine in participants with acromegaly. In these studies, clinically and statistically significant suppression of IGF-1 and GH and a reduction of acromegaly symptoms were demonstrated with once-daily oral paltusotine doses of 40 mg and 60 mg.

5.2.3.2. Primary and secondary pharmacology

Primary pharmacology

1) Study **CRN00808-01** was a single and multiple ascending doses study which included a PD objective to determine the effect on serum IGF-1 and growth-hormone releasing hormone (GHRH) analog-stimulated GH levels after single or multiple ascending doses of paltusotine or placebo.

91 participants were enrolled and randomized for the study.

In the single dose cohorts, all randomized subjects who received any amount of study drug (CRN00808 or placebo), who had results from baseline and from ≥1 post-baseline PD assessment, were included in the PD population (n=39).

In the multiple dose cohorts, the PD population included 21 (87.5%) subjects in receipt of CRN00808 and 10 (83.3%) placebo subjects.

All subjects in the single-dose and multiple-dose cohorts were male.

The PD activities of paltusotine on IGF-1 and GH levels were assessed in single-dose cohorts of paltusotine oral solution at 1.25 mg (Cohort S1), 2.5 mg (Cohort S2), 5 mg (Cohort S3), 10 mg (Cohort S4 Period A), and 20 mg (Cohort S5) vs placebo. There were also single-dose cohorts of paltusotine capsules at 40 mg (S6) and 60 mg (S7) vs placebo.

The PD activities were also assessed in the multiple-dose cohorts of paltusotine capsule administered at 5 mg for 7 days (Cohort M1; IGF-1 and GH) and 10 mg (Cohort M2), 20 mg (Cohort M3), or 30 mg (Cohort M4) for 10 days (IGF-1 only) vs placebo.
The pharmacodynamic activity of paltusotine was assessed in the single-dose cohorts (Cohorts S1 to S5 only) through a GHRH challenge, where GHRH-stimulated GH levels in serum were measured.
Serum GH can be difficult to detect in healthy volunteers because GH has a short half-life and is secreted in a pulsatile fashion. Therefore, a GHRH challenge was performed to cause a reproducible temporary elevation of serum GH and assess the ability of CRN00808 to suppress stimulated GH secretion.

Serum IGF-1 levels as a measure of PD parameters were also assessed in single-dose cohorts (Cohorts S1 to S5 only).
Suppression of GHRH-stimulated GH secretion occurred for all single-dose 1.25 mg to 20 mg paltusotine oral solutions tested. Suppression of GH was observed at all dose levels tested in the single-dose range of 5 mg to 20 mg QD paltusotine oral solution. This response was dose dependent, reaching near-maximal inhibition of GH suppression at the 10 mg dose (91% suppression of stimulated GH secretion).

Similar effects have been observed with other peptide SST agonists. Minimal changes in GH secretion were observed following GHRH challenge in placebo subjects on both Day-1 and Day 1. Reductions in mean GH AUC (0-2 hours) percent change of baseline levels were significant compared to placebo for all CRN00808 single-dose levels >1.25 mg.

No changes in serum IGF-1 levels were observed following single-dose administration of paltusotine over the assessment period, regardless of dose level. The lack of observed change in serum IGF-1 following single-dosing was expected. In both acromegaly patients and healthy volunteers, sustained suppression of GH results in lowering of serum IGF-1 levels. In contrast to the rapid effects of the GH response, IGF-1 levels are known to change more gradually and continuous exposure to somatostatin agonists for several days is generally required to produce an observable reduction.

In the multiple cohorts, the reduction in GH post-dose did not translate to changes in mean GH AUC (0-24 hours) percent change of baseline on Day 1. The median GH AUC0-24 change from baseline in participants receiving daily doses of 5 mg paltusotine for 7 days was significantly lower than the placebo at day 7. The other doses of paltusotine were not investigated as regards to the assessment of GH levels.

No changes in serum IGF-1 levels were observed following single-dose administration of paltusotine over the assessment period, regardless of dose level.

Administration of CRN00808 in the multiple-dose cohorts did not result in any change from baseline in mean IGF-1 AUC (0-24 hours) on Day 1. However, suppression of IGF-1 was observed with the 10 mg to 30 mg QD paltusotine oral solution dose range, and mean IGF-1 changes from baseline were between -26.8% to -36.4% on 10 days after daily dosing of 10, 20 or 30 mg CRN00808, compared to +10.6% change of baseline levels with placebo. The percentage decrease in IGF-1 AUC (0-24 hours) from baseline at Day 10 was statistically significant in all active cohorts (M2 (10 mg), M3 (20 mg) and M4 (30 mg)) compared to placebo. The differences between CRN00808 and placebo were -41.9 (-64.1; 19.7), -47.0 (-70.4; -23.7), -37.4 (-60.7; -14.0) for the M2, M3 and M4 active cohorts respectively.

As CRN00808 concentrations reached steady state, serum IGF-1 concentrations began to decline. This decline reached steady state in approximately seven days. IGF-1 remained suppressed for approximately 3 to 4 days after the final dose and began to recover as CRN00808 plasma concentrations fell.

The PD effect of paltusotine on GH and IGF-1 in healthy participants is consistent with the literature that describes the pharmacological activity of somatostatin agonists. Significant suppression of IGF-1 was not observed for the dose of paltusotine 5 mg vs placebo at day 7.

This suggests that drug concentrations that result in maximal suppression of IGF-1 in healthy volunteers would translate to meaningful suppression of IGF-1 in acromegaly patients. Of note, although the investigators attempted to enrol both male and female participants, all participants were men, the great majority of whom were under 30 years of age.

2) Study PA0002 was a phase 1, single-centre, open-label, multiple-dose, 2-period crossover study in healthy Japanese adult male participants designed to assess the PK, PD, safety, and food effects of paltusotine in healthy Japanese participants.
Twelve healthy adult Japanese males (22 to 37 years of age) were assigned to 2 groups to receive daily oral dosing of paltusotine 40 (2×20) mg (15% drug load) SDD tablets in 2 study cycles.
Following 7-day dosing of paltusotine 40 mg QD, similar decreases in serum IGF-1 were observed in healthy Japanese adult participants when administered at 3 hours after a meal or 1 hour prior to a meal.

Under both dosing conditions, similar reductions in mean serum IGF-1 concentrations were observed on Day 7. Serum IGF-1 concentrations were decreased by approximately 60 to 66 ng/mL relative to baseline.

In conclusion, these 2 phase 1 studies demonstrated a rapid dose-dependent suppression of stimulated GH and IGF-1 secretion, observed as early as Day 1, with sustained decline in serum IGF-1 concentrations observed once paltusotine steady state was achieved at Day 7. Maximal IGF-1 suppression reached its nadir in approximately 7 days. Unlike the rapid suppression of GH, IGF-1 levels decrease gradually and require 4 to 10 days of exposure to SST agonists to produce an observable effect. The gradual decrease of IGF-1 is likely due to its long t1/2 (approximately 15 h), which is due to high affinity IGF-1 binding proteins in plasma.

The degree of IGF-1 suppression observed in study CRN00808-01 compared to placebo (approximately 37-47%) by multiple doses of paltusotine was similar to that observed for peptide somatostatin analogs (octreotide, lanreotide) in previously reported healthy volunteer studies.

The distinction however is that paltusotine achieves a steady state within 7 days, whereas depot injections of other SRLs treatments require several weeks or months to reach steady state and dose optimization with paltusotine is possible in much shorter time. Unlike the rapid suppression of GH, IGF-1 levels decrease gradually and require 4 to 10 days of exposure to SST agonists to produce an observable effect. The gradual decrease of IGF-1 is likely due to its long t1/2 (approximately 15 h), which is due to high affinity IGF-1 binding proteins in plasma. After the final paltusotine dose, IGF-1 remained suppressed for several days but began to recover as paltusotine plasma concentrations

declined. Analogous to the observation that it takes several days to achieve the nadir of IGF-1 suppression with once-a-day dosing of paltusotine, it takes several days for IGF-1 to recover back to baseline levels upon paltusotine withdrawal.

Secondary pharmacology

According to clinical and non-clinical data, paltusotine normalizes excess hormone secretion of GH by tumour cells to moderate the clinical signs and symptoms associated with acromegaly, through selective binding to SST2. Excess GH levels result in increased secretion of IGF-1 from the liver and other organs.

Paltusotine exerts its agonist activity to moderate excess hormone secretion via highly selective binding to SST2, thereby reducing clinical signs and symptoms with minimal off-target toxicities from the liver and other organs.

Based on the results of the clinical program, the safety profile of paltusotine includes ADRs of gastrointestinal events (diarrhoea, abdominal pain, nausea, and abdominal discomfort), sinus bradycardia, and cholelithiasis, consistent with other SRL treatments. These AEs are generally mild or moderate and can be managed through the appropriate risk mitigation measures (e.g. clinical monitoring, safety surveillance).

Indeed, based on the clinical data from the phase 3 studies, and phase 2 studies, there were no safety signals were identified on the basis of the QTcF analysis. The events occurred in participants with and without a history of bradycardia, occurred in the first three months of treatment and there was no clear dose association. At 4.6 times the exposure of the Invented name 60 mg therapeutic dose, clinically significant QTc interval prolongation was not observed.
However, paltusotine may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder stones or sludge.
There was not a higher incidence of cholelithiasis in the paltusotine group compared with the placebo group (2% versus 4%, respectively, in the RC phases of studies CRN00808-08 and CRN00808-09). However, events continued to accrue over time, particularly between 6 and 9 months, and an analysis of gall bladder ultrasound data showed a higher incidence of gallstones in the paltusotine group compared to the placebo group. Cholelithiasis occurred in 4.7% and bile duct stone in 0.4% of all participants exposed to paltusotine in the clinical development program.

In participants who had not received previous treatment with SRL therapies, cholelithiasis was reported in 8.3% (2/24) of participants. No participants discontinued paltusotine due to cholelithiasis. There were 3 serious adverse reactions (SARs) of cholelithiasis.

Gastrointestinal symptoms of diarrhoea, abdominal pain, nausea and abdominal discomfort were collectively the most frequently reported adverse reactions with paltusotine. The majority of these events were mild, did not require treatment, occurred mostly during the first three months of treatment, and did not lead to discontinuation of paltusotine. Most events of diarrhoea lasted $\leq$3 days.

No hepatic indicative of DILI, metabolic and hormonal disorders (which included thyroid hormones) were reported.

The effects of paltusotine on the developing human foetus are not known; however, the completed non-clinical studies and available clinical data with paltusotine do not indicate teratogenicity.

No human data on the effect of paltusotine on fertility are available. Studies in animals showed no impaired fertility and no effect on mating at human exposure of Paltusotine.

It is unknown whether paltusotine is excreted in human milk. Available toxicology data in animals have shown excretion of paltusotine in milk. A risk to the newborns/infants cannot be excluded.

Exposure-response analyses were performed separately for each of the two phase 3 studies **CRN00808-08** and **CRN00808-09**. The exposure –safety analysis evaluated potential relationships between paltusotine steady-state exposure and safety measures including AEs, out of range laboratory values, vital signs, gallbladder ultrasounds, and ECGs (Report CRNT-Proj1-23-0006).

No definitive relationships between any AEs, ECGs, or vital measures and paltusotine exposure were identified in either study. HbA1c showed a likely linear relationship with Paltusotine exposure in Study **CRN00808-08** but increases in HbA1c from baseline were not considered clinically meaningful (60 mg paltusotine dose was associated with 0.23% increase in HbA1c).

The predicted placebo-corrected LS mean change from baseline in QTcF was less than 5 ms and the upper bound of the 90% CI was less than 10 ms at the geometric mean Cmax of 1341 ng/mL, which was 4.6-fold of the Cmax,ss at the dose level of 60 mg (290 ng/mL). Collective review of data as described in the paltusotine TQT Study Waiver Request demonstrated there is low to minimal risk for potential effects on cardiac repolarization with paltusotine.

New incidences of gallbladder sludge appeared elevated in study **CRN00808-08** only for the highest quintile of paltusotine exposure where 4 of 10 (40%) participants showed the presence of sludge. There was no relationship between new cases of gallstones and paltusotine exposure.

Exposure-safety analyses of AEs and out-of-range laboratory, gallbladder ultrasound, ECG, and vitals data showed no relationships between paltusotine exposure and safety measures in Study **CRN00808-09**.

For each potential and identified safety concerns, specific measures were recommended in the SmPC of paltusotine.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

No dedicated PD DDI studies were conducted, and this was acceptable. However, paltusotine potential PD interactions with glucose metabolism may lead to DDI with some diabetes treatment. Please refer to the section *Safety related drug –drug interactions*.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure-response analysis

ER analysis for efficacy and safety was performed for the pivotal studies **CRN00808-08** and **CRN00808-09**.

- Efficacy

CRN00808-08

The ER dataset consisted of 111 subjects who received either paltusotine or a placebo dose.

A total of 409 unique paltusotine PK data (Ctrough) and 645 unique IGF-1 levels (635 observations before rescue therapy) were available from 54 subjects who received the paltusotine SDD tablet. Overall paired PK/PD consisted of 349 matched observations between observed paltusotine concentration and IGF1, and 635 between predicted paltusotine concentrations.

In contrast, in subjects receiving placebo (57 subjects), a total of 405 unique paltusotine PK data (Ctrough) and 662 unique IGF-1 levels (598 observations before rescue therapy) were available. Overall

paired PK/PD consisted of 332 matched observations between observed paltusotine concentration and IGF1, and 598 between predicted paltusotine concentrations.

The final PK/PD model parameter estimates are presented in Table 10.

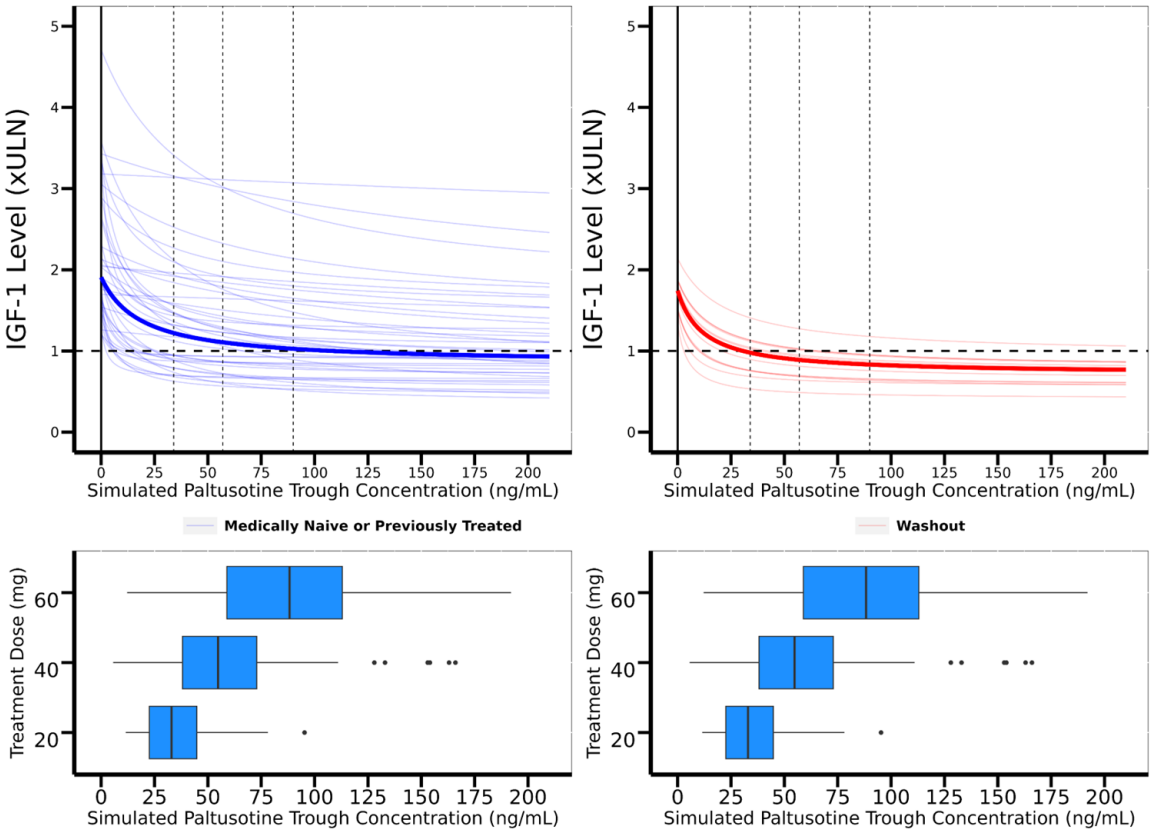
Table 10 Summary of PD parameters estimates and bootstrap results for the final exposure-response model

Parameter [units]	Final Model		Bootstrap (N=1000)	
	Estimate (SE)	**RSE (%)**	**Estimate (SE)**	**RSE (%)**
Model Metrics	-2LL: 106.2 BIC: 168.1		-	
Condition Number	28.32		-	
tvIMAX [%]	0.57 (0.05)	9.4	0.57 (0.05)	9.4
tvIC50 [ng/mL]	17.74 (7.58)	42.7	17.74 (8.39)	47.3
tvBL [×ULN]	1.98 (0.03)	1.4	1.98 (0.03)	1.4
tvDisBl_BaseIGF	0.96 (0.03)	3.2	0.96 (0.03)	3.4
Between-Subject Variability (%)				
Ω IMAX	48.7 (26.3)	27.0	48.7 (26.2)	26.9
Ω IC50	141.3 (62.5)	22.1	141.3 (69.0)	24.4
Ω Disease Baseline on Stratum 1	33.1 (15.7)	23.8	33.1 (15.8)	23.8
Ω Disease Baseline on Stratum 2	66.3 (25.3)	19.1	66.3 (26.5)	20.0
Residual Variability				
Proportional	0.127 (0.008)	-	0.127 (0.008)	-

-2LL=minus 2 × log-likelihood, BIC=Bayesian information criterion, IC50=exposure at which a 50% decrease in absolute insulin-like growth factor 1 occurs, IMAX=maximum increase in absolute insulin-like growth factor 1, RSE=relative standard error, SE=standard error, tvBL=typical value baseline, tvDisBL_BaseIGF=typical value of the exponent describing baseline IGF-1 on the disease baseline, tvIC50=typical value exposure at which a 50% decrease in absolute insulin-like growth factor 1 occurs, tvIMAX= typical value maximum proportional decrease in insulin-like growth factor 1, ULN=upper limit of normal

The population parameter estimates from the final model were used to create a population E-R curve overlaid on the model-predicted E-R curves for each of the individual subjects in CRN00808-08. This plot with an accompanying plot of the steady-state exposure distributions associated with the 20, 40, and 60 mg daily doses (Per strata) is presented in Figure 2. The percent IGF-1 reduction based on the median steady-state trough paltusotine concentration associated with each dose is presented in Table 11.

Figure 2 Steady-State Exposure-Response for Paltusotine Trough Concentration and IGF-1 in Subjects on Active Therapy in CRN00808-08 by Strata



The blue lines represent the concentration-response profile based on the median projected EBEs with the individual lighter lines representing the individual E-R profiles for all subjects in CRN00808-08 in Stratum 1. The red lines represent the same for subjects in Stratum 2 of CRN00808-08. The boxplots in the lower plot represent the range of simulated trough concentrations at each dose in CRN00808-08. The vertical lines represent the median simulated trough concentration at 20, 40, and 60 mg of paltusotine.
IGF-1=insulin-like growth factor 1, ULN=upper limit of normal

Table 11 Percent IGF-1 Reduction Based on Dose of Paltusotine

Parameter	Median Trough Concentration	Dose	IGF-1 Reduction
IC66	34 ng/mL	20 mg	-37.4%
IC76	57 ng/mL	40 mg	-43.4%
IC83	89 ng/mL	60 mg	-47.5%
IC87	115 ng/mL	*80 mg	-49.3%

IGF-1=insulin-like growth factor-1.
The parameter ICx represents the exposure at which a X% decrease in absolute insulin-like growth factor 1 occurs.
*The median trough concentration at 80 mg is based on linear extrapolation from data for 60 mg dose.

CRN00808-09

The ER dataset consisted of 58 subjects who received either paltusotine or a placebo dose.

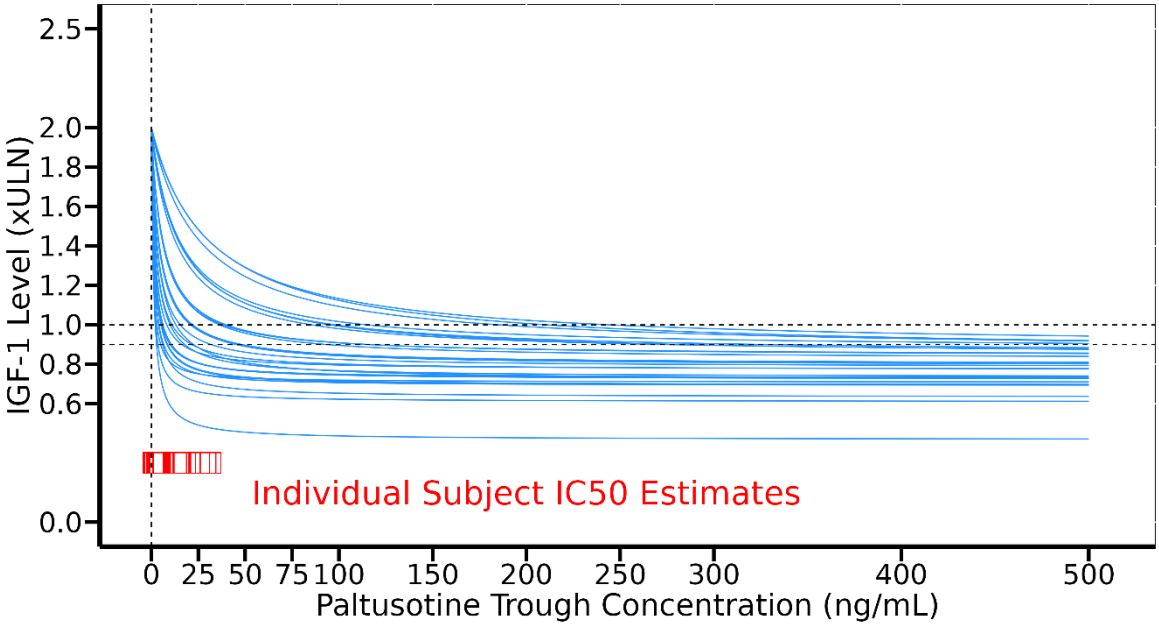
A total of 291 unique paltusotine PK data (Ctrough) and 335 unique IGF-1 levels (322 observations before rescue therapy) were available from 30 subjects who received the paltusotine SDD tablet. Overall

paired PK/PD consisted of 285 matched observations between observed paltusotine concentration and IGF1, and 320 between predicted paltusotine concentrations.

In contrast, in subjects receiving placebo (28 subjects), a total of 241 unique paltusotine PK data (Ctrough) and 318 unique IGF-1 levels (209 observations before rescue therapy) were available. Overall paired PK/PD consisted of 167 matched observations between observed paltusotine concentration and IGF1, and 209 between predicted paltusotine concentrations.

The final E-R model developed for **CRN00808-08** was used to predict IGF-1 results for **CRN00808-09**. A plot of the predicted E-R curves for the 30 subjects on active therapy is presented in Figure 3.

Figure 3 Post-hoc estimation of CRN00808-09 exposure-response using CRN00808-08 ER model



Blue lines represent the individually estimated concentration-response profiles for subjects in CRN00808-09 based on the PD model developed from data in CRN00808-08. The red squares represent the individual estimated IC50 values for the same subject profiles that were generated.
IGF-1=insulin-like growth factor 1, PD=pharmacodynamic

- Safety

No strong relationship was found between paltusotine Ctrough and any of the safety endpoints.

5.2.5. Dose selection and therapeutic window

Oral paltusotine doses were evaluated in 2 phase 1 studies in healthy participants including study **CRN00808-01** that evaluated an oral solution (1.25 to 20 mg) and in study **CRN00808-07** that evaluated SDD tablets (20 mg to 80 mg). Paltusotine doses (5 mg to 40 mg as capsule) were evaluated in 2 phase 2 studies in acromegaly (studies **CRN00808-02** and **CRN00808-03**).

Based on these results, a 40 mg QD dose of the SDD tablet was expected to result in paltusotine systemic exposures similar to those achieved with the 40 mg dose of the capsule formulation used in the phase 2 studies. Combined with E-R modelling, data from the phase 2 studies suggested that a paltusotine dose

of 40 mg QD was likely to achieve IGF-1 suppression consistent with that achieved by depot SRLs for most participants with acromegaly.

In the phase 3 studies **CRN00808-08** and **CRN00808-09**, a titration scheme was applied 20 to 60 mg and 40 to 60 mg based on IGF-1 level. The efficacy E-R model showed that the paltusotine median Ctrough at steady-state associated with 20 mg (34 ng/mL), 40 mg (57 ng/mL), and 60 mg (89 ng/mL) were at approximately the IC66, IC76, and IC83 of the E-R curve, respectively. Based on a population maximum IGF-1 reduction of 57%, doses of 20 mg, 40 mg, and 60 mg corresponded to IGF-1 reductions of approximately 37%, 43%, and 47%, respectively. Accordingly, at a population-level, the 20 mg QD dose of paltusotine appeared submaximal, while the 60 mg QD dose approached the asymptotic nadir of the E-R curve.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetics

Impaired renal function

The results of Pop-PK and observed data analyses stratified according to renal function indicate comparable paltusotine exposures between subjects with normal and mild renal impairment, confirming that mild impairment has no clinically relevant effect. However, only a few subjects with moderate renal impairment (n=2 observed; n=4 Pop-PK) were available, and no data were provided for severe impairment, preventing formal conclusions for these subgroups. The SmPC section 5.2 was amended to reflect the available PK data in all subgroups.

Impaired hepatic function

Mean plasma concentrations of paltusotine over time between 0-24 hours post-dose in study CRN00808-10 showed a higher exposure in subjects with hepatic impairment, up to approximately 6 h post dose. However, statistical analysis reports that mild hepatic impaired patients had the higher value (133.28 ng/mL), the following is the Cmax value for the severe hepatic impaired patients (110.33 ng/mL), while normal and moderate hepatic impaired patients show similar values (101.35 ng/mL and 100.21 ng/mL respectively). AUC0-24 values were comparable. Overall, it is thought that the exposure differences are not clinically relevant. Cigarette smokers were allowed in this study, but since only one participant was an on-going smoker, smoking is considered unlikely to have influenced the summary statistics of paltusotine exposure.

Race / Ethnicity

Based on observed steady-state dose-normalised Ctrough data (N=109), geometric mean ratios (GMRs) relative to White subjects were 0.95, 1.15, and 0.83 for Black/African American, Chinese, and Japanese subjects, respectively, suggesting slightly higher exposure in Chinese (+15%; 95% CI [0.85–1.55]) and lower exposure in Japanese subjects (–17%; 95% CI [0.59–1.17]). These differences were considered modest and not clinically meaningful.

Notably, single-dose NCA data (AUC0-24h and Cmax) indicated higher exposures in Chinese subjects compared with White subjects (+25% and +60%, respectively), broadly consistent with the steady-state trend. In contrast, Japanese subjects showed higher single-dose exposure (AUC0-24h +13%; Cmax +45%), inconsistent with the lower steady-state Ctrough (–17%). This discrepancy was acknowledged

but could not be explained by the Applicant. Its regulatory impact was considered limited in view of the greater clinical relevance of steady-state exposure, and therefore not further pursued.

The totality of evidence, with emphasis on observed steady-state Ctrough data, does not indicate a clinically relevant impact of ethnicity on paltusotine PK.

Body weight

Based on Pop-PK analyses (N=315; mean 76 kg, median 73 kg, IQR 65–85 kg, range 45–138 kg), paltusotine exposure varied by less than ±5% across the BW range, indicating no clinically meaningful effect. The SmPC was amended accordingly.

Elderly

Additional Pop-PK analyses (N=315) included 20 subjects (6.4%) aged 65–74 years, only 5 subjects (1.6%) aged 75–84 years, and none aged ≥85 years, indicating that no clinically relevant effect of age was identified. The SmPC was explicitly reflects the limited PK data in subjects aged 75–84 years and the absence of data in subjects aged ≥85 years.

PK interactions

Paltusotine as victim

Paltusotine is mainly metabolised by glucuronidation (fm=0.38) and mostly by UGT1A1 (fm UGT1A1=0.29). Based on a worst-case scenario, it is not expected that paltusotine drug increase following UGT1A1 should significantly affect UGT1A1 drug substrate as these are, mostly, not NTI drugs.

Inducers

Following the administration of 60 mg paltusotine, the clinical study in healthy subjects showed that carbamazepine, a strong inducer of CYP3A4/5, UGT1A1, and P-gp, decreased paltusotine Cmax and AUC by approximately 40% and 70%, respectively. Co-administration of paltusotine with strong inducers may thus decrease the therapeutic response. Therefore, in case such association cannot be avoided, the paltusotine dose should be increased up to three-fold the therapeutic dose, based on IGF-1 levels, and safety monitoring. The dose should not exceed 120 mg due to the absence of safety data, the lack of dose proportionality demonstration beyond this dose and the expected limited gain in efficacy of an increased dose from 120 mg up 180 mg as a 5% gain in IGF-1 inhibition is expected from a 40 to 60 mg increase when paltusotine is administered alone.

Based on the observed 70% decrease in paltusotine exposure following strong inducer (carbamazepine), a smaller decrease in exposure following moderate or weak inducer of CYP3A4/5, UGT1A1, or P-gp, is expected. Co-administration of paltusotine with a moderate (e.g. efavirenz) or weak (prednisone) inducer of CYP3A4/5, UGT1A1, or P-gp may thus decrease the therapeutic response and dose adjustment may be necessary according to the clinical response. In case of minimal induction that may require paltusotine dose increase, it must not exceed the maximal dose of 120 mg as this corresponds to safe exposure limits of the no-effect exposure boundaries.

Acid reducing agent

Co-administration of paltusotine with PPIs demonstrated a dose-dependent decrease in paltusotine exposure that may decrease thus decrease therapeutic response and dose adjustment may be necessary according to the clinical response.

Cyclosporine

A clinical study conducted in healthy subjects showed following 200 mg cyclosporine administration, paltusotine exposure was increased by two-fold. Nevertheless, no dose adjustment is considered needed as no clinically significant adverse events is expected.

Paltusotine as perpetrator

Based on *in vitro* studies, it cannot be excluded that paltusotine could inhibit P-gp and CYP2D6 drug substrate respectively. The provided PBPK model predictions of expected DDI mediated by P-gp or CYP2D6 inhibition respectively cannot be used to rule out clinically significant DDI due to insufficient qualification dataset and inconsistent results in the demonstration of the predictive capacity of drug interaction of the compound file of the drug substrates used to perform simulations.

Caution of use with P-gp and CYP2D6 drug substrates have been included in SmPC 4.5 section.

Exposure-Response safety

Regarding the proposed 80%-200% no effect boundary, the upper boundary of +200% has been justified based on the only safety outcome for which an E-R relationship has been established.

Dose rationale and justification

The dosing rationale appears sound for subjects switching from standard therapy (octerotide or lanreotide) to paltusotine at the 40 mg dose, as IGF-1 levels were similar to those at baseline during treatment with octreotide LAR or lanreotide injections.

For naïve subjects, it was questioned whether maintaining a paltusotine dose of 60 mg in patients with high levels of IGF-1 at baseline (1.7xULN) would be beneficial given the predicted effects of a 60 mg dose of paltusotine on IGF-1 dynamics (reduction by 47.5%). A plot showing the simulations of post-treatment IGF-1 based on varying levels of baseline IGF-1 for a QD dose of 60 mg was provided, concluding that a dose of 60 mg is expected to provide IGF-1 levels ≤1.0xULN across a broad range of baseline IGF-1 levels (>1.7xULN to 4.0xULN). Such conclusion can only be agreed at the more for an IGF-1 at baseline of 2.5x ULN and by considering an IMAX effect of 57%. Based on the provided plot, the applicant was asked to compute for each Baseline IGF-1(xULN) of 2.0, 2.5, …, 5.0, the proportion of subjects who are expected to achieve Post-treatment IGF-1(xULN) of 0.5-<1, 1-<1.5, 1.5-<2, 2-above. Results of the simulation were provided in the table below and clearly demonstrate that the probability of achieving IGF-1 normalisation (≤ 1xULN) or near-normalisation (≤ 1.3xULN) markedly decreases with increasing baseline IGF-1 levels.

Table 12 Simulated proportion of patients achieving each post-treatment IGF-1 category based on baseline IGF-1 for paltusotine 60 mg daily dosing

Baseline IGF-1 Scenario	**Simulated Post-Treatment IGF-1 (xULN) Category**			
	≤ 1.0	**> 1.0 & ≤ 1.5**	**> 1.5 & ≤ 2.0**	**> 2.0**
1.5	67.4%	32.6%	0.00%	0.00%
2.0	29.1%	48.9%	22.0%	0.00%
2.5	12.8%	40.1%	31.2%	16.0%
3.0	5.92%	23.2%	37.7%	33.1%
3.5	3.61%	13.1%	29.7%	53.6%
4.0	2.52%	7.33%	19.2%	70.9%
4.5	1.55%	4.52%	13.4%	80.6%
5.0	1.18%	3.01%	8.44%	87.4%

In addition, the applicant discussed the results available from the 40 patients on active treatment in Stratum 1 of study CRN00808-08 who had a mean (SD) baseline IGF-1 of 2.2 (0.83) xULN from which efficacy results observed were compared to those predicted by the IMAX model (provided a Ctrough paltusotine was available). The percentage of patients achieving a post treatment IGF-1 of ≤ 1xULN, 1 to ≤ 1.5 and> 1.5 were as follows for observed vs predicted: 42.5% vs 45%, 25% vs 22.5%, 32.5% vs 32.5% demonstrating the accuracy of the model predictions, this was agreed.

Of note, the efficacy results for the subjects from study CRN00808-08 were more precisely addressed in section 5.1 of the SmPC. Furthermore, we can observe that baseline IGF-1 decreased no more than 0.8 to 1 xULN. With a baseline IGF-1 >2.5xULN in naïve patients, a normalisation or a near normalisation of IGF-1 cannot be achieved and this was reflected in the SmPC section 4.2.

Finally, it is worth noting that the PK/PD model (given its efficacy predictive performance, see above), and in particular the monitoring of trough concentrations (predictive of efficacy in patients), could be useful in treatment-naïve patients during the gradual dose increase (from 20 to 60 mg). Failure to reach a certain concentration level could allow for anticipation of IGF-1 normalization and justify further measures (reassessment of the B/R).

Primary pharmacology

The primary pharmacodynamic (PD) effect of paltusotine is a reduction of GH and IGF-1 levels which may enable normalisation of these hormone levels in patients with acromegaly. The PD effect of paltusotine on GH and IGF-1 was assessed in healthy volunteers in phase 1 studies (study **CRN00808-01** (IGF-1 and GH) and study **PA0002** (IGF-1 only).

Serum IGF-1 and GH are known biomarkers of acromegaly disease. IGF-1 has been reported to be the most reliable biomarker to monitor the efficacy of SRL-treatments in acromegaly. Most symptoms of acromegaly are non-specific, so a normal IGF-1 level in the presence of persistent symptoms has been considered controlled disease.
Of note, serum GH can be difficult to detect in healthy volunteers because GH has a short half-life and is secreted in a pulsatile fashion. Therefore, a GHRH challenge was performed in study **CRN00808-01** to cause a reproducible temporary elevation of serum GH and assess the ability of CRN00808 to suppress stimulated GH secretion.

The 2 phase 1 studies demonstrated a rapid dose-dependent suppression of stimulated GH and IGF-1 secretion, observed as early as Day 1, with sustained decline in serum IGF-1 concentrations observed once paltusotine steady state was achieved at Day 7.

The degree of IGF-1 suppression observed in study **CRN00808-01** compared to placebo (approximately 37-47%) by multiple doses of paltusotine was similar to that observed for peptide somatostatin analogs (octreotide, lanreotide) in previously reported healthy volunteer studies (*Tiberg et al, 2015 and Kuhn et al, 1994*). Indeed, in both acromegaly patients and healthy volunteers, sustained suppression of GH release results in lowering of serum IGF-1 levels.

However, in contrast to the rapid effects of the GH response, IGF-1 levels decrease more gradually and require several days of exposure to SST agonists to produce an observable effect (*Tiberg et al, 2015 and Kuhn et al, 1994*). Plasma concentrations of somatostatin analogs that result in this level of suppression in healthy volunteers are comparable to the trough concentrations in acromegaly patients on their highest approved dose (*Tiberg et al, 2015; Kuhn et al, 1994*).

Indeed, as trough paltusotine concentrations reached steady state, serum IGF-1 concentrations began to decline. Maximal IGF-1 suppression reached its nadir in approximately 7 days, whereas depot injections of SRL treatments require several weeks or months to reach steady state and dose optimization with paltusotine is possible in much shorter time. Unlike the rapid suppression of GH, IGF-1 levels

decrease gradually and require 4 to 10 days of exposure to SST agonists to produce an observable effect. The gradual decrease of IGF-1 is likely due to its long t1/2 (approximately 15 h), which is due to high affinity IGF-1 binding proteins in plasma. After the final paltusotine dose, IGF-1 remained suppressed for several days but began to recover as paltusotine plasma concentrations declined. Analogous to the observation that it takes several days to achieve the nadir of IGF-1 suppression with once-a-day dosing of paltusotine, it takes several days for IGF-1 to recover back to baseline levels upon paltusotine withdrawal.
Proof of principle in healthy participants informed the acromegaly clinical development program but it is difficult to extrapolate these results to patients with acromegaly. Moreover, the forms of paltusotine were different in the single dose cohorts of **CRN00808-01**, it was an oral solution and in the multiple-dose cohorts and in the phase 2 studies, it was the capsules and in the phase 3 studies, it was the SDD tablets as in the phase 1 **PA002** study. Only men were included in these 2 phase 1 studies.
Given that healthy subjects did not present with the elevated IGF-1 level at baseline typical for untreated patients with acromegaly and that dose-response relationship in healthy adults is relatively flat due to the low IGF-1 levels in this population, the difference in IGF-1 response between the paltusotine doses might not be detectable. Compared to placebo, suppression of IGF-1 levels on the last day of dosing for the 10 mg, 20 mg and 30 mg cohorts was similar indicating that the 10 mg dose achieved a near-maximal response.
The results of study CRN00808-01 in healthy volunteers which was an exploratory, proof-of-pharmacology trial, suggested that paltusotine was well tolerated at doses that 10 mg to 30 mg/day resulted in PD activity, as measured by suppression of GHRH-stimulated GH and IGF-1 secretion. These results were also consistent with literature that describes the pharmacological activity of somatostatin agonists and fulfilled the main objectives of that study.
Then, the doses of paltusotine used in the phase 3 studies were justified with the E-R modelling analysis and the phase 2 studies.

Secondary pharmacology

According to clinical and non-clinical data support that through selective binding to SST2, paltusotine normalizes excess hormone secretion of GH by tumour cells to moderate the clinical signs and symptoms associated with acromegaly. Excess GH levels result in increased secretion of IGF-1 from the liver and other organs.

Paltusotine exerts its agonist activity to moderate excess hormone secretion via highly selective binding to SST2, thereby reducing clinical signs and symptoms with minimal off-target toxicities from the liver and other organs.

Based on the results of the clinical program, paltusotine was generally well tolerated across all studies in the clinical program with no unexpected safety signals. The safety profile of paltusotine includes ADRs of gastrointestinal events (diarrhoea, abdominal pain, nausea, and abdominal discomfort), sinus bradycardia, and cholelithiasis, consistent with other SRL treatments. These AEs are generally mild or moderate and can be managed through the appropriate risk mitigation measures (e.g. clinical monitoring, safety surveillance).

Exposure-response analyses were performed separately for each of the two phase 3 studies **CRN00808-08** and **CRN00808-09**. The exposure –safety analysis evaluated potential relationships between paltusotine steady-state exposure and safety measures including AEs, out of range laboratory values, vital signs, gallbladder ultrasounds, and ECGs. No definitive relationships between any AEs, ECGs, or vital measures and paltusotine exposure were identified in either study. HbA1c showed a likely linear relationship with paltusotine exposure in Study **CRN00808-08** but increases in HbA1c from baseline were not considered clinically meaningful (60 mg paltusotine dose was associated with 0.23% increase in HbA1c).

New incidences of gallbladder sludge appeared elevated in study **CRN00808-08** only for the highest quintile of paltusotine exposure, where 4 of 10 (40%) participants showed the presence of sludge. There was no relationship between new cases of gallstones and paltusotine exposure. However, paltusotine may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder stones or sludge. This was reflected in the SmPC section 4.4.

Exposure-safety analyses of AEs and out-of-range laboratory, gallbladder ultrasound, ECG, and vitals data showed no relationships between paltusotine exposure and safety measures in Study CRN00808-09.

For each potential and identified safety concern, there are specific measures which are already recommended in the SmPC of paltusotine as regards bradycardia, cholelithiasis and pregnancy.

As Paltusotine is a SRLs, although no glycaemic, thyroid or hepatic disorders have been reported during the clinical trials with Paltusotine, in line with the other SRLs, appropriate recommendations were added in section 4.4 of the SmPC and in the PL.

For hepatic function, given the reported cases of ALT/AST increases >3×ULN, the consistency with class-related effects, and the importance of adequately inform prescribers, a statement on mild to moderate transaminase elevations was included in section 4.8 of the SmPC, in line with other SRL therapies.

5.2.6.2. Conclusions

Overall, the PK and PD of paltusotine has been sufficiently characterized.

5.3. Clinical efficacy

5.3.1. Dose response studies

2 phase 2 studies (**CRN00808-03** and **CRN00808-02)** and a long-term extension of these 2 phase-2 studies (**CRN00808-05)** were conducted to determine the dose of paltusotine to be chosen for the phase 3 studies.

Phase 2 study CRN00808-03 "Acrobat EDGE"

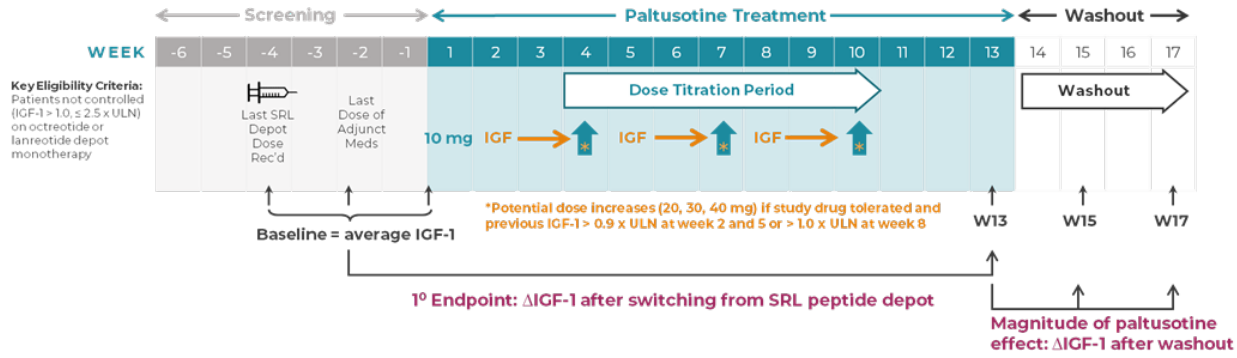
- **Study Design**

Study **CRN00808-03** was **an open-label, dose blinded**, exploratory study designed to evaluate the efficacy, safety, and PK of paltusotine **in participants with acromegaly treated with SRL-based treatment regimens.** In this study, subjects were to be switched from their current monthly depot regimen of 1) octreotide LAR or lanreotide depot; 2) combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline); 3) combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline); 4) pasireotide LAR; or 5) combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and pegvisomant to a once-daily regimen of oral paltusotine **without a washout** to loss of IGF-1 control.

First patient enrolled: 12 March 2019

Last patient completed: 31 August 2020

Figure 4 Study design



EoT, end of treatment; IGF-I, insulin-like growth factor I; med, medication; SRL, somatostatin receptor ligands; ULN, upper limit of normal; V, visit. *IGF-I measurements. **If study drug tolerated and previous IGF-I>0.9×ULN at wk 2 and 5 or >1.0×ULN at wk 8.

- **Description of the participants, baseline characteristics and extent of exposure**

To be eligible to enter the Treatment Period, participants were required to have Screening IGF-1 measurements in the ranges specified for Group 1 (primary analysis cohort) and Groups 2 through 5 (exploratory analysis cohorts), based on prior SRL and IGF-1 status.

- Participants in **Group 1** were **partial responders** to stable treatment with octreotide LAR or lanreotide depot **monotherapy**, with at least 1 screening IGF-I value **greater than 1× ULN and the Visit 2 value ≤2.5×ULN.**

- Participants in **Group 2** were **partial responders** to a stable combination of octreotide LAR or lanreotide depot **plus a dopamine agonist** (cabergoline), with the same IGF-1 criteria as Group 1.

- Participants in **Group 3** were **complete responders** (mean of screening IGF-1 values <1×ULN) to a stable combination of octreotide LAR or lanreotide depot **plus a dopamine agonist**, in all cases cabergoline.

- Participants in **Group 4** were **complete responders** to a stable dose of pasireotide LAR (mean of Screening IGF-1 values were ≤ULN).

- Participants in **Group 5** were **complete responders** to a stable combination of octreotide LAR or lanreotide depot **plus pegvisomant** (mean of Screening IGF-1 values were ≤ULN).

A total of **47 adult subjects** were enrolled in the study on stable doses of SRL-based pharmacotherapy for the treatment of acromegaly were planned to be recruited for this study. **42 subjects (89.4%)** completed the trial.

A washout (ie, demonstration of increased IGF-1 levels and/or return of symptoms) before switching from parenteral to oral therapy with paltusotine was not required.

Approximately 57% of participants were female, the median age was **51 years** (IQR, 43.0 to 61.0 years), the majority of subjects (83%) were <65 years of age; 17% were ≥65 years of age.

The median duration since acromegaly diagnosis was **112.50 months** (IQR, 59.80 to 143.60 months). The majority of participants had prior surgery for pituitary tumour (**78.7%).**

Pretrial acromegaly therapies: Of the **25 participants** in Group 1 **EAS** (efficacy analysis set), **12 participants** were on lanreotide depot (1 participant on 60 mg/month, 4 participants on 90 mg/month, and 7 participants on 120 mg/month). The remaining **13 participants** were on octreotide LAR (1 participant on 10 mg/month, 9 participants on 30 mg/month, and 3 participants on 40 mg/month).

Medically naïve patients were excluded. Subjects who were complete responders (both Screening IGF-1 values ≤ULN) to octreotide LAR or lanreotide depot monotherapy were excluded.

- **Objectives**

• To evaluate the efficacy of paltusotine in acromegaly subjects treated with somatostatin receptor ligand (SRL) based treatment regimens based on IGF-1 levels, GH levels, PRO questionnaires (Investigator Assessed Symptoms of Acromegaly, ASD, AcroQoL, EQ-5D-5L, Patient Global Impression of Severity (PGI-S), and Patient Global Impression of Improvement (PGI-I).

• To evaluate the safety and tolerability of paltusotine in acromegaly subjects.

• To evaluate the pharmacokinetics (PK) of paltusotine in acromegaly subjects.

- Primary and secondary endpoints

Primary endpoint

• Change from baseline in IGF-1 level at W13/EoT **in Group 1** subjects Efficacy Analysis Set (EAS). The Baseline value was defined as the mean of the IGF-1 prior to first dose of study drug.

Secondary endpoints

· Proportion of subjects with IGF-1 ≤ULN **in Groups 3, 4, and 5** subjects only at W13/EoT.

· Proportion of subjects with IGF-1 ≤1.5× ULN at W13/EoT in group 1.

Main Exploratory endpoints:

. Change from baseline in integrated serum GH levels measured at W13/EoT.

. Change from baseline in IGF-1 level at W13/EoT in subjects in Groups 2 through 5.

. Change from baseline in symptoms of acromegaly as measured by **total ASD*** (Acromegaly Symptom Diary) score at W13/EOT was evaluated as an exploratory endpoint.

. Change from baseline in EuroQoL-5 dimensions-5 levels (EQ-5D-5L) score at W13/EoT.

. Change from baseline in acromegaly QoL questionnaire (AcroQoL) at W13/EoT.

. Patient Global Impression of Improvement (PGI-I) scores at W13/EoT.

***ASD:** The ASD is a brief disease-specific symptoms diary developed and validated by the Sponsor in accordance with the FDA Patient-Focused Drug Development Guidance and Patient-Reported Outcome Measures Guidance. The ASD was developed to fill a recognized need in the availability of a patient-reported measure of acromegaly. Other commonly used measures either lack items specific to acromegaly or sufficient content related to symptoms. Thus, the ASD was developed as a novel, daily diary **to assess important symptoms of acromegaly from the patient perspective**. The ASD consists of 7 symptoms (headache pain, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling). Two additional items, difficulty sleeping and difficulty with short-term memory, are also included in the diary. **Patients rate the severity of each symptom using a 0 to 10 numeric rating** scale; the ASD weekly total score describes the average severity of all 7 symptoms across a single week. The ASD weekly total score ranges from 0 to 70; for all ASD items, **a higher score indicates greater severity.** The proposed preliminary threshold range to characterize a meaningful change from the patients' perspective for the ASD total is a **4- to 6-point change** for improvement or worsening out of a total score of 70 (*Martin et al 2023*).

- Treatments Administered

Paltusotine was supplied as **5 mg and 10 mg** solid dose **HMG capsules**.

The starting dose of 10 mg QD paltusotine was found to be the lowest dose that was maximally effective in suppressing IGF-1 in healthy volunteers at steady-state and this level of suppression mirrored that achieved by either octreotide or lanreotide. The doses can be increased up to 40 mg/day or reduced in case of intolerance.

If at any time, the participant experienced a significant worsening of symptoms associated with acromegaly, and in the Investigator's opinion would not benefit from continuing in the study, **standard acromegaly treatment was to be resumed**, and participants were to be discontinued from the study and an early termination visit was to be scheduled, before resuming standard pharmacotherapy whenever possible.

Of note, due to COVID-19 pandemics, some participants were up-titrated during specific study visits without availability of prior IGF-1 data.

In group 1, all patients commenced paltusotine at 10 mg once daily and most patients were titrated to the maximum dose of 40 mg by the EoT period (week 13). By week 13, 18/23 (**78%**) patients in group 1 who completed the treatment period titrated to the maximal dose of 40 mg/day, 2 ended treatment at 30 mg, 2 at 20 mg, and 1 at 10 mg/day.

Of note, doses for most patients in groups 2 and 3 were also increased to 40 mg/day.

- **Results and outcomes**

- **Primary Endpoint: "Change from Baseline in IGF-1 at Week 13/End of Treatment at Week 13/EOT in Group 1 participants of the Efficacy Analysis Set (EAS)."**

The median change from baseline in IGF-1 values at W13/EoT **in Group 1** subjects (EAS) was not significant, at approximately zero, indicating no change, **-0.03**× ULN (IQR, -0.107 to 0.107× ULN; **p=0.6285**).
At baseline, median IGF-I for patients was **1.34× ULN** (IQR: 1.08, 1.47× ULN) and remained relatively stable throughout the 13-week paltusotine treatment period.
Of **23 participants** who completed the dosing period in Group 1, 20 participants (**87.0%**) achieved IGF-1 levels at EOT **within 20% of Baseline or lower**. Overall, the IGF-1 values for participants in Group 1 were found to be maintained.

Table 13 IGF-1 (× ULN) at Baseline and End of Paltusotine Treatment in Group 1 (EAS)

Time Point	Lanreotide depot (N=12)	Octreotide LAR (N=13)	Group 1 (N=25)
Baseline[a]			
n	12	13	25
Mean (SD)	1.468 (0.2696)	1.215 (0.2598)	1.337 (0.2893)
95% CI	(1.297, 1.640)	(1.058, 1.372)	(1.217, 1.456)
Median	1.424	1.078	1.335
Q1, Q3	1.262, 1.650	0.998, 1.384	1.078, 1.471
Min, Max	1.14, 1.97	0.96, 1.78	0.96, 1.97

Time Point	Lanreotide depot (N=12)	Octreotide LAR (N=13)	Group 1 (N=25)
Week 13 (Visit 14) / End of Treatment			
n	12	13	25
Mean (SD)	1.381 (0.2731)	1.277 (0.3182)	1.327 (0.2959)
95% CI	(1.207, 1.554)	(1.085, 1.470)	(1.205, 1.449)
Median	1.313	1.381	1.343
Q1, Q3	1.174, 1.613	0.967, 1.437	1.169, 1.448
Min, Max	1.07, 1.93	0.71, 1.94	0.71, 1.94
Week 13 (Visit 14) / End of Treatment Change from Baseline			
n	12	13	25
Mean (SD)	-0.088 (0.1349)	0.062 (0.2309)	-0.010 (0.2021)
95% CI	(-0.173, -0.002)	(-0.078, 0.201)	(-0.093, 0.074)
Median	-0.071	0.011	-0.034
Q1, Q3	-0.164, 0.008	-0.096, 0.178	-0.107, 0.107
Min, Max	-0.33, 0.11	-0.37, 0.45	-0.37, 0.45
p-value[b]	0.0640	0.3757	0.6285

Notes: ULN is determined based on the subject's age and sex. Week 13 (Visit 14) / End of Treatment is defined as the last on treatment assessment.
Abbreviations: CI = confidence interval, EAS = efficacy analysis set, Q1 = 25th percentile, Q3 = 75th percentile, SD = standard deviation
[a] Baseline was defined as the mean of all available values prior to first dose of study drug (Visit 1b, Visit 2, Visit 3)
[b] P-value from a Wilcoxon Signed Rank test.

- **Secondary Endpoints**

1) Proportion of Participants with IGF-1 ≤ULN at Week 13/End of Treatment (this endpoint was limited to only complete responders at baseline in Groups 3, 4 and 5 who started the study with IGF-1 ≤ 1×ULN).

At W13/EOT, of the 12 participants in Groups 3, 4, and 5, the percentage of participants who maintained IGF-1 level of ≤1.0× ULN was **33.3%** (n=4) and the percentage of participants who did not maintain IGF-1 level of ≤1.0× ULN was **66.7%** (n=8), **p= 0.8448.**

2) Proportion of Participants with IGF-1 ⩽1.5×ULN at Week 13/End of Treatment

At Baseline, of the 25 participants **in Group 1** (EAS), the proportion of participants who had IGF-1 level of ≤1.5× ULN was **80.0%** (n=20).

At W13/EOT, the proportion of participants with **IGF-1 ≤1.5× ULN** remained the same [80.0% (n=20)] and the proportion of participants with IGF-1 >1.5× ULN was **20.0%** (n=5).

Overall, at baseline, of the **47 subjects** (FAS), the percentage of subjects who had IGF-1 level of ≤1.5 × ULN was **83.0%** (n=39).

At W13/EoT, the percentage of subjects with IGF-1 level of ≤1.5× ULN was **68.1%** (n=32, responders) and the percentage of subjects with IGF-1 >1.5× ULN was **31.9%** (n=15, **non-responders**).

- **Key exploratory endpoints**

1) Change from Baseline in Serum GH Levels Measured at Week 13/End of Treatment

The median change from baseline in serum GH levels at W13/EoT in **Group 1** subjects (EAS) was not significant, at approximately zero, indicating no change, **-0.05** ng/mL (IQR, -0.29 to 0.20 ng/mL; **p=0.6285**).

At baseline, median integrated GH levels in group 1 were 0.69 ng/mL (IQR: 0.49-1.55 ng/mL) and were unchanged at week 13/EoT.

The median baseline GH for groups 2 and 3 was **1.04 ng/mL** (IQR: 0.51-1.61 ng/mL). The median GH increase from baseline to week 13/EoT was **0.68 ng/mL** (IQR: 0.10-1.58; **P =.0067**). Four weeks after withdrawing paltusotine, the integrated GH had significantly increased from week 13/EoT by a median of **15.0%** (IQR: 1.8%-134.4%; **P=.0419**).

2) Change from Baseline in IGF-1 level at W13/EoT in subjects in Groups 2 through 5

Median IGF-I levels were **1.21× ULN** (IQR: 0.93-1.50× ULN) at baseline.

After discontinuation of cabergoline and conversion from depot SRL to paltusotine, the median change from baseline in IGF-1 levels at W13/EoT in **Groups 2 and 3** subjects was **0.28× ULN** (IQR, 0.149 to 0.985× ULN; **p=0.0020**) suggesting a contribution to baseline IGF-1 control from the pre-trial dopamine agonist.

Patients who had received octreotide LAR or lanreotide depot plus cabergoline before the trial (n =15) showed a small **but statistically significant increase in median IGF-I concentrations** when switched from combination therapy to paltusotine monotherapy, followed by a significant and more robust increase in IGF-I during the 4 weeks after discontinuation of paltusotine of **22%.**

3) Change from Baseline in Symptoms of Acromegaly as Measured by Total ASD Score at Week 13/End of Treatment

For the total enrolled population (**n=47**), out of a maximally symptomatic total score of 70, median total ASD scores were low at Baseline [median =**12.00** (IQR: 4.21, 23.93) **n=20**], suggesting low symptom burden at Baseline in this study population.

These low scores were maintained or numerically lower as of the end of the paltusotine treatment period [median (IQR) = **7.86** (3.43, 18.38) **n=32**]. Scores showed no significant change from baseline to week 13/EoT (median [IQR] = **−0.43** [−5.0 to 2.4], **n=18**).

The median change from baseline in total ASD score at W13/EOT **in Group 1** participants (EAS) was **0.21** (IQR: -2.71 to 2.43), **p = 0.8657.**

4) Plasma Octreotide and Lanreotide Concentrations

In the overall study population, **24 subjects** switched from octreotide LAR and **19** switched from lanreotide depot.

In the case of octreotide, median residual concentrations fell to the LLOQ of the octreotide assay **by W7** (12 weeks after last depot injection). In the case of lanreotide, residual concentrations had fallen by a median of **50.1% by W7 and by 77.3% at W13**.

To evaluate the potential impact of residual octreotide and lanreotide on the change from baseline in IGF-1 and GH values, **sensitivity analyses evaluating the octreotide vs. lanreotide subsets were performed in Group 1 subjects.**

The median change from baseline in IGF 1 values at W13/EoT in subjects (n=12) on pre-trial lanreotide depot [**-0.07**× ULN (IQR, -0.16 to 0.01× ULN); **0.0640**] was similar to that in subjects (n=13) on pre-trial octreotide LAR [**0.01**× ULN (IQR, -0.10 to 0.18× ULN); **p=0.3757**].

The median change from baseline in GH values at W13/EoT in subjects on pre-trial lanreotide depot [-**0.03 ng/mL** (IQR, -0.24 to 0.17 ng/mL); p=**0.7334**] was similar to that in subjects on pre-trial octreotide LAR **[-0.11 ng/mL** (IQR, -0.30 to 0.22 ng/mL); p=**0.8394**].

5) Patient Global Impression of Improvement (PGI-I) scores at W13/EoT.

At W13/EoT, 11 (**23.4%**) subjects had "very much improved" or "much improved", whereas 26 (**55.3%**) subjects had "minimally improved" or reported "no change" compared to before starting the study, while treated with depot SRLs. No patients reported any degree of worsening while treated with paltusotine.

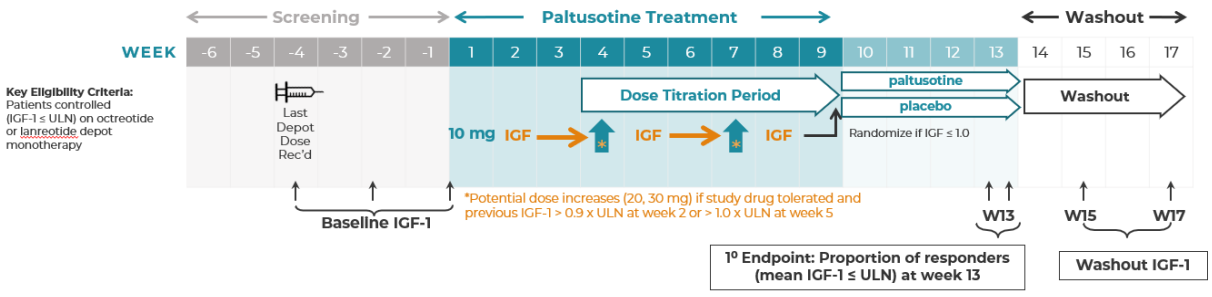
Phase 2 Study CRN00808-02 "Acrobat EVOLVE"

- **Study design**

Study **CRN00808-02** was a placebo-controlled, double-blind, **randomized withdrawal study** designed to evaluate the safety, efficacy, and PK of **4 different doses** of paltusotine in a sample of participants, **with a confirmed acromegaly diagnosis that was controlled** (mean of IGF-1≤ULN) values, as confirmed by central laboratory on two occasions measured 1-2 weeks apart during the Screening Period) on a stable approved dose of octreotide LAR or lanreotide depot (stable defined as no change in dose for the last 3 months). This study was conducted at 45 clinical sites in 13 countries. Enrolment in this study was halted due to business reasons/considerations as of 31 March 2020, with 13 participants receiving paltusotine.

First patient enrolled: 11 March 2019
Last patient completed: 31 March 2020

Figure 5 Study design



Abbreviations: IGF-1=insulin-like growth factor-1; V=visit; W=week

All subjects were switched to 10 mg of paltusotine once daily, four weeks after receiving the last injection of depot SRL during the screening period. At predetermined timepoints, IGF-1 levels and tolerability were assessed, and doses were increased in 10 mg increments as dictated by the protocol up to a

maximum of 30 mg. After this dose titration phase, participants were randomized to receive paltusotine or placebo for four additional weeks if their week eight IGF-1 was <1.0×ULN.

A total of **58 participants** were screened for eligibility, only 13 subjects enrolled in the study with confirmed diagnoses of acromegaly whose levels of IGF-1 **were biochemically controlled (IGF-1≤ ULN)** on standard-of-care SRL depot injections completed participation in the study.

Of the 13 treated participants, 11 participants were evaluated for eligibility to randomize at the Week 10 visit (1 participant discontinued early from the study, and 1 participant was not eligible to randomize due to a dose dispensing error prior to Week 10). Of the 11 participants evaluated for eligibility to randomize, 7 participants (63.6%) were randomized into the RWP, and 4 participants (36.4%) did not enter the RWP due to IGF-1>ULN at Week 8.

A washout (ie, demonstration of increased IGF-1 levels and/or return of symptoms) before switching from parenteral to oral therapy was not required.

- **Description of the participants and baseline characteristics**

The median (range) age of subjects was **50 years** (29 - 75 years) for the 13 subjects included in the ITT analysis set. The median (range) duration since diagnosis of acromegaly was **145.3 months** (17.2 - 253.1 months) for the 13 subjects included in the ITT analysis.

- **Treatments Administered and extent of exposure**

Paltusotine was administered as a **5 mg or 10 mg HMG capsule**. During the titration period (up to 13 weeks), participants received an oral once-daily dose of either 5 mg, 10 mg, 20 mg, or 30 mg paltusotine based on the titration schedule.

During the RWP (4 weeks), participants received either matching placebo or 5 mg, 10 mg, 20 mg, or 30 mg paltusotine based on their previously optimized dose. At any point during the titration period, participants who were treated with 10 mg or 20 mg QD and were judged by the Investigator as intolerant to the current dose of the study drug were to undergo a one-time dose reduction (from 10 mg to 5 mg QD or from 20 mg to 10 mg QD).

- Study Objectives and Efficacy Endpoints

The objectives of study **CRN00808-02** study were to evaluate the efficacy, safety, tolerability, and PK of paltusotine in acromegaly participants.

The primary endpoint was the **proportion of randomized participants who met responder criteria (based on the mean of two consecutive IGF-1 measurements ≤1×ULN) at Week 13.**

Key secondary endpoints were:

Change in IGF-1 levels between Week 10 and Week 13

Change in GH levels between Week 8 and Week 13

Change in symptoms of acromegaly as measured by total ASD Score between Week 10 and Week 13.

- **Results and outcomes**

- **Primary Efficacy Endpoint: "proportion of randomized participants who met responder criteria (based on the mean of two consecutive IGF-1 measurements ≤1×ULN) at Week 13.**

Seven (7) of the 11 participants (64%) who completed the titration period per protocol maintained normal IGF-1 at Week 8, allowing entry into the RWP.

- **Secondary Endpoints**

As expected with the small sample size (n=7), no significant differences (p>0.05) between paltusotine and placebo were seen in the secondary endpoints of IGF-1, GH, or total ASD score during the RWP.

The **median treatment difference** between paltusotine and placebo in IGF-1 change from Week 10 to Week 13 was **-0.27×ULN** (95% CI: -1.2 to -0.052×ULN) and the median treatment difference between paltusotine and placebo in IGF-1 **percent change** from Week 8 to Week 13 was **-37.2%** (95% CI: -104.7% to -1.2%).

The median treatment difference in GH change from Week 10 to Week 13 was **0.11** ng/mL (95% CI, -2.6 to 0.60 ng/mL) and the median treatment difference in GH percent change from Week 10 to Week 13 was **40.6%** (95% CI, -361.6% to 106.5%).

The median treatment difference in total ASD score change from baseline was **1.1** (95% CI, -4.3 to -1.9).

- **Exploratory efficacy analyses**

- Changes in IGF-1 and changes in GH levels: not relevant

- Plasma Concentrations of Paltusotine, Octreotide, and Lanreotide

At the end of the titration period (Week 10/Visit 11 pre-dose), median (n; range) paltusotine concentrations appeared dose-proportional in the limited number of subjects at each dose: 10 mg (6.56 ng/mL [n=4; 4.27 – 11.5 ng/mL]); 20 mg (13.1 ng/mL [n=6; 7.14 – 91.4 ng/mL]); and 30 mg (38.6 ng/mL [n=2; 28.8 – 48.4 ng/mL]). All paltusotine concentrations had washed out at the end of the 4 weeks follow-up.

Residual octreotide plasma concentrations were below the lower limit of quantitation of 100 pg/ml at Week 10 (Visit 11) and Week 13 (Visit 14). Residual lanreotide was still detectable at Week 13 (Visit 14). The median (range) percent reduction in residual lanreotide plasma concentrations from Screening Visit 2 to Week 13 (Visit 14) was **-72.6%** (-83.4%, -71.7%).

Phase 2 study CRN00808-05 "Acrobat ADVANCE"

First patient enrolled: 26 February 2020.

On-going: the data cut-off date for the interim analysis study was **21 May 2025**, providing up to approximately 5.5 years of long-term data for paltusotine.

- **Study design**

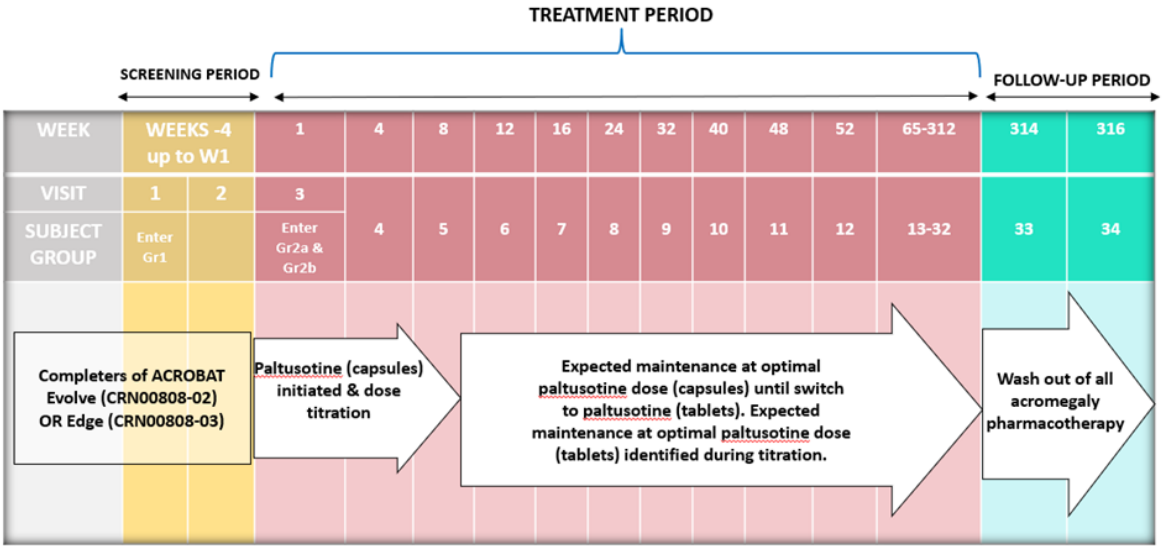
Eligible participants from studies **CRN00808-03** and **CRN00808-02** were invited to participate in the **on-going OLE Study CRN00808-05**, which provides long-term safety, tolerability, and efficacy data for paltusotine. **The starting daily dose for the tablet formulation was 40 mg (2×20 mg tablets) QD for oral self-administration.**

Study **CRN00808-05** is an on-going phase 2, 6-year, **OLE study** designed to evaluate the long-term safety and efficacy of paltusotine in adult participants with acromegaly who completed either of the parent studies **CRN00808-02** or **CRN00808-03**.

Two groups of participants were enrolled: (1) Group 1 participants who were not currently enrolled in study **CRN00808-02** or study CR**N00808-03**, but had completed study **CRN00808-02** or study **CRN00808-03** and had resumed standard acromegaly medications (Delayed Rollover), and (2) Group 2a participants who were completing study **CRN00808-02** or study **CRN00808-03** and had not resumed standard acromegaly medication (Direct Rollover).

Eligible participants entered a Treatment Period of up to **312 weeks**, followed by a 28-day Follow-up Period.

Figure 6 ***Study design***



- Study Objectives and Endpoints

The **objective** of this study is to evaluate the long-term safety and efficacy of paltusotine in acromegaly.

The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs) throughout the study.

The secondary endpoints are the change from the Week 16 visit (15 weeks of study treatment) in IGF-1 levels and the change from Week 16 in GH levels.

* Change from Week 16 was utilized for these analyses as all participants were expected to have been up-titrated to the maximum dose by that time-point.

Exploratory efficacy endpoints included:

Proportion of participants with IGF-1 measurements ≤ ULN at each post-baseline visit

Proportion of participants who achieve serum GH <1.0 ng/mL

Number of consecutive visits with IGF-1 ≤ ULN

Change from baseline in AcroQoL total score

Change from baseline in ASD total score

Additional exploratory analysis were evaluated at the interim analysis:

Participants treatment preference, as assessed by the Treatment Preference Questionnaire (TPQ) at W52

Participants medication assessment as measured by the treatment satisfaction questionnaire for medication (TSQM-9) at, W312/V32 or early termination (ET)

- Disposition and baseline characteristics

A total of **45 participants** were screened, of which **43 participants** were enrolled and included in the Safety Population.

11 participants enrolled from parent Study **CRN00808-02**, of whom 7 were delayed rollover and 4 were direct rollover. **32** participants enrolled from parent Study **CRN00808-03**, of whom 17 were delayed rollover and 15 were direct rollover.

No participants had completed the Treatment Period (Week 207) or the Follow-up Period (Week 211) as of the data cut-off date.

Eight participants (18.6%) discontinued from the study early, two (25%) of which were due to AE, and two (25%) of which were due to inability to fulfil study requirements and procedures, four (50%) were due to other reasons.

Participant demographics and baseline characteristics were generally consistent between the two parent studies. The median age was **52 years** (range, 30 to 76), with 35 participants (81.4%) falling in the ≥18 to <65 age group, and **55.8%** of participants were female.

Study participants had a median duration since acromegaly diagnosis of **123.7** months, ranging from 25 to 369 months. Most participants (**86%**) had prior pituitary surgery.

Pre-trial therapies consisted of octreotide LAR (**48.8%** of participants; mean dose 30 mg/month), lanreotide depot **(44.2%;** mean dose 108.9 mg/month), cabergoline (**30.2%**; mean dose 3.4 mg/week), pasireotide LAR (**14.0%;** mean dose 46.7 mg/month), and pegvisomant (**2.3%** [n=1]; 20 mg/week).

- Treatments Administered and extent of exposure

Paltusotine **capsules or tablets** were taken once a day in the morning after an overnight fast (at least 6 hours). No food was allowed for at least **2 hours after capsule** administration and **1 hour** after tablet administration including time for study medication administration.

The recommended initiation dose of paltusotine for all participants was 10 mg per day (QD) at the Week 1/Visit 3.

Participants received an oral once daily dose of either 10, 20, 30, or 40 mg paltusotine capsules based on titration. If tolerated, the dose of study medication was to be increased to 20 mg QD at the Week 4 Visit **if the IGF-1 value measured was >ULN** range provided by the central laboratory.

At the **Week 8 Visit**, the dose of study medication was to be increased to a maximum **of 40 mg QD** if IGF-1 remained >ULN and the participant was tolerating the study medication.

Doses could be decreased from doses of 20 mg QD or above, to improve tolerability, as necessary, at any time during the study.

Switching from capsules to tablets allowed participants to shorten the post-dose fasting to 1 hour because of the lessened food effect, and tablets were chosen as commercial formulation.

Thirty-six participants (**83.7%**) were switched from paltusotine capsules to tablets, which reflected all active participants as of the data cut-off date. The participants who were not switched from capsules to tablets terminated Study **CRN00808-05** prior to the introduction of tablets.

After the switch, dose levels for tablets could be increased from 40 mg (2×20 mg tablets) to 60 mg (3×20 mg tablets) QD based on IGF-1 response; down-titration was allowed based on tolerability.

Table 14 ***Tablet Dose Titration Options for Study CRN00808-05***

Tablet Dose Titration/Adjustment	IGF-1 Criteria	Tolerability Criteria
40 mg→60 mg	Participant's most recent IGF-1 results on 40 mg is >1.0×ULN	Increase allowed due to acceptable tolerability on 40 mg
40 mg→20 mg	--	Dose reduction required due to unacceptable tolerability on 40 mg
20 mg→40 mg	Participant's most recent IGF-1 results on 20 mg is >1.0×ULN	Tolerability is acceptable on 20 mg
60 mg→40 mg	--	Dose reduction required due to unacceptable tolerability on 60 mg

IGF-1=insulin-like growth factor-1, mg=milligram, ULN=upper limit of normal

Adjunctive acromegaly treatments (ie, dopamine agonists and/or pegvisomant) were permitted to be initiated in combination with paltusotine if IGF-1 levels were still elevated after the participant had been taking paltusotine 40 mg QD (or maximally tolerated lower dose) **for 2 to 4 weeks**, if clinically appropriate: this would generally have occurred by the **Week 12** visit.
If it was determined that adjunctive medication was required, then use of a dopamine agonist (e.g. cabergoline, bromocriptine) was the expected first-line adjunct, as clinically appropriate. If after an adequate period of assessment, study medication combined with a dopamine agonist did not achieve therapeutic targets, then pegvisomant could be added as a second-line adjunct, if clinically appropriate.
No participants received cabergoline-adjunctive therapy **prior to Week 15**. The highest frequency of participants (**n=18**) receiving cabergoline occurred at Week 64 and beyond.
Only one participant from parent study **CRN00808-02** received cabergoline, which was one dose of 1.8 mg/week given at Week 47. All remaining cabergoline doses were taken by participants from parent study **CRN00808-03**.

Two participants (4.7%) took adjunctive pegvisomant, both of whom were enrolled in parent Study **CRN00808-03.**

Of the 43 participants enrolled, **34 participants** were continuing in the study at the data snapshot date of 31 August 2025. No participants have completed the Treatment Period (Week 311) or the Follow-up Period (Week 315).

Most participants (**65.1%)** were being treated with paltusotine 60 mg QD, and **27.9%** were being treated with 40 mg QD. Approximately half of participants from parent Study CRN00808-02 (n=6,

54.5%) were receiving a paltusotine dose of 40 mg QD, whereas the majority of participants from parent Study CRN00808-03 (n=24, **75.0%)** were receiving paltusotine 60 mg QD, which was expected as most of the latter participants were sub-optimally controlled on monotherapy with octreotide or lanreotide prior to enrolment in the parent study.

The number of paltusotine who required paltusotine down titration due to treatment-emergent adverse events in the OLE phase was: 1/43 participants (2.3%) had reduced the dose of paltusotine from 60 mg to 40 mg and 1/43 (2.3%) had reduced the dose of paltusotine from 40 mg to 20 mg.

- **Results and outcomes as regards efficacy endpoints**

1) "Proportion of Participants with IGF-1 Measurements ≤ ULN at each Post-baseline Visit" (interim analysis at the data snapshot date of 31 August 2025)

At Week 3, the overall proportion of participants of study CRN00808-05 with IGF-1 ≤ 1.0 x ULN was **34.9% (15/43)**, with **81.8%** (9/11) from study CRN00808-02 and **18.8%** (6/32) from study CRN00808-03.

Among participants on paltusotine only, the overall proportion of participants of study CRN00808-05 with IGF-1 ≤ 1.0 x ULN was **50%** (8/16) with **77.8%** (7/9) from study CRN00808-02 and 14.3% (1/7) from study CRN00808-03.

At Week 15, **31.0%** (13/43) of participants in the overall CRN00808-05 population achieved IGF-1 level ≤1.0xULN. As expected, based on baseline characteristics and clinical status of participants in the parent studies, the proportion of participants who achieved IGF-1 level ≤1.0xULN at Week 15 was higher in participants from parent study CN00808-02 (**63.6%: 7/11)** than in participants from parent study CRN00808-03 (**19.4%: 6/32),** though participants were not fully up-titrated at the Week 15 timepoint.

Among **62.5%** (10/16) participants with "paltusotine only" in the overall CRN00808-05 population who achieved IGF-1 level ≤1.0xULN, **77.8%** (7/9) were from study CRN00808-02 and 42.9% (3/7) from study CRN00808-03.

The proportion of IGF-1 responders (IGF-1 level ≤1.0xULN) increased over time and was generally maintained through Week 272 in the overall study population and within the subgroups by parent study.

For participants from study CRN00808-02, the IGF-1 response rate increased to **90.0% (9/10)** by Week 23, with IGF-1 response rates at subsequent visits ranging from **62.5% (5/8) to 100% (4/4)** through Week 259.

For participants from study CRN00808-03, the IGF-1 response rate increased to **30.0% (9/30)** by Week 31, with IGF-1 response rates at subsequent visits ranging from **24.1%** (7/29) **to 69.2%** (18/26) through Week 27.

The median IGF-1 level (×ULN) at Week 3 was similar to the baseline median IGF-1 level (×ULN) on SRL-based therapy (ie, long-acting somatostatin receptor ligand [LA SRL] Baseline) from the parent studies and was <1.5 (×ULN) from Week 3 through Week 272.

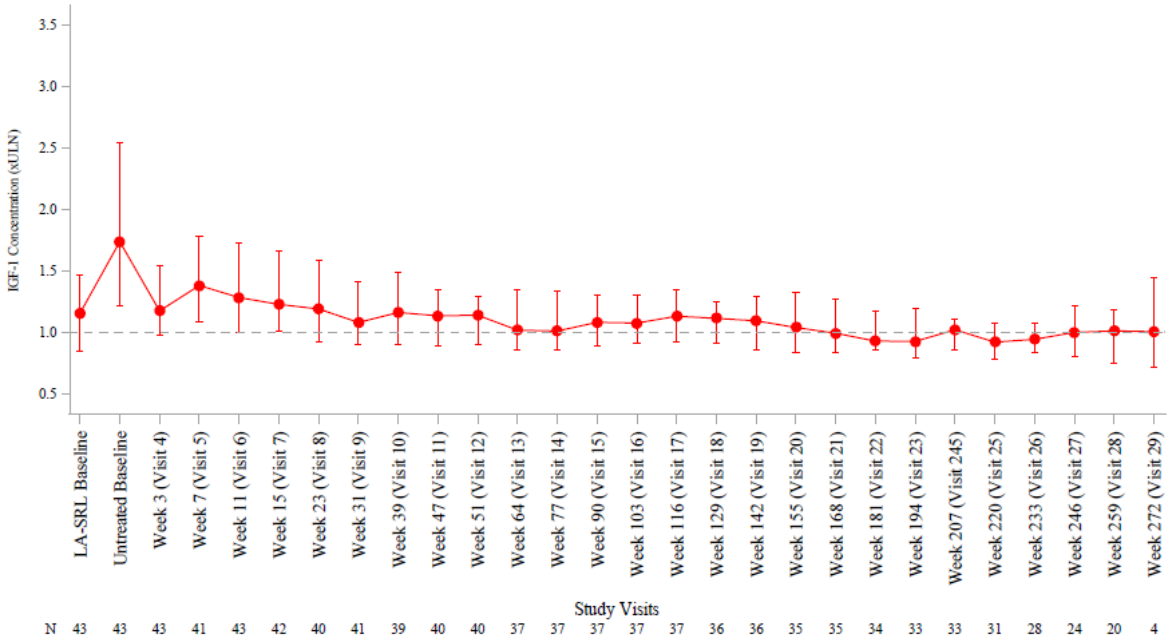
The median IGF-1 level (xULN) after Week 15 was decreased at each visit from Week 23 through Week 272 (22 consecutive visits).

In participants from parent study CRN00808-02, median (range) IGF-1 level (×ULN) at Week 15 was **0.91** (0.2 to 1.4). In these participants (who were previously controlled on SRLs), median IGF-1 levels were similar to their baseline levels on SRL based therapy and stayed below 1.0×ULN for most of the study.

In participants from parent study CRN00808-03, median (range) IGF-1 level (xULN) at Week 15 was **1.37** (0.8 to 2.8). Small decreases in median IGF-1 level (×ULN) were observed after Week 23 through Week 272.

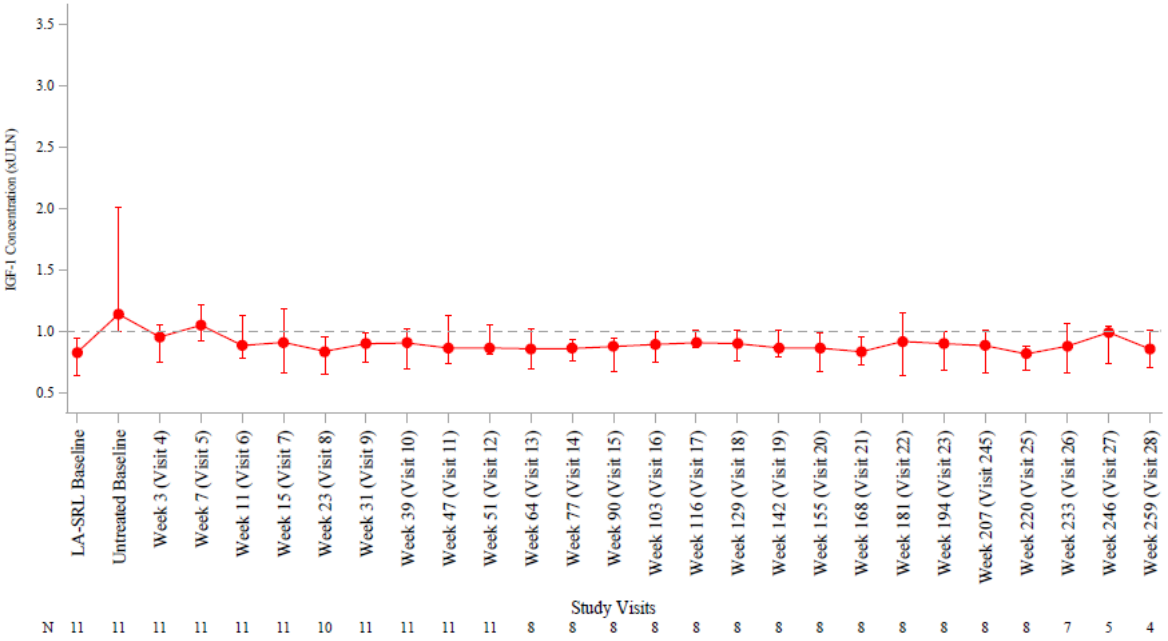
As described previously, most participants from study CRN00808-03 required pre-trial combination therapy and were taking adjunctive medication (cabergoline and/or pegvisomant as per protocol) during study CRN00808-05. Paltusotine monotherapy was able to maintain IGF-1 levels similar to previous SRL-based therapy, and for participants who were treated with paltusotine and adjunctive therapy, additional treatment benefits were observed, as evidenced by the continued improvement in IGF-1 levels during the study.

Figure 7 Median (+/- IQR) Overall IGF-1 x ULN by Visit CRN00808-05 Safety population



IGF-1=insulin-like growth factor-1; IQR=interquartile range; LA-SRL=long-acting somatostatin receptor ligand; ULN=upper limit of normal
Notes: Safety Population is participants who received at least 1 dose of study drug. ULN is determined based on the participant's age and sex. Error bars represent 25th and 75th percentiles.
LA-SRL Baseline is the baseline from the parent study (Study CRN00808-02 or Study CRN00808-03). Untreated Baseline is the last non-missing assessment in the parent study when in the untreated withdrawal phase.
Data snapshot date: 31 August 2025

Figure 8 Median (+/- IQR) IGF-1 x ULN by Visit: Parent Study CRN00808-02 Safety population



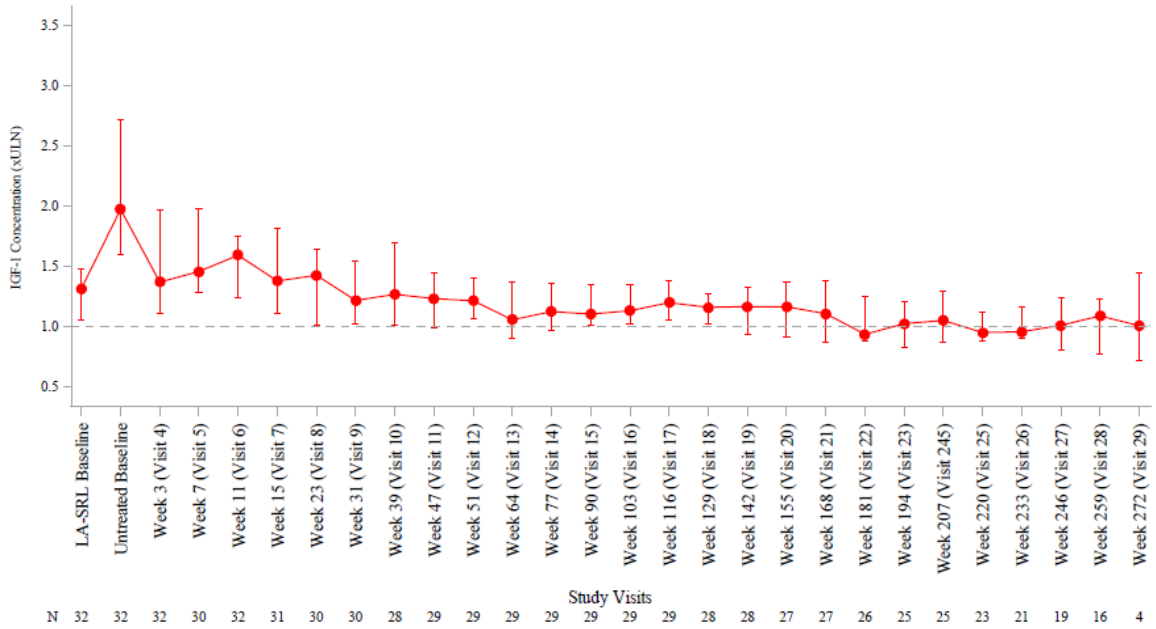
IGF-1=insulin-like growth factor-1; IQR=interquartile range; LA-SRL=long-acting somatostatin receptor ligand; ULN=upper limit of normal

Notes: Safety Population is participants who received at least 1 dose of study drug. ULN is determined based on the participant's age and sex. Error bars represent 25th and 75th percentiles.

LA-SRL Baseline is the baseline from the parent study (Study CRN00808-02). Untreated Baseline is the last non-missing assessment in the parent study when in the untreated withdrawal phase.

Data snapshot date: 31 August 2025

Figure 9 Median (+/- IQR) IGF-1 x ULN by Visit: Parent Study CRN00808-03 Safety population



IGF-1=insulin-like growth factor-1; IQR=interquartile range; LA-SRL=long-acting somatostatin receptor ligand; ULN=upper limit of normal
Notes: Safety Population is participants who received at least 1 dose of study drug. ULN is determined based on the participant's age and sex. Error bars represent 25th and 75th percentiles.
LA-SRL Baseline is the baseline from the parent study (Study CRN00808-03). Untreated Baseline is the last non-missing assessment in the parent study when in the untreated withdrawal phase.
Data snapshot date: 31 August 2025

2) Proportion of Participants who Achieve GH <1.0 ng/mL (31 August 2025)

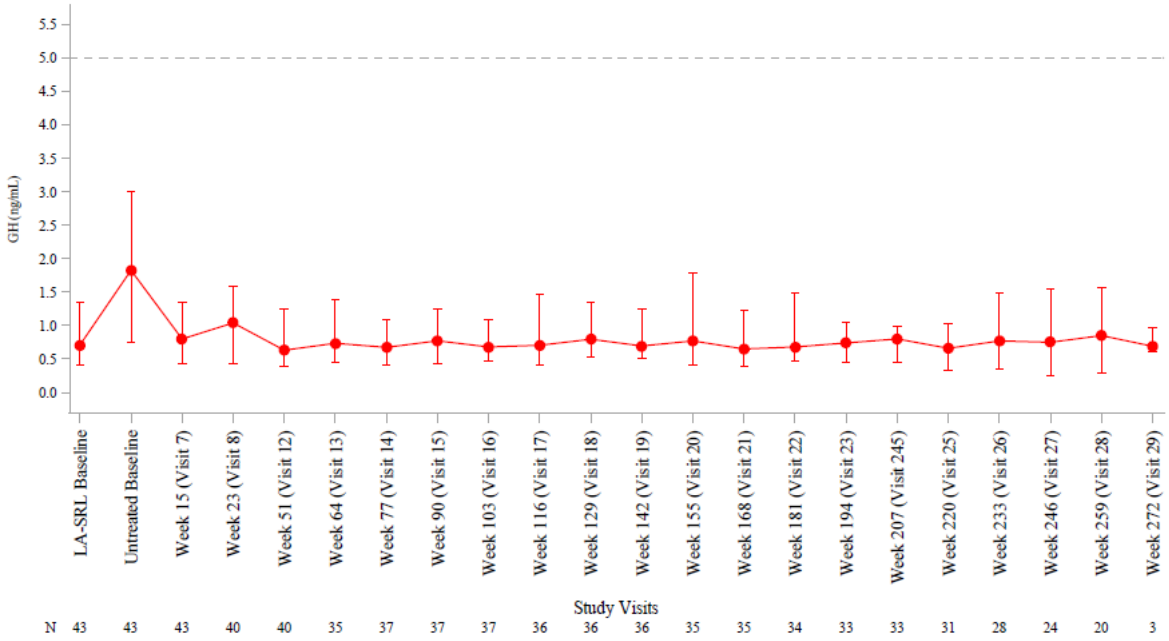
At Week 15, **53.5%** of participants in the overall CRN00808-05 population achieved GH level <1.0 ng/mL (**63.6%** in participants from parent Study CN00808-02 and **50.0%** in participants from parent Study CRN00808-03 group).

The proportion of participants with GH level <1.0 ng/mL ranged from **50.0%** to **100.0%** from Week 23 to Week 272 in the overall study population.

For participants from Study CRN00808-02, the proportion of participants with GH level <1.0 ng/mL ranged from **50.0% to 87.5%** from Week 23 to Week 259. For participants from Study CRN00808-03, the proportion of participants with GH level <1.0 ng/mL ranged from **50.0% to 100.0%** from Week 23 to Week 272 (the Week 272 timepoint represents only 3 participants).

The overall median (range) GH level at Week 15 was 0.7990 (0.045 to 28.960) ng/mL with overall median GH levels remaining <1.0 ng/mL after Week 23 up to Week 272.

Figure 10 Median (+/-IQR) Overall GH Level (ng/mL) by Visit in Study CRN00808-05 (Safety Population)



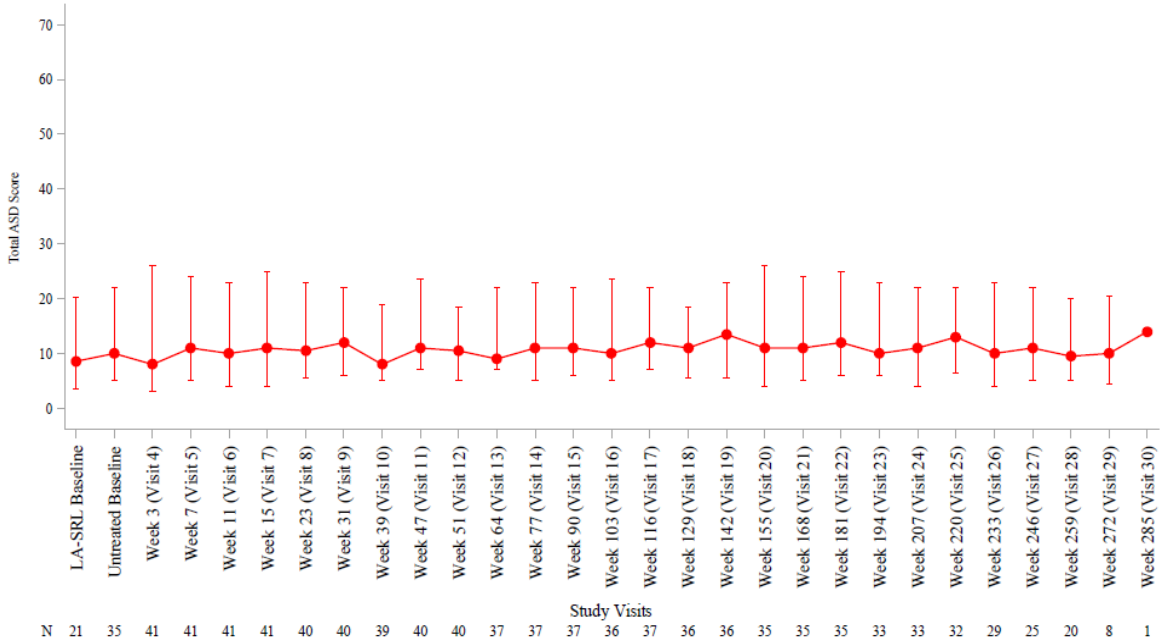
GH=growth hormone; IQR=interquartile range; LA-SRL=long-acting somatostatin receptor ligand
Notes: Safety Population is participants who received at least 1 dose of study drug in Study CRN00808-05. Error bars represent 25th and 75th percentiles. LA-SRL Baseline is the baseline from the parent study (Study CRN00808-02 or Study CRN00808-03). Untreated Baseline is the last non-missing assessment in the parent study when in the untreated withdrawal phase.
Data snapshot date: 31 August 2025

3) Exploratory efficacy endpoints

Acromegaly Symptoms Diary (ASD)

ASD Total Score generally remained stable from LA-SRL Baseline and at each subsequent visit.

Figure 11 Median (+/- IQR) Acromegaly Symptoms Diary Total Score by Visit CRN00808-05 (31 August 2025)



ASD=Acromegaly Symptoms Diary; IQR=interquartile range; LA-SRL=long-acting somatostatin receptor ligand
Notes: Safety Population is participants who received at least 1 dose of study drug. Error bars represent 25th and 75th percentiles. ASD was performed only at each visit. LA-SRL Baseline is the baseline from the parent study (Study CRN00808-02 or Study CRN00808-03). Untreated Baseline is the last non-missing assessment in the parent study when in the untreated withdrawal phase.
Data snapshot date: 31 August 2025

Treatment Preference Questionnaire (TPQ) at W51

At the cut-off date of 5 December 2023, data were available on 36 participants **at Week 51**, of whom **91.7%** indicated a preference for a once daily oral medication compared to a preference for previous injections among **2.8%** or no preference (**5.6%).** For Week 51 and Early Termination combined, the preference was once daily oral medication among **87.2%** of participants.

S**ummary for AcroQoL, EQ-5D-5L, PGI-S, PGI-I at W51**

AcroQoL, and EQ-5D-5L were generally stable throughout the study.

Tumour volume

There were no clinically significant tumour changes as assessed by the Investigator.

5.3.2. Main studies

2 phase 3 studies have been conducted by the applicant. Studies CRN00808-08 and CRN00808-09 were similar with respect to the duration of washout of existing SRLs, dose titration, and treatment with stable doses of paltusotine in the RC Phases.

5.3.2.1. Study CRN00808-08

5.3.2.1.1. Study title

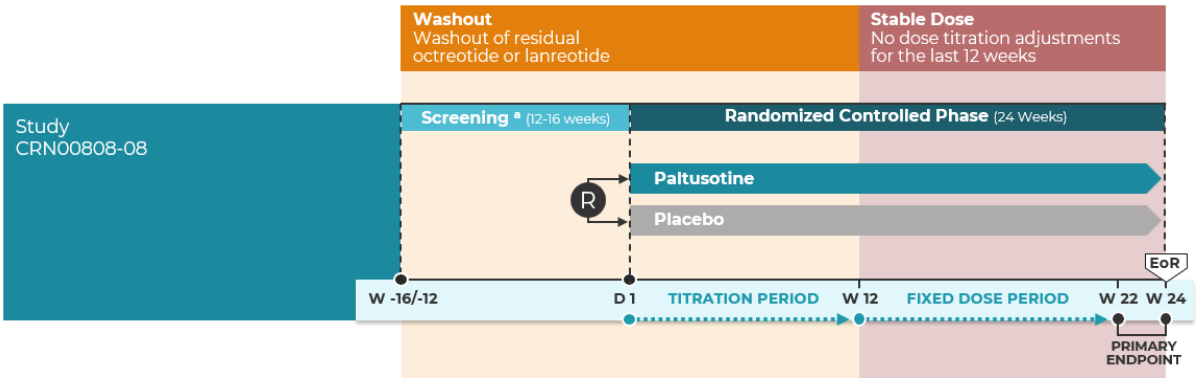
PATHFNDR-2: Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen

5.3.2.1.2. Study design

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study where participants with non-pharmacologically treated acromegaly including participants with no prior medical therapy, participants who last received medical therapy at least 4 months prior to screening, and participants who were controlled on medical therapy for at least 3 months but agreed to wash out prior to beginning study treatment, were randomly allocated to receive either paltusotine or placebo.

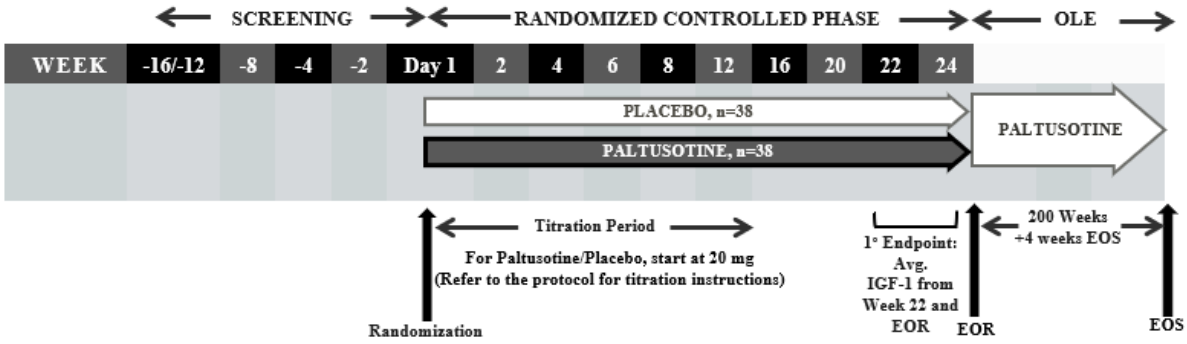
Figure 12 Study schema

RC phase



D=day, EoR=End of Randomized Controlled Phase, R=randomization, RC=randomized controlled, W=week
a During the Screening Period of Study CRN00808-08, a washout period of up to 12 to 16 weeks was included for the group of participants who were controlled on medical therapy but agreed to washout of long-acting octreotide or lanreotide prior to study enrolment.

RC Phase + OLE Phase



EOR=End of RC Phase, EOS=End of Study, IGF-1=insulin-like growth factor-1, OLE=Open-label Extension, RC=Randomized Controlled

EOR was defined as the end of the RC Phase at Week 24.

EOS is defined as the day final study data are collected and should occur 4 weeks after the last dose of study drug. The end of Week 228/EOS Visit (Follow-up Visit for the OLE Phase) is the last planned visit of the study, but the EOS Visit could occur at Week 28 (Follow-up Visit for the RC Phase) in participants who did not enter the OLE Phase.

After the screening period, all eligible participants were randomized in a 1:1 ratio to receive paltusotine or matching placebo, **stratified by prior treatment** (medically naïve or previously treated versus washout). The RC phase treatment period was **24 weeks**.

After randomization in the RC phase, all participants had a dose-titration period (based on IGF-1 levels and tolerability) of 12 weeks.

This study was designed to provide an **adequate washout duration** of long-acting octreotide or lanreotide of up to approximately 24-weeks (**at least 12 weeks in the screening period plus the 12-week dose titration period in the RC Phase**).

After the first 12 weeks of study treatment including dose titration in the RC phase, no further dose titration was permitted for the remaining 12 weeks of study treatment in the RC phase. This allowed for **an additional 12 weeks on a stable dose** of study treatment to adequately assess the effectiveness of paltusotine.

Participants who completed the 24-week RC phase or who met rescue criteria and completed the 24-week RC phase with rescue medication could continue participation in the OLE phase.

At the completion of study target enrolment for the RC phase, the remaining participants in the washout group who had entered screening and met eligibility criteria were eligible to directly enrol into the OLE for **up to 200 weeks plus a 4-week follow-up**.

The RC phase was completed, and the OLE phase is on-going with **113 participants** treated with paltusotine **for up to 60 weeks**, as of the data cut-off date of **20 January 2024**.

This study was conducted at **56 sites in 15 countries**: Argentina, Brazil, Bulgaria, China, France, Germany, Greece, Hungary, India, Israel, Italy, Poland, Spain, United Kingdom (UK), and United States (US).

Treatment

Participants received paltusotine or matching placebo during the RC phase and paltusotine during the

OLE phase.

Paltusotine was available as immediate-release **20 mg tablets**. Matching placebo tablets were identical in appearance to paltusotine tablets and **were administered orally** according to the randomization scheme, on an identical schedule to those receiving paltusotine.

During the RC and OLE phases, study drug was to be taken in the morning, with water, after an overnight fast of at least 6 hours. No food or drink (except for water) was allowed for at least 1 hour after drug administration, starting from the time study drug was administered.

In the RC phase, the starting dose was **20 mg QD** (1×20 mg tablet of active paltusotine or matching placebo) for oral self-administration. A dose of 20 mg was selected to minimize potential gastrointestinal side effects in participants washed out from medical therapy or naïve to medical therapy. After confirming tolerability with the participant, **the dose was increased to 40 mg QD** (2×20 mg tablets of active paltusotine or matching placebo) **at the Week 2 visit**.

Dose down-titration was allowed at any time during the RC phase of the study if the dose was not tolerated in the judgement of the investigator.

Beginning **at Week 6**, the dose could be increased to 60 mg QD (3×20 mg tablets of active paltusotine or matching placebo) if the 40 mg dose was acceptably tolerated and based on biochemical control and the **Week 4 IGF-1 was >0.9×ULN**. If the Week 4 IGF-1 was ≤0.9×ULN, the dose was maintained at 40 mg QD until the end of the RC phase, unless an unscheduled measurement obtained at any time from Week 4 to prior to or at Week 12 showed IGF-1 >0.9×ULN, in which case the dose was increased from 40 mg to 60 mg QD if the 40 mg dose was acceptably tolerated. It was anticipated that the study drug dose would be stable, and titration completed prior to or at Week 12, with no dose titrations/adjustments after Week 12. Participants who required dose up-titration after Week 12 were considered non-responders.

Table 15 Dose Titration Options

Dose Titration/Adjustment	IGF-1 Criteria	Tolerability Criteria
20 mg→40 mg	--	Increase required at Week 2 visit if acceptable tolerability on 20 mg
40 mg→60 mg	Week 4 IGF-1 >0.9×ULN or at any time prior to or at the Week 12 visit	Acceptable tolerability on 40 mg
60 mg→40 mg	--	Dose reduction required due to unacceptable tolerability on 60 mg
40 mg→20 mg	--	Dose reduction required due to unacceptable tolerability on 40 mg

If the investigator determined that a dose titration/adjustment after Week 12 was required, the investigator had to contact the Medical Monitor to ensure that a consistent approach to dose titration/adjustment was applied across the study.

In the **OLE phase**, **the starting dose** regimen for participants is paltusotine **20 mg QD** at the week **24/EOR visit**, and if tolerated, the dose can be increased to **40 mg QD at the Week 26 visit**.

Dose escalation in the OLE phase generally occurred once the first IGF-1 result was available. At that time, the investigator could determine whether the dose could be up-titrated to 60 mg (3×20 mg tablets). The dose could be increased to 60 mg QD if the 40 mg dose was acceptably tolerated and based on biochemical control. Dose down-titration was allowed if the dose was not tolerated in the judgement of the investigator.

Study medication could be held for up to a total of 14 days, but no more than 7 consecutive days per year in the OLE.

Concomitant medications

Prohibited Medications

Prohibited medications during the study included the following:

- Proton pump inhibitors

- Use of famotidine in the evenings

- Oral estrogen, except for monophasic estrogen-progestin oral contraception or stable estrogen replacement

- Strong inducers of the drug metabolizing enzyme CYP3A4, including but not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort (because these medicines could decrease the concentration of paltusotine in the systemic circulation)

- Any standard acromegaly drug that was not used as a rescue medication during the RC Phase (or an allowed adjunctive medication in the OLE Phase

- Octreotide (any form), lanreotide, or pasireotide during the OLE

- Any other investigational drug, unless approved by the Medical Monitor (eg, COVID-19 therapies)

Rescue therapies

During the RC Phase, rescue criteria were in place to ensure safety for participants who required resumption of standard acromegaly treatment (ie, 2 consecutive IGF-1 levels $\geq 1.5 \times$ ULN* at the highest dose of study treatment [60 mg/day] **and** new or worsening of acromegaly symptoms as assessed by the investigator for at least 2 weeks).

*Of note, in a large study of naïve acromegaly patients, octreotide LAR monotherapy achieved mean IGF-1 of 1.5× ULN (*Colao A 2014*) at 3 months of treatment through 12 months.

Symptoms had to be attributed to uncontrolled acromegaly in the opinion of the investigator and could include but were not limited to the following: headache, arthralgia, fatigue, hyperhidrosis, or soft tissue swelling.

Significant worsening was defined as symptoms requiring a substantial increase in level of clinical care (e.g. significant intervention needed to avert hospitalization or a clinically notable increase in frequency or intensity of patient contact required) or substantial clinical deterioration (e.g. worsening from a mild to severe AE or the onset of an SAE would meet these criteria).

Octreotide LAR or lanreotide depot monotherapy (approved SRLs) were the only rescue therapies permitted during the RC phase of the study.

Participants who met rescue criteria in the RC phase were to be discontinued from study drug (paltusotine or placebo). These participants were considered non-responders, and they were encouraged to continue

in the study on rescue therapy for assessment and observation in the remainder of the 24-week RC phase.

All participants treated with paltusotine or placebo who completed the RC phase, including those who received rescue therapy, could participate in the OLE phase if they met all eligibility requirements.

OLE Phase Adjunctive Treatments

If there was evidence of paltusotine efficacy at 6 months but participants had not reached therapeutic target goals, adjunctive treatment could be initiated if clinically appropriate beginning **at Week 48**. If these criteria were met, non-SRL acromegaly treatments, such as cabergoline or GH receptor antagonist (ie, pegvisomant), were permitted and could be initiated as an adjunctive treatment when a participant experienced at least 2 consecutive elevated IGF-1 (≥1.3×ULN) measurements at the highest paltusotine dose level (60 mg) or was otherwise not at the participant's therapeutic target in the judgement of the investigator.

If adjunctive medications were not appropriate or not accessible under local regulations, and the participant was not under acceptable biochemical control while treated with Paltusotine monotherapy at the maximal tolerated dose in the opinion of the investigator, the participant was discontinued from the OLE portion of the study.

Randomisation

Randomization was performed using a fixed-block randomization scheme. The randomization scheme was generated prior to the initiation of the study by an independent statistician/programmer who was not a member of the study team. Randomization was stratified by prior treatment (medically naïve or previously treated [Stratum 1] versus washout [Stratum 2]).

Blinding

The Sponsor, contract research organizations (CROs), investigators, study site personnel, and study participants were blinded to treatment assignment during the RC Phase. The randomization schedule was kept strictly confidential and accessible only to authorized persons. The randomization schedule was made available for unblinding and analysis only after the RC phase was completed, the protocol deviations were determined, and the study database was locked.

The IRT system was programmed with blind-breaking instructions in case of an emergency for participant safety and for expedited reporting of SAEs to regulatory agencies, when required.

Patient population

- **Main inclusion criteria**

Three groups of participants were enrolled:

- Participants with no prior medical therapy (Group 1/Stratum 1): "medically naïve group" who at screening had IGF-1 ≥1.3×ULN. **Group 1 subjects must have had at least 1 pituitary surgery 3 months or more prior to screening**
- Participants who last received medical therapy **at least 4 months** prior to screening (Group 2/Stratum 1) who had IGF-1 ≥1.3×ULN at screening

- Participants who were controlled on stable dose of medical therapy with octreotide or lanreotide monotherapy for at least 3 months before screening but agreed to washout prior to beginning study treatment (Group 3/Stratum 2) who had **IGF-1 ≤1.0×ULN at screening**. After informed consent was provided, the participant was not to receive, further pretrial acromegaly medication. **IGF-1 had to rise from the first screening visit by at least 30% and be ≥1.1×ULN** (the lower limit for eligibility is IGF-1 of 1.05 when rounded to 2 decimal places).

Of note, during the screening period, a washout period of up to **12 to 16 weeks** was included for the Group 3 participants who were controlled on medical therapy but agreed to washout of long-acting octreotide or lanreotide prior to study enrolment. Participants who were controlled on short-acting octreotide or lanreotide had a washout period of approximately **8 weeks**.

The screening period for the medically naïve group and the previously treated group (no treatment within previous 4 months) was approximately **4 weeks** in duration and consisted of one screening visit.

Other inclusion criteria

1. Previous diagnosis of acromegaly confirmed by the Investigator and approved by the Medical Monitor. This requires evaluable documentation of a pituitary adenoma.

2. Females who engage in heterosexual intercourse must be of non-childbearing potential, defined as either surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), OR be postmenopausal with at least 1 year of amenorrhea, OR must agree to use either a highly effective or a clinically acceptable method of contraception from the beginning of screening until at least 30 days after the last dose of study drug.

3. If the subject is male, the subject should agree to use a condom when sexually active with a female partner of childbearing potential from screening until at least 30 days after the last dose of study drug or remain abstinent. Male subjects should also agree to not donate sperm for the duration of the study and until at least 30 days after the last dose of study drug.

- **Main exclusion criteria**

- History of ineffectiveness or significant intolerance of octreotide or lanreotide treatment
- History of pituitary radiation therapy **within 3 years** of screening
- Subjects with adrenal insufficiency, diabetes insipidus, or central hypogonadism who are not receiving adequate hormone replacement therapy at the time of screening
- High-risk pituitary tumour (compression of the optic chiasm or invasion of adjacent brain structures, history of tumour growth within 1 year after surgery or radiation)
- Diabetes mellitus treated with insulin for less than 6 weeks prior to the study entry, or with change in total daily insulin dose by >15% within 6 weeks prior to screening.
- Use of prohibited medications such as

    . Lanreotide depot or octreotide LAR (**within 16 weeks before screening**) (Group 2only)

    . Pasireotide LAR (**within 24 weeks prior to screening**)

    . Pegvisomant (**within 16 weeks before screening**)

    . Dopamine agonists (**within 16 weeks before screening**)

    . Current use of oral estrogen replacement therapy for **<12 weeks** prior to screening

. Current use of medications that are strong inducers of CYP3A4 **within 2 weeks** prior to screening

- Poorly controlled diabetes mellitus defined as having a haemoglobin A1c (HbA1c) ≥8.5% (≥69 mmol/mol), or estimated HbA1c based on fructosamine if HbA1c is not evaluable (eg, due to hemoglobinopathies).
- Female subjects who are pregnant or lactating. Subjects must have a negative pregnancy test during screening and prior to the first dose of study drug.

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective of the RC phase was to evaluate the efficacy of paltusotine versus placebo on IGF-1 response in participants with non-pharmacologically treated acromegaly who were randomly allocated to receive either paltusotine or placebo.

The primary efficacy endpoint was: "**Proportion of participants who achieved biochemical response in IGF-1 (≤1.0× ULN) at EOR".**

IGF-1 response was defined as IGF-1 level ≤1.0×ULN based on the average of the last 2 measurements prior to EOR (Weeks 22 and 24), rounded to 2 significant figures. If only 1 measurement was available at Weeks 22 and 24, this 1 measurement was used to define response.

Non-response was defined as IGF-1 level >1.0×ULN based on the average of the last 2 measurements or with IGF-1 missing at both Week 22 and Week 24.

Participants who discontinued treatment for any reason prior to EOR, received prohibited standard acromegaly treatment, received rescue therapy with criteria met, **or titrated up in dose after Week 12** were also considered non-responders.

Estimand for the primary objective

Table 16 Estimand for primary objective

Population	Patients with acromegaly (medically naïve, previously treated, or post-washout) who would encounter the intercurrent event of discontinuation, rescue medication, prohibited medication, or dose up-titration after Week 12 if assigned to either paltusotine or placebo.
Treatment conditions	Assignment to paltusotine, regardless of discontinuation and use of rescue medication, compared to assignment to placebo, regardless of discontinuation and use of rescue medication.
Endpoint (variable)	Proportion of participants achieving IGF-1 ≤ 1.0×ULN at end of randomized treatment, based on the average of Weeks 22 and 24. If only one of the two values was available, that single result (rounded to two significant figures) was used.
Population-level summary	Proportion of responders in each treatment group; comparison via odds ratio using exact logistic regression.

Intercurrent events and strategy to handle them	
Discontinuation of treatment	Composite: to reflect treatment failure
Rescue medication use	Composite: to reflect treatment failure
Use of prohibited medication	Composite: to reflect treatment failure
Up-titration after Week 12	Composite: to reflect treatment failure

The primary estimand assesses the effect of paltusotine versus placebo on biochemical control of acromegaly, defined as achieving IGF-1 ⩽ 1.0×ULN at Week 24 (based on the average of Weeks 22 and 24, or a single value if only one is available). Participants who discontinued treatment, received rescue or prohibited medication, or had dose up-titration after Week 12 were considered non-responders. These intercurrent events were addressed using a composite strategy, reflecting clinical failure.

Statistical methods for estimation and sensitivity analysis on primary estimand

The primary efficacy analysis was based on the Full Analysis Set (FAS). The estimand targeted the proportion of participants with IGF-1 ⩽1.0×ULN at End of Randomisation (EOR), defined as the average of Weeks 22 and 24 (rounded to two significant figures). Participants with missing IGF-1 values at both visits or with intercurrent events (treatment discontinuation, rescue/prohibited medications, or dose titration after Week 12) were considered non-responders.

The primary analysis used an exact logistic regression model adjusting for prior treatment strata; Firth logistic regression was prespecified as a fallback. Multiplicity was controlled through a hierarchical testing procedure.

Sensitivity analyses explored variations in the estimand, including per-protocol, completers, and alternate handling of intercurrent events (e.g. up-titration not considered treatment failure).

Secondary objectives

Secondary objectives were to evaluate the effects of paltusotine versus placebo on IGF-1 level, IGF-1 response (≤1.3 × ULN), GH response (< 1 ng/mL), and acromegaly symptoms in the RC phase. The objective of the OLE Phase is to evaluate the long-term safety and efficacy of paltusotine.

The key secondary efficacy endpoint for the RC Phase was as follows:

- *Change from Baseline in IGF-1, in units of ULN, to EOR*

Additional secondary efficacy endpoints were:

- *Proportion of participants who achieved IGF-1 <1.3×ULN at EOR*

- Proportion of participants with GH <1 ng/mL at Week 22

- Change from Baseline in Total Acromegaly Symptoms Diary (ASD) score to EOR

Table 17 Estimand for the secondary objectives

Population	Patients with acromegaly (medically naïve, previously treated, or post-washout) who would encounter the intercurrent event of discontinuation, rescue medication, prohibited medication, or dose up-titration after Week 12 if assigned to either paltusotine or placebo.
Treatment conditions	Assignment to paltusotine, regardless of discontinuation and use of rescue medication, compared to assignment to placebo, regardless of discontinuation and use of rescue medication.
Endpoint (variable)	Change from baseline to EOR in IGF-1, expressed in ULN units. EOR defined as average of Weeks 22 and 24, or last available IGF-1 prior to rescue or discontinuation.
Population-level summary	Treatment group difference in ranks based on an ANCOVA (fixed effects for treatment group and baseline IGF-1 level as covariates), with associated 95% confidence interval.
Intercurrent events and strategy to handle them	
Rescue medication use	While-on-treatment: IGF-1 value prior to rescue is used (LOCF).

Statistical methods for estimation and sensitivity analysis on the secondary estimand

The key secondary endpoint was the change from baseline in IGF-1 (×ULN) at EOR, analysed in the FAS using an ANCOVA model with treatment group, prior treatment strata, and baseline IGF-1 as covariates. The EOR value was defined as the average of IGF-1 at Weeks 22 and 24, or the last pre-rescue or available value if data were missing.

A sensitivity analysis was conducted using multiple imputation based on on-treatment intermediate placebo values to handle missing post-baseline data and assessments following rescue therapy.

Exploratory objectives

Exploratory objectives were to evaluate the effect of paltusotine versus placebo on GH level, need for rescue therapy, time to need for rescue treatment, GH response (<2.5 ng/mL), and tumour volume. The pharmacokinetic objective was to evaluate the pharmacokinetic parameters of paltusotine in participants with acromegaly.

Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for the RC Phase were as follows:

- *Change from Baseline to Week 22 in GH*

- *Proportion of participants who receive rescue therapy by EOR*

- *Time from randomization to first dose of rescue treatment*

- *Time to initial response of IGF-1 ≤1.0×ULN*

- *Proportion of participants with GH <2.5 ng/mL at Baseline and Week 22*

- *Change from Baseline in residual pituitary tumour volume at EOR*

- Change from Baseline to EOR in EuroQol-5 Dimensions 5-Level (EQ-5D-5L) health index, Visual Analogue Scale (VAS), and dimension scores

- Change from Baseline to EOR in Patient Global Impression of Severity (PGI-S)

- Patient Global Impression of Improvement (PGI-I) at EOR

- Treatment preference questionnaire at EOR

- Change from Baseline to EOR in Acromegaly Quality of Life (AcroQOL) total score

- Proportion of participants who achieved IGF-1≤1.0×ULN and GH<1.0 ng/mL at EOR

- Proportion of participants who achieved IGF-1≤1.0×ULN and GH<2.5 ng/mL at EOR

- Proportion of participants who achieved IGF-1<1.3×ULN and GH<1.0 ng/mL at EOR

- Proportion of participants who achieved IGF-1<1.3×ULN and GH<2.5 ng/mL at EOR

5.3.2.1.4. Results

Participant flow and numbers analysed

Study start: 17 Dec 2021

Study initiation: 23 Aug 2022 (first participant randomized)

Last Participant Visit: 20 Jan 2024 (RC Phase)

Data Cut-off Date: 20 Jan 2024 (RC Phase)

Interim analysis: 31 August 2025 (OLE Phase)

A total of **111** participants were randomized (**54** participants in the paltusotine group and **57** participants in the placebo group) and included in the **FAS**.

Of the total participants randomized, **52 participants** (96.3%) in the paltusotine group and **54 participants** (94.7%) in the placebo group completed the RC Phase of the study.

In the paltusotine group, **4** of 54 participants (**7.4%**) discontinued study treatment in the RC Phase.

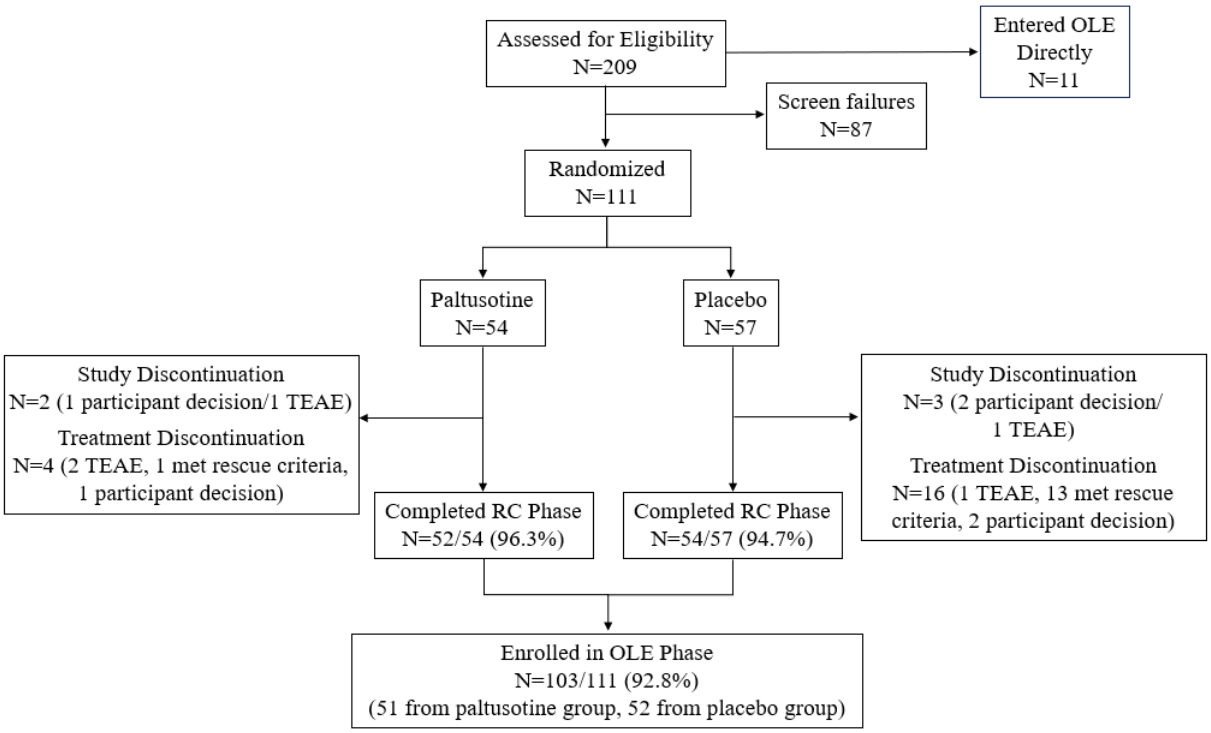
The primary reasons for treatment discontinuation in the paltusotine group were treatment-emergent adverse events (TEAEs) for 2 participants, meeting rescue criteria therapy for 1 participant, and withdrawal of consent for 1 participant.

In the placebo group, **16** of 57 participants (**28.1%**) discontinued study treatment in the RC Phase. The primary reason for treatment discontinuation for most participants (13 of 16) in the placebo group was meeting rescue therapy criteria. Two participants (3.5%) withdrew consent, and 1 participant (1.8%) discontinued treatment due to a TEAE.

All 13 participants in the placebo group who received rescue therapy met the protocol-defined criteria for rescue therapy.

Of the 111 participants randomized in this study, **103** participants (**92.8**%) entered the OLE Phase.

Figure 13 Participant Disposition for RC Phase of Study CRN00808-08



OLE=Open-label Extension, RC=Randomized Controlled, TEAE=treatment-emergent adverse event

Table 18 Participant Enrolment and Disposition in RC Phase of Study CRN00808-08 (All Participants)

	Paltusotine Final Dose					
	20 mg n (%)	40 mg n (%)	60 mg n (%)	Total Paltusotine n (%)	Placebo n (%)	Overall n (%)
Total Participants Screened						209
Screen Failure Set						87
Randomized[1]				54	57	111
Randomized and Not Treated				0	0	0
Direct Enrolled to OLE phase				11		11
Safety Analysis Set	3 (100)	15 (100)	36 (100)	54 (100)	57 (100)	111 (100)
Full Analysis Set	3 (100)	15 (100)	36 (100)	54 (100)	57 (100)	111 (100)
Stratification Factors – per IRT						
Medically Naive Or Previously Treated	2 (66.7)	11 (73.3)	27 (75.0)	40 (74.1)	42 (73.7)	82 (73.9)
Medically Naive	1 (33.3)	3 (20.0)	18 (50.0)	22 (40.7)	24 (42.1)	46 (41.4)
Previously Treated	1 (33.3)	8 (53.3)	9 (25.0)	18 (33.3)	18 (31.6)	36 (32.4)
Washout	1 (33.3)	4 (26.7)	9 (25.0)	14 (25.9)	15 (26.3)	29 (26.1)
Per-Protocol Analysis Set (PPS)	1 (33.3)	15 (100)	36 (100)	52 (96.3)	53 (93.0)	105 (94.6)
Reasons Excluded from PPS						
Randomization/Treatment Error	0	0	0	0	0	0
< 75% Compliance	1 (33.3)	0	0	1 (1.9)	0	1 (0.9)
Major Protocol Deviation (PD)	0	0	0	0	1 (1.8)	1 (0.9)
Did Not Complete the RC phase	2 (66.7)	0	0	2 (3.7)	3 (5.3)	5 (4.5)

	Paltusotine Final Dose					
	20 mg n (%)	40 mg n (%)	60 mg n (%)	Total Paltusotine n (%)	Placebo n (%)	Overall n (%)
Completed RC Phase	1 (33.3)	15 (100)	36 (100)	52 (96.3)	54 (94.7)	106 (95.5)
Treatment Discontinuation in RC Phase	2 (66.7)	1 (6.7)	1 (2.8)	4 (7.4)	16 (28.1)	20 (18.0)
Primary Reason						
Adverse Event	1 (33.3)	1 (6.7)	0	2 (3.7)	1 (1.8)	3 (2.7)
Rescue Therapy Required	0	0	1 (2.8)	1 (1.9)	13 (22.8)	14 (12.6)
Withdrawal By Subject	1 (33.3)	0	0	1 (1.9)	2 (3.5)	3 (2.7)
Study Discontinuation in RC Phase	2 (66.7)	0	0	2 (3.7)	3 (5.3)	5 (4.5)
Primary Reason						
Adverse Event	1 (33.3)	0	0	1 (1.9)	1 (1.8)	2 (1.8)
Withdrawal By Subject	1 (33.3)	0	0	1 (1.9)	2 (3.5)	3 (2.7)
Completed RC and Enrolled in Open Label Extension (OLE) Phase	1 (33.3)	14 (93.3)	36 (100)	51 (94.4)	52 (91.2)	103 (92.8)
Completed Study Treatment in RC Phase	1 (33.3)	14 (93.3)	35 (97.2)	50 (92.6)	40 (70.2)	90 (81.1)
Did not Complete Study Treatment in RC Phase	0	0	1 (2.8)	1 (1.9)	12 (21.1)	13 (11.7)
Completed RC but Not Enrolled in OLE Phase	0	1 (6.7)	0	1 (1.9)	2 (3.5)	3 (2.7)
Reasons						
Subject's Decision	0	1 (6.7)	0	1 (1.9)	2 (3.5)	3 (2.7)

IRT = Interactive Response Technology.
Percentages are calculated based on the number of participants in the Full Analysis Set.

[1] DE007-08001 underwent randomization in the IRT system by mistake before completing the screening procedures and being assessed for study eligibility. After completing the screening period, this participant was assessed as a screening failure and was never dosed. This randomization error is considered a protocol deviation. This participant is categorized under screening failures and is not included in the randomized set.

OLE Phase

A total of **114 participants** enrolled in the OLE Phase of Study CRN00808-08. 51 participants were from the prior paltusotine group; 52 participants were from the prior placebo group.

In addition, **11 participants** directly entered the OLE Phase of the study. These participants were in the washout group at completion of study target enrolment for the RC Phase and had entered screening and met eligibility criteria.

A total of **44 participants** from the medically naïve group in the RC Phase continued in the OLE Phase (**21** in the prior paltusotine group and **23** in the prior placebo group).

A total of **34 participants** from the previously treated group in the RC Phase continued in the OLE Phase (**16** in the prior paltusotine group and **18** in the prior placebo group).

A total of **36 participants** comprised the washout group in the OLE Phase, which consists of 14 participants from the prior paltusotine group, 11 participants from the prior placebo group, and 11 participants who enrolled directly into the OLE Phase.

At the data snapshot date of 31 August 2025, 22 participants overall (**19.3%)** discontinued the OLE Phase of the study.

A summary of participants who discontinued up to the 31 August 2025 data snapshot is provided below:

- 12 participants in the prior paltusotine group discontinued the study, the majority from the medically naïve group and did not demonstrate adequate clinical or biochemical benefit with paltusotine: 9 due to investigator decision, 1 due to withdrawal by subject, 1 due to pregnancy, and 1 due to other [for planned neurosurgery].
- 9 participants in the prior placebo group discontinued the study, the majority from the medically naïve group and did not demonstrate adequate clinical or biochemical benefit with paltusotine due to investigator decision, 2 due to adverse events, and 1 due to "other" [investigator decision]).
- 1 participant in the directly enrolled group discontinued due to prohibited medication.

No important or major protocol deviations were reported during the OLE Phase.

Deviations from study plan

Important protocol deviations were reported for 10 participants (9.0%) in the FAS, most of which pertained to ASD questionnaires not being completed during Screening or prior to Week 24.

Table 19 Summary of Important Protocol Deviations in RC Phase of Study CRN00808-08 (Full Analysis Set)

Protocol Deviation Category	Paltusotine (N=54) n (%) PDs	Placebo (N=57) n (%) PDs	Total (N=111) n (%) PDs
Any Important Protocol Deviations	3 (5.6) 3	7 (12.3) 7	10 (9.0) 10
Study procedures	3 (5.6) 3	4 (7.0) 4	7 (6.3) 7
Biological sample handling	0 (0.0) 0	1 (1.8) 1	1 (0.9) 1
Eligibility Criteria	0 (0.0) 0	2 (3.5) 2	2 (1.8) 2
Any COVID-19 Protocol Deviations	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any Major Protocol Deviations	0 (0.0) 0	1 (1.8) 1	1 (0.9) 1
Eligibility Criteria	0 (0.0) 0	1 (1.8) 1	1 (0.9) 1

Percentages are calculated based on the number of participants in the Full Analysis Set. Participants may have had more than one protocol deviation but are only counted once within each deviation category.

Baseline data

RC PHASE

Baseline characteristics were consistent between treatment groups. The median age for all participants was **46.7 years**, ranging from 18 to 80 years. Most participants were <65 years of age (**91.0%**).

Median BMI was **29.01 kg/m^2**, ranging from 19.0 to 47.9 kg/m^2.

A slightly higher percentage of participants in the paltusotine group were **male** compared with the placebo group (**51.9%** versus **42.1%**).

Table 20 Demographic and Other Baseline Characteristics for RC Phase of Study CRN00808-08 (Full Analysis Set) based on paltusotine final dose

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Sex - n (%)						
Male	2 (66.7)	9 (60.0)	17 (47.2)	28 (51.9)	24 (42.1)	52 (46.8)
Female	1 (33.3)	6 (40.0)	19 (52.8)	26 (48.1)	33 (57.9)	59 (53.2)
Age at Informed Consent (years)						
n	3	15	36	54	57	111
Mean	48.0	55.1	44.4	47.5	45.9	46.7
SD, SE	21.28, 12.29	13.20, 3.41	12.22, 2.04	13.59, 1.85	12.30, 1.63	12.91, 1.23
Median	44.0	56.0	45.5	46.5	45.0	46.0
Min, Max	29, 71	32, 80	18, 67	18, 80	23, 75	18, 80
Age Group - n (%)						
< 65 years	2 (66.7)	11 (73.3)	34 (94.4)	47 (87.0)	54 (94.7)	101 (91.0)
>=65 years	1 (33.3)	4 (26.7)	2 (5.6)	7 (13.0)	3 (5.3)	10 (9.0)
65 to <=74 years	1 (33.3)	3 (20.0)	2 (5.6)	6 (11.1)	2 (3.5)	8 (7.2)
>74 to <=84 years	0	1 (6.7)	0	1 (1.9)	1 (1.8)	2 (1.8)
> 84 years	0	0	0	0	0	0
Geographic Region - n (%)						
United States (US)	0	2 (13.3)	4 (11.1)	6 (11.1)	3 (5.3)	9 (8.1)
Non-US	3 (100)	13 (86.7)	32 (88.9)	48 (88.9)	54 (94.7)	102 (91.9)
Europe	1 (33.3)	7 (46.7)	6 (16.7)	14 (25.9)	17 (29.8)	31 (27.9)
Rest of the World	2 (66.7)	6 (40.0)	26 (72.2)	34 (63.0)	37 (64.9)	71 (64.0)
India	1 (33.3)	0	6 (16.7)	7 (13.0)	4 (7.0)	11 (9.9)
China	0	0	8 (22.2)	8 (14.8)	15 (26.3)	23 (20.7)
Others	1 (33.3)	6 (40.0)	12 (33.3)	19 (35.2)	18 (31.6)	37 (33.3)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Ethnicity - n (%)						
Hispanic or Latino	1 (33.3)	5 (33.3)	12 (33.3)	18 (33.3)	18 (31.6)	36 (32.4)
Not Hispanic or Latino	2 (66.7)	9 (60.0)	20 (55.6)	31 (57.4)	36 (63.2)	67 (60.4)
Not Reported	0	0	0	0	1 (1.8)	1 (0.9)
Unknown	0	1 (6.7)	4 (11.1)	5 (9.3)	2 (3.5)	7 (6.3)
Race - n (%)						
White	2 (66.7)	12 (80.0)	14 (38.9)	28 (51.9)	30 (52.6)	58 (52.3)
All Other Races	1 (33.3)	2 (13.3)	20 (55.6)	23 (42.6)	24 (42.1)	47 (42.3)
Asian	1 (33.3)	0	14 (38.9)	15 (27.8)	19 (33.3)	34 (30.6)
Black or African American	0	0	2 (5.6)	2 (3.7)	1 (1.8)	3 (2.7)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Multiple/Other	0	2 (13.3)	4 (11.1)	6 (11.1)	4 (7.0)	10 (9.0)
Unknown	0	1 (6.7)	2 (5.6)	3 (5.6)	3 (5.3)	6 (5.4)
Height (cm)						
n	3	15	36	54	57	111
Mean	172.00	172.35	168.96	170.07	169.30	169.68
SD, SE	14.933, 8.622	14.070, 3.633	11.046, 1.841	11.991, 1.632	12.284, 1.627	12.093, 1.148
Median	166.00	175.00	168.50	169.70	167.00	168.00
Min, Max	161.0, 189.0	150.0, 192.0	142.7, 198.8	142.7, 198.8	149.0, 200.0	142.7, 200.0
Weight (kg)						
n	3	15	36	54	57	111
Mean	80.23	89.87	85.04	86.12	82.36	84.19
SD, SE	29.456, 17.007	18.140, 4.684	20.259, 3.377	19.936, 2.713	18.671, 2.473	19.301, 1.832
Median	71.00	92.00	82.34	83.80	76.50	82.30
Min, Max	56.5, 113.2	56.0, 116.5	57.0, 138.1	56.0, 138.1	56.5, 141.7	56.0, 141.7

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
BMI (kg/m^2)						
n	3	15	36	54	57	111
Mean	26.42	30.01	29.74	29.63	28.66	29.13
SD, SE	4.979, 2.874	3.474, 0.897	6.081, 1.013	5.402, 0.735	5.230, 0.693	5.312, 0.504
Median	25.77	29.92	29.18	29.36	28.76	29.01
Min, Max	21.8, 31.7	24.6, 35.2	19.0, 47.9	19.0, 47.9	19.3, 45.7	19.0, 47.9
BMI Groups - n (%)						
< 30 kg/m^2	2 (66.7)	8 (53.3)	22 (61.1)	32 (59.3)	34 (59.6)	66 (59.5)
>= 30 kg/m^2	1 (33.3)	7 (46.7)	14 (38.9)	22 (40.7)	23 (40.4)	45 (40.5)
US Ring Size						
n	3	15	36	54	57	111
Mean	10.50	11.80	11.10	11.26	11.16	11.21
SD, SE	2.500, 1.443	2.569, 0.663	2.888, 0.481	2.760, 0.376	3.362, 0.445	3.071, 0.291
Median	10.50	12.00	11.75	11.75	11.00	11.00
Min, Max	8.0, 13.0	8.0, 17.0	5.5, 16.0	5.5, 17.0	3.5, 17.0	3.5, 17.0
Hemoglobin Alc(%)(HbAlc)						
n	3	15	36	54	57	111
Mean	5.87	5.77	5.59	5.66	5.59	5.62
SD, SE	0.473, 0.273	0.647, 0.167	0.498, 0.083	0.540, 0.074	0.526, 0.070	0.532, 0.050
Median	5.70	5.90	5.55	5.65	5.50	5.50
Min, Max	5.5, 6.4	4.9, 7.4	4.7, 7.1	4.7, 7.4	4.9, 7.2	4.7, 7.4

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
HbAlc Groups - n (%)						
< 6.5%	3 (100)	14 (93.3)	34 (94.4)	51 (94.4)	52 (91.2)	103 (92.8)
>= 6.5%	0	1 (6.7)	2 (5.6)	3 (5.6)	5 (8.8)	8 (7.2)
Screening IGF-1xULN						
n	3	15	36	54	57	111
Mean	1.523	1.487	2.233	1.987	2.173	2.083
SD, SE	0.2732, 0.1577	0.2544, 0.0657	0.8863, 0.1477	0.8141, 0.1108	1.1164, 0.1479	0.9811, 0.0931
Median	1.600	1.370	2.015	1.750	1.870	1.780
Min, Max	1.22, 1.75	1.16, 1.97	1.06, 4.99	1.06, 4.99	0.88, 7.24	0.88, 7.24
<= 1.0xULN	0	0	0	0	1 (1.8)[a]	1 (0.9)
> 1.0xULN to <= 1.3xULN	1 (33.3)	3 (20.0)	5 (13.9)	9 (16.7)	8 (14.0)	17 (15.3)
> 1.3xULN	2 (66.7)	12 (80.0)	31 (86.1)	45 (83.3)	48 (84.2)	93 (83.8)
UGT1A1 Genotype - n (%)						
*1/*1	1 (33.3)	6 (40.0)	15 (41.7)	22 (40.7)	24 (42.1)	46 (41.4)
*1/*6	0	0	4 (11.1)	4 (7.4)	1 (1.8)	5 (4.5)
*1/*28	0	5 (33.3)	7 (19.4)	12 (22.2)	10 (17.5)	22 (19.8)
*1/*80	0	3 (20.0)	1 (2.8)	4 (7.4)	4 (7.0)	8 (7.2)
*28/*28	0	0	1 (2.8)	1 (1.9)	1 (1.8)	2 (1.8)
*80/*80	1 (33.3)	1 (6.7)	1 (2.8)	3 (5.6)	5 (8.8)	8 (7.2)
*1/*28 and *1/*6	0	0	1 (2.8)	1 (1.9)	0	1 (0.9)
Missing	1 (33.3)	0	6 (16.7)	7 (13.0)	12 (21.1)	19 (17.1)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Stratification Factors per EDC- n (%)						
Medically Naïve or Previously Treated	2 (66.7)	11 (73.3)	27 (75.0)	40 (74.1)	41 (71.9)	81 (73.0)
Washout	1 (33.3)	4 (26.7)	9 (25.0)	14 (25.9)	16 (28.1)	30 (27.0)
Stratification Factors per IRT- n (%)						
Medically Naïve or Previously Treated	2 (66.7)	11 (73.3)	27 (75.0)	40 (74.1)	42 (73.7)	82 (73.9)
Medically Naïve	1 (33.3)	3 (20.0)	18 (50.0)	22 (40.7)	24 (42.1)	46 (41.4)
Previously Treated	1 (33.3)	8 (53.3)	9 (25.0)	18 (33.3)	18 (31.6)	36 (32.4)
Washout	1 (33.3)	4 (26.7)	9 (25.0)	14 (25.9)	15 (26.3)	29 (26.1)
Use of H2 Blockers - n (%)						
Yes	0	1 (6.7)	1 (2.8)	2 (3.7)	1 (1.8)	3 (2.7)
No	3 (100)	14 (93.3)	35 (97.2)	52 (96.3)	56 (98.2)	108 (97.3)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)

IRT = Interactive Response Technology. Percentages are calculated based on the number of participants in the Full Analysis Set. a=Subject US031-08001 is in strata of washout, but was mistakenly randomized in strata of Medically naïve or Previously treated in IRT. The Screening 1 IGF-1 was 0.88 x ULN and the Screening 2 IGF-1 was 1.16 x ULN.

Disease Characteristics

Disease characteristics were generally consistent between the paltusotine and placebo groups. Most participants had a screening IGF-1 >1.3×ULN (**83.8%**).

Baseline mean (SD) IGF-1×ULN levels (**1.985** [0.8086] and **2.207** [1.1049] in the paltusotine and placebo groups respectively.

Although Baseline mean (SD) GH (ng/mL) levels were different between the paltusotine and placebo groups (**3.026** [2.9035] and **9.448** [24.1484]), Baseline median values were similar between the paltusotine and placebo groups (**2.138** versus **2.300**).

Study participants overall had a long-standing disease history, with a median of **72.2 months**, ranging from 5 to 388 months. However, participants in the paltusotine group had a longer median time since diagnosis (**77.5 months** versus **51.3 months**), and a longer median time since pituitary surgery (**66.5 months** versus **22.0 months**).

The majority of participants (**89.2%**) had documented prior pituitary surgery; **all participants** in the medically naïve group had documented prior pituitary surgery.

In the majority of participants, pituitary tumours prior to first surgery were macroadenomas (>10 mm), with **72%** in the paltusotine group and **83%** in the placebo group meeting this criterion.

Five participants (2 paltusotine and 3 placebo) received prior radiotherapy; the mean time from radiotherapy was **21.8 years** in the paltusotine group and **10.8 years** in the placebo group.

Table 21 Baseline Acromegaly Disease Characteristics for RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Duration (months) since acromegaly diagnosis						
n	3	15	36	54	57	111
Mean	120.6	153.4	72.8	97.9	77.1	87.2
SD, SE	75.56, 43.62	114.21, 29.49	79.46, 13.24	95.69, 13.02	69.37, 9.19	83.49, 7.92
Median	136.5	130.6	28.8	77.5	51.3	72.2
Min, Max	38, 187	14, 388	5, 299	5, 388	6, 309	5, 388
Duration since acromegaly diagnosis groups - n (%)						
< 1 year	0	0	8 (22.2)	8 (14.8)	8 (14.0)	16 (14.4)
>= 1 to < 5 years	1 (33.3)	4 (26.7)	12 (33.3)	17 (31.5)	22 (38.6)	39 (35.1)
>= 5 years	2 (66.7)	11 (73.3)	16 (44.4)	29 (53.7)	27 (47.4)	56 (50.5)
Acromegaly diagnosis based on testing - n (%)						

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Elevated IGF-1 prior to pituitary surgery	3 (100)	10 (66.7)	26 (72.2)	39 (72.2)	41 (71.9)	80 (72.1)
Confirmed pituitary tumor	3 (100)	13 (86.7)	35 (97.2)	51 (94.4)	54 (94.7)	105 (94.6)
Growth Hormone level after oral glucose load	1 (33.3)	4 (26.7)	13 (36.1)	18 (33.3)	16 (28.1)	34 (30.6)
Other	0	3 (20.0)	5 (13.9)	8 (14.8)	4 (7.0)	12 (10.8)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
IGF-1xULN prior to pituitary surgery[a]						
n	3	9	24	36	38	74
Mean	24.343	9.435	27.868	22.966	53.497	38.644
SD, SE	38.5135, 22.2358	16.4721, 5.4907	84.7614, 17.3019	70.2263, 11.7044	107.6791, 17.4679	92.0728, 10.7032
Median	3.086	4.275	3.301	3.640	3.167	3.540
Min, Max	1.14, 68.80	1.80, 53.26	1.16, 334.98	1.14, 334.98	1.33, 297.52	1.14, 334.98
IGF-1xULN prior to pituitary surgery - n (%)						
>= 2.0xULN	2 (66.7)	8 (53.3)	18 (50.0)	28 (51.9)	29 (50.9)	57 (51.4)
>=1.3xULN to < 2.0xULN	0	1 (6.7)	5 (13.9)	6 (11.1)	9 (15.8)	15 (13.5)
>=1.0xULN to < 1.3xULN	1 (33.3)	0	1 (2.8)	2 (3.7)	0	2 (1.8)
Missing	0	6 (40.0)	12 (33.3)	18 (33.3)	19 (33.3)	37 (33.3)
IGF-1 assay platform prior to pituitary surgery - n (%)						
IDS iSYS	0	0	1 (2.8)	1 (1.9)	0	1 (0.9)
DiaSorin Liaison XL	0	0	1 (2.8)	1 (1.9)	3 (5.3)	4 (3.6)
Siemens IMMULITE 2000	0	3 (20.0)	7 (19.4)	10 (18.5)	11 (19.3)	21 (18.9)
Roche COBAS	0	0	3 (8.3)	3 (5.6)	0	3 (2.7)
Cisbio IGF1-RIACT	1 (33.3)	0	0	1 (1.9)	1 (1.8)	2 (1.8)
Other	2 (66.7)	4 (26.7)	11 (30.6)	17 (31.5)	24 (42.1)	41 (36.9)
Missing	0	8 (53.3)	13 (36.1)	21 (38.9)	18 (31.6)	39 (35.1)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Tumor size (mm) prior to first pituitary surgery						
n	3	12	30	45	50	95
Mean	18.57	18.79	19.40	19.18	21.58	20.45
SD, SE	6.493, 3.749	6.013, 1.736	10.154, 1.854	8.889, 1.325	8.841, 1.250	8.899, 0.913
Median	15.70	18.00	17.00	17.00	20.00	19.00
Min, Max	14.0, 26.0	8.5, 30.0	2.5, 40.0	2.5, 40.0	2.2, 47.0	2.2, 47.0
Tumor size (mm) prior to first pituitary surgery - n (%)						
<=10 (microadenoma)	0	1 (6.7)	5 (13.9)	6 (11.1)	3 (5.3)	9 (8.1)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
> 10 (macroadenoma)	3 (100)	11 (73.3)	25 (69.4)	39 (72.2)	47 (82.5)	86 (77.5)
Tumor confirmed with - n (%)						
MRI	3 (100)	12 (80.0)	30 (83.3)	45 (83.3)	49 (86.0)	94 (84.7)
CT Scan	0	2 (13.3)	2 (5.6)	4 (7.4)	7 (12.3)	11 (9.9)
Surgical Pathology	1 (33.3)	7 (46.7)	13 (36.1)	21 (38.9)	24 (42.1)	45 (40.5)
Other	0	1 (6.7)	0	1 (1.9)	0	1 (0.9)
Pituitary surgery performed - n (%)						
Yes	3 (100)	13 (86.7)	34 (94.4)	50 (92.6)	49 (86.0)	99 (89.2)
No	0	0	1 (2.8)	1 (1.9)	5 (8.8)	6 (5.4)
Missing	0	2 (13.3)	1 (2.8)	3 (5.6)	3 (5.3)	6 (5.4)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Duration (months) since pituitary surgery						
n	3	13	34	50	49	99
Mean	117.1	128.8	69.8	88.0	61.9	75.1
SD, SE	74.54, 43.04	97.97, 27.17	82.01, 14.07	88.50, 12.52	70.99, 10.14	80.96, 8.14
Median	128.6	76.9	25.8	66.5	22.0	41.7
Min, Max	37, 185	11, 299	4, 297	4, 299	3, 309	3, 309
Radiotherapy treated - n (%)						
Yes	0	1 (6.7)	1 (2.8)	2 (3.7)	3 (5.3)	5 (4.5)
Years after radiotherapy						
n	0	1	1	2	3	5
Mean		32.000	11.581	21.791	10.815	15.205
SD, SE		NE, NE	NE, NE	14.4383, 10.2094	3.2229, 1.8607	9.6670, 4.3232
Median		32.000	11.581	21.791	10.979	11.581
Min, Max		32.00, 32.00	11.58, 11.58	11.58, 32.00	7.51, 13.95	7.51, 32.00

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Tumor size (mm) prior to first pituitary surgery						
n	3	12	30	45	50	95
Mean	18.57	18.79	19.40	19.18	21.58	20.45
SD, SE	6.493, 3.749	6.013, 1.736	10.154, 1.854	8.889, 1.325	8.841, 1.250	8.899, 0.913
Median	15.70	18.00	17.00	17.00	20.00	19.00
Min, Max	14.0, 26.0	8.5, 30.0	2.5, 40.0	2.5, 40.0	2.2, 47.0	2.2, 47.0
Tumor size (mm) prior to first pituitary surgery - n (%)						
<=10 (microadenoma)	0	1 (6.7)	5 (13.9)	6 (11.1)	3 (5.3)	9 (8.1)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
> 10 (macroadenoma)	3 (100)	11 (73.3)	25 (69.4)	39 (72.2)	47 (82.5)	86 (77.5)
Tumor confirmed with - n (%)						
MRI	3 (100)	12 (80.0)	30 (83.3)	45 (83.3)	49 (86.0)	94 (84.7)
CT Scan	0	2 (13.3)	2 (5.6)	4 (7.4)	7 (12.3)	11 (9.9)
Surgical Pathology	1 (33.3)	7 (46.7)	13 (36.1)	21 (38.9)	24 (42.1)	45 (40.5)
Other	0	1 (6.7)	0	1 (1.9)	0	1 (0.9)
Pituitary surgery performed - n (%)						
Yes	3 (100)	13 (86.7)	34 (94.4)	50 (92.6)	49 (86.0)	99 (89.2)
No	0	0	1 (2.8)	1 (1.9)	5 (8.8)	6 (5.4)

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
GH (ng/mL) after oral glucose load[a]						
n	1	4	13	18	16	34
Mean	23.880	35.225	50.148	45.373	11.313	29.345
SD, SE	NE, NE	49.2779, 24.6389	124.4514, 34.5166	106.9120, 25.1994	12.9418, 3.2354	79.1339, 13.5714
Median	23.880	15.350	13.600	14.000	4.015	8.455
Min, Max	23.88, 23.88	2.20, 108.00	0.44, 461.00	0.44, 461.00	1.20, 40.00	0.44, 461.00
> 1.0 ng/mL	1 (33.3)	4 (26.7)	12 (33.3)	17 (31.5)	16 (28.1)	33 (29.7)
> 2.5 ng/mL	1 (33.3)	3 (20.0)	11 (30.6)	15 (27.8)	12 (21.1)	27 (24.3)
IGF-1xULN most recent prior to screening						
n	3	14	36	53	56	109
Mean	3.349	1.171	12.406	8.926	21.120	15.191
SD, SE	4.3732, 2.5249	0.3590, 0.0960	43.6856, 7.2809	36.2168, 4.9748	62.4035, 8.3390	51.4994, 4.9327
Median	1.443	1.340	1.763	1.506	1.637	1.609
Min, Max	0.25, 8.35	0.56, 1.64	0.40, 207.14	0.25, 207.14	0.26, 260.77	0.25, 260.77
Duration (days) since most recent IGF-1 prior to screening						
n	3	15	36	54	56	110
Mean	37.0	91.0	61.9	68.6	147.7	108.9
SD, SE	38.97, 22.50	120.85, 31.20	93.46, 15.58	99.56, 13.55	371.46, 49.64	275.72, 26.29
Median	30.0	42.0	30.0	34.0	50.0	42.0
Min, Max	2, 79	1, 477	-117, 363	-117, 477	-78, 2197	-117, 2197

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Baseline IGF-1xULN						
n	3	15	36	54	57	111
Mean	1.481	1.523	2.220	1.985	2.207	2.099
SD, SE	0.4607, 0.2660	0.2464, 0.0636	0.8852, 0.1475	0.8086, 0.1100	1.1049, 0.1463	0.9741, 0.0925

	Paltusotine Final Dose					
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)	Overall (N=111)
Median	1.332	1.500	1.990	1.768	1.895	1.837
Min, Max	1.11, 2.00	1.21, 1.94	1.13, 4.84	1.11, 4.84	1.08[b],7.07	1.08, 7.07
Baseline GH(ng/mL)						
n	3	15	36	54	57	111
Mean	3.831	1.195	3.721	3.026	9.448	6.323
SD, SE	2.3835, 1.3761	0.7034, 0.1816	3.2021, 0.5337	2.9035, 0.3951	24.1484, 3.1985	17.6446, 1.6748
Median	2.516	1.162	2.675	2.138	2.300	2.294
Min, Max	2.39, 6.58	0.28, 2.78	0.27, 15.40	0.27, 15.40	0.09, 168.02	0.09, 168.02

a=Data were collected retrospectively; IGF-1 and GH levels were assessed locally at each site, with various IGF-1 and GH assays and different reference ranges
b= US031-08001 had baseline IGF1 = 1.08 (average of Screening 2 [1.16] and Day 1 predose [1.01]). This participant is in strata of washout, but was mistakenly randomized in strata of Medically naïve or Previously treated in IRT.
Percentages are calculated based on the number of participants in the Full Analysis Set. Baseline IGF-1 value is defined as the average of the measurements taken on Day 1 on or prior to first dose of study drug and the last IGF-1 value measured just prior to this day. Baseline GH is defined as the average from the fasting integrated GH samples at Screening Visit.

Medical history

No medical history conditions were reported at a higher incidence (a difference of at least 10%) in the paltusotine group than in the placebo group, either on a SOC or PT basis.

Rescue Therapy

A total of **15 participants** (**2 in the paltusotine group** and **13 in the placebo group**) received pituitary and hypothalamic hormones and analogues as rescue medications, including octreotide and lanreotide.

In the paltusotine group, **1 participant** received octreotide as rescue therapy during the RC Phase of the study. This participant completed the RC Phase and continued to the OLE Phase of the study. The other participant received lanreotide as rescue therapy **after discontinuing paltusotine** treatment due to an adverse event; this participant completed the RC phase but declined entering the OLE Phase of the study. All 13 participants in the placebo group (**22.8%**) received somatostatin analogues (octreotide or lanreotide) as rescue therapy during the RC Phase.

Extent of Exposure

RC PHASE

Of the **54 participants** randomized in the paltusotine group, **3** participants (**5.6%**) received paltusotine 20 mg QD, **15** participants (**27.8%**) received paltusotine 40 mg QD, and **36** participants (**66.7%**) received paltusotine 60 mg QD as their final dose.

A total of **22 medically naïve participants** were randomized to paltusotine in the RC Phase of the study and completed 24 weeks of treatment; **14%** were receiving paltusotine 40 mg QD and **86%** were receiving paltusotine 60 mg QD at the end of the RC Phase.

A total of **18 previously treated participants** were randomized to paltusotine in the RC and completed the 24 weeks of treatment, 1 (**5.5%**) received 20 mg, 8 (**44.4%**) received 40 mg and 9 (**50%**) received 60 mg. at the end of RC phase

A total of **14 Washout participants** were randomized in the RC phase and completed the 24 weeks of treatment, 1 (**7.14**%) received 20 mg, 4 (**28.57**%) received 40 mg and 9 (**64.28**%) received 60 mg at the end of the RC phase.

In the paltusotine group, **3 participants** had dose reductions to paltusotine 20 mg QD due to TEAEs during the RC Phase.

OLE Phase

Of the **113 participants** in the total OLE population (included in the OLE Safety Analysis Set), **50 participants received paltusotine** and **52 participants received placebo in the RC Phase. 11 washout participants** entered the OLE Phase directly.

At the data snapshot date of 31 August 2025, the median duration (range) of exposure to paltusotine in the OLE Phase was **94.9 weeks** (0.71 to 128.6 weeks) for the total population (**94.0 weeks** [11.6 to 128.6 weeks] for the prior paltusotine group, **93.9 weeks** [3.6 to 124.6 weeks] for the prior placebo group, and **99.6 weeks** [0.71 to 105.6] for the directly enrolled group).

- Medically naïve group:

A total of **46 medically naïve participants** were treated with paltusotine (n=22) or placebo (n=24) in the Randomized Controlled (RC) Phase of Study CNR00808-08;

44 participants (21 in the prior paltusotine group and 23 in the prior placebo group) continued treatment in the Open-label Extension (OLE) Phase.

- During the OLE Phase (data snapshot 21 May 2025),

After starting at paltusotine 20 mg QD at Week 24, the majority of participants in the prior paltusotine group (81.0%, 17 of 21) and the prior placebo group (61.1%, 11 of 18) up-titrated to paltusotine 60 mg QD by Week 48. The majority of participants continued to receive paltusotine 60 mg QD at subsequent timepoints in the OLE Phase.

- Previously treated group

36 participants previously treated were randomized in the RC (18 in the paltusotine group and 18 in the placebo group);

- During the OLE Phase (data snapshot 21 May 2025),

After starting at paltusotine 20 mg QD at Week 24, the majority of participants (**66.7%,** 10 of 15) in the prior paltusotine group up-titrated to paltusotine 40 mg QD by Week 36. The majority of participants continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE Phase. One participant was on paltusotine 20 mg QD at Week 96.

In the prior placebo group, after starting at paltusotine 20 mg QD at Week 24, the majority of participants (58.8%, 10 of 17) up-titrated to 60 mg QD by Week 60. The majority of participants in the prior placebo group continued to receive paltusotine 60 mg QD at subsequent timepoints in the OLE Phase. Two participants in the prior placebo group were receiving paltusotine 20 mg QD at Week 108 and 1 participant at Week 120.

- Washout group

29 washout participants were randomized in the RC (14 in the paltusotine group and 15 in the placebo group).

- During the OLE Phase (data snapshot 21 May 2025),

After starting at paltusotine 20 mg QD at Week 24, the majority of participants (84.6%, 11 of 13) in the prior paltusotine group up titrated to paltusotine 40 mg QD by Week 36. The majority of participants in the prior paltusotine group continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE Phase. One participant in the prior paltusotine group was on paltusotine 20 mg QD at Week 96.

In the prior placebo group, after starting at paltusotine 20 mg QD at Week 24, the majority of participants (90.9%, 10 of 11) up-titrated to 40 mg QD by Week 36. The majority of participants in the prior placebo group continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE Phase.

Outcomes and estimation

Primary Endpoint – RC Phase

Study **CRN00808-08** met statistical significance on the primary endpoint (**p<0.0001**) favouring paltusotine over placebo.

Table 29 presents results for the primary efficacy endpoint of the proportion of participants who achieved a biochemical response in IGF-1 (≤1.0×ULN) at EOR.

The proportion of participants who achieved IGF-1 level ≤1.0×ULN was **55.6%** (30 of 54) in the paltusotine group compared with **5.3%** (3 of 57) in the placebo group, providing evidence of significant efficacy.

At EOR, **3 patients (5.6%)** were treated with **paltusotine 20 mg**, **15 (27.7%) patients** were treated with **paltusotine 40 mg** and **36 patients (66.7%)** were treated with **paltusotine 60 mg**.

Among these patients, 1/3 (**33.3%**) treated with paltusotine 20 mg, 13/15 (**86.7%**) treated with paltusotine 40 mg and 16/36 (**44.4%)** treated with paltusotine 60 mg were responders.

Table 22 Primary Efficacy Analysis: IGF-1⩽1.0×ULN at EOR in RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine Final Dose				
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)
IGF-1 <= 1.0xULN at EOR - n (%)					
Responder	1 (33.3)	13 (86.7)	16 (44.4)	30 (55.6)	3 (5.3)
Non-Responder	2 (66.7)	2 (13.3)	20 (55.6)	24 (44.4)	54 (94.7)
IGF-1 > 1.0xULN	0	2 (13.3)	20 (55.6)	22 (40.7)	46 (80.7)
Missing IGF-1 at Week 22 and Week 24	2 (66.7)	0	0	2 (3.7)	3 (5.3)
Prohibited acromegaly medication	0	0	0	0	0
Rescue medication	0	1 (6.7)	1 (2.8)	2 (3.7)	13 (22.8)
Dose up-titration after Week 12	0	0	1 (2.8)	1 (1.9)	0
Discontinuation of treatment	2 (66.7)	1 (6.7)	1 (2.8)	4 (7.4)	16 (28.1)
Odds ratio (Paltusotine/Placebo)				42.806	
95% CI for odds ratio				(8.444, 455.821)	

	Paltusotine Final Dose				
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)
P-value				<0.0001	

CI=confidence interval; EOR = end of randomized controlled phase; IGF-1=insulin-like growth factor-1; IRT = Interactive Response Technology, ULN= upper limit of normal.

IGF-1 at EOR is based on the average of the last 2 measurements of IGF-1 collected at Weeks 22 and 24. When one of the two last IGF-1 measurements is missing a single value is used. ULN is determined based on the participant's age and sex.

Percentages are calculated based on the number of participants in the Full Analysis Set. P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT (medically naïve or previously treated versus washout). For the odds ratio, placebo participants are the reference group.

Key Secondary Efficacy Endpoint – RC Phase

Change from Baseline to EOR in IGF-1×ULN

The LS mean (±SE) changes from Baseline to EOT in IGF-1×ULN were **-0.819** (±0.0789) for the paltusotine group and **0.087** (±0.0751) for the placebo group, with a treatment difference of **-0.906** (95% CI: -1.106, -0.706). This difference was statistically significant (**p<0.0001**).

Table 23 Secondary Efficacy Endpoint: Change from Baseline to EOT in IGF-1 (×ULN) in RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine (N=54)	Placebo (N=57)	Treatment Difference (95% CI)	P-value
IGF-1xULN Change from Baseline to EOT – Primary Analysis				
LS Mean	-0.819	0.087	-0.906 (-1.106, -0.706)	<0.0001
LS Standard Error	0.0789	0.0751		
IGF-1xULN Change from Baseline to EOT – Multiple Imputation - Control-based Pattern Imputation				
LS Mean	-0.827	0.124	-0.950 (-1.166, -0.735)	<0.0001
LS Standard Error	0.0823	0.0855		

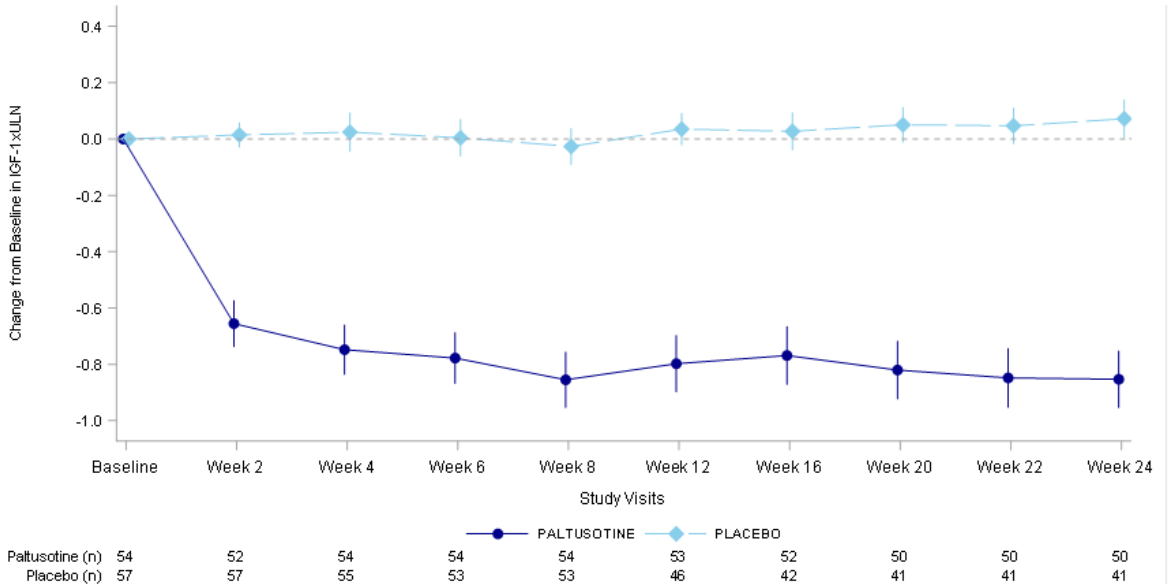
CI=confidence interval; EOT = the average of week 22 and week 24 if no rescue therapy, otherwise EOT= last assessment prior to rescue therapy; IGF-1=insulin-like growth factor-1; IRT = Interactive Response Technology, LS= least squares; ULN= upper limit of normal.

Baseline IGF-1 is the average of the measurements taken on Day 1 on or prior to first dose of study drug and the last IGF-1 value measured just prior to this day. Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, prior treatment strata per IRT (medically naïve or previously treated versus washout) as fixed effects, baseline IGF-1xULN as a covariate.

Figure 14 shows the mean IGF-1×ULN (±SE) change from Baseline in IGF-1×ULN levels by visit in the RC Phase of the study for all participants without or prior to rescue at each visit by treatment group. IGF-1 values after rescue use were excluded.

In the paltusotine group, mean IGF-1 levels rapidly decreased by Week 2 and remained stable from Week 4 to Week 24, whereas in the placebo group, mean IGF-1 levels remained at Baseline levels through Week 8 and slightly decreased through Week 24, by which time 13 participants had received rescue therapy.

Figure 14 Mean (±SE) IGF-1xULN Change from Baseline by Visit in Randomized Controlled (RC) Phase of Study CRN00808-08 (Full Analysis Set) Participants Without/Prior to Rescue

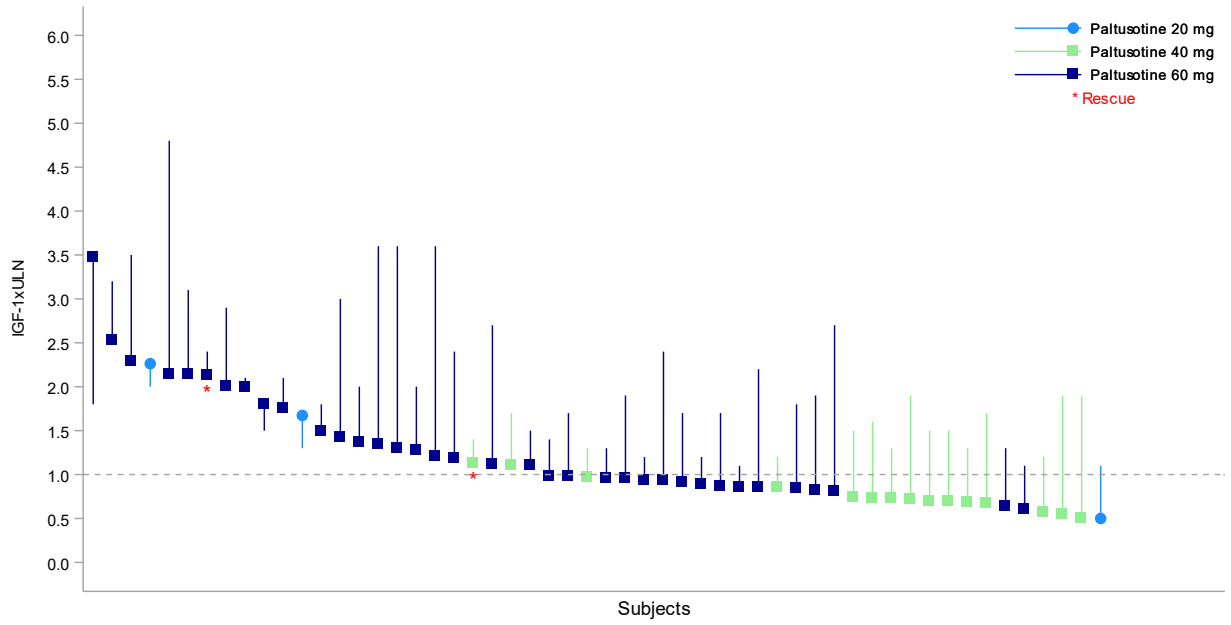


IGF-1=insulin-like growth factor-1; SE= standard error; ULN= upper limit of normal.
Pre-dose values are presented in the graph, except for Week 16 - post dose and Week 24 – anytime.

The majority of participants in the paltusotine group demonstrated reductions in IGF-1 level from Baseline that occurred rapidly between baseline and week 2 and continued, whereas those in the placebo group showed little change or increases from Baseline.

Approximately half of individual participants in the paltusotine group achieved IGF-1 levels ≤1.0×ULN compared to only a few participants in the placebo group, which is consistent with the proportion of participants who achieved IGF-1 levels ≤1.0×ULN for the primary endpoint.

Figure 15 IGF-1xULN from Baseline to EOT by Participant in the Paltusotine Group in RC Phase of Study CRN00808-08 (Full Analysis Set)



EOT = the average of Week 22 and Week 24 if no rescue therapy, otherwise EOT = last assessment prior to rescue therapy; IGF-1=insulin-like growth factor-1; RC= Randomized Controlled; ULN= upper limit of normal.

Other Secondary Efficacy Endpoints – RC Phase

1) Proportion of Participants with IGF-1 <1.3×ULN at EOR

The proportion of participants who achieved IGF-1 level <1.3×ULN was **66.7%** (36 of 54) in the paltusotine group compared with **14.0%** (8 of 57) in the placebo group. This difference was statistically significant (**p<0.0001**).

Table 24 Secondary Efficacy Endpoint: Proportion of Participants with IGF-1<1.3×ULN at EOR in RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine Final Dose				
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)
IGF-1 < 1.3xULN at EOR - n (%)					
Responder	1 (33.3)	14 (93.3)	21 (58.3)	36 (66.7)	8 (14.0)
Non-Responder	2 (66.7)	1 (6.7)	15 (41.7)	18 (33.3)	49 (86.0)
IGF-1 >= 1.3xULN	0	1 (6.7)	15 (41.7)	16 (29.6)	39 (68.4)
Missing IGF-1 at Week 22 and Week 24	2 (66.7)	0	0	2 (3.7)	3 (5.3)
Prohibited acromegaly medication	0	0	0	0	0
Rescue medication	0	1 (6.7)	1 (2.8)	2 (3.7)	13 (22.8)
Dose up-titration after Week 12	0	0	1 (2.8)	1 (1.9)	0
Discontinuation of treatment	2 (66.7)	1 (6.7)	1 (2.8)	4 (7.4)	16 (28.1)
Odds ratio (Paltusotine/Placebo)				18.319	
95% CI for odds ratio				(5.637, 79.156)	
P-value				<0.0001	

IGF-1=insulin-like growth factor-1, EOR = end of randomized controlled phase, IRT = Interactive Response Technology, RC=randomized controlled, ULN=upper limit of normal.

IGF-1 at EOR is based on the average of the last 2 measurements of IGF-1 collected at Weeks 22 and 24. When one of the two last IGF-1 measurements is missing a single value is used. Percentages are calculated based on the number of participants in the Full Analysis Set. P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT (medically naïve or previously treated versus washout). For the odds ratio, placebo participants are the reference group.

2) Proportion of Participants with GH<1.0 ng/mL at Week 22

The proportion of participants who achieved GH level <1.0 ng/mL at Week 22 (EOR) was **57.4%** (31 of 54) in the paltusotine group compared with **17.5%** (10 of 57) in the placebo group. This difference was statistically significant (**p<0.0001**).

Table 25 Secondary Efficacy Endpoint: Proportion of Participants with GH<1.0 ng/mL at Week 22 (EOR) in RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine Final Dose				
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)
GH < 1.0 ng/mL at Week 22 - n (%)					
Responder	1 (33.3)	13 (86.7)	17 (47.2)	31 (57.4)	10 (17.5)

	Paltusotine Final Dose				
	20 mg (N=3)	40 mg (N=15)	60 mg (N=36)	Total Paltusotine (N=54)	Placebo (N=57)
Non-Responder	2 (66.7)	2 (13.3)	19 (52.8)	23 (42.6)	47 (82.5)
GH >= 1.0 ng/mL	0	1 (6.7)	19 (52.8)	20 (37.0)	39 (68.4)
Missing GH Result at Week 22	2 (66.7)	0	0	2 (3.7)	4 (7.0)
Prohibited acromegaly medication	0	0	0	0	0
Rescue medication	0	1 (6.7)	1 (2.8)	2 (3.7)	13 (22.8)
Dose up-titration after Week 12	0	0	1 (2.8)	1 (1.9)	0
Discontinuation of treatment	2 (66.7)	1 (6.7)	1 (2.8)	4 (7.4)	16 (28.1)
Odds ratio (Paltusotine/Placebo)				7.588	
95% CI for odds ratio				(2.776, 23.483)	
P-value				<0.0001	

EOR = end of Randomized Controlled Phase; GH=growth hormone; IRT = Interactive Response Technology.

Average from the integrated GH sampling at week 22 is used to determine response. Percentages are calculated based on the number of participants in the Full Analysis Set. P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT (medically naïve or previously treated versus washout). For the odds ratio, placebo participants are the reference group.

3) Change from Baseline to EOR in Total ASD Score

The LS mean (±SE) changes from Baseline to EOT in total ASD score were **-2.669** (±1.4221) for the paltusotine group and **2.754** (±1.3641) for the placebo group, with a treatment difference of **-5.423** (95% CI: -9.070, -1.776) indicating an improvement and stabilization of symptoms for the paltusotine group, and worsening of symptoms for the placebo group. This difference was statistically significant (**p=0.0039**) and clinically meaningful.

Table 26 Secondary Efficacy Endpoint: Change from Baseline to EOT in Total ASD Score in RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine (N=54)	Placebo (N=57)	Treatment Difference (95% Confidence Interval)	P-value
Total ASD Change from Baseline to EOT				
LS Mean	-2.669	2.754	-5.423 (-9.070, -1.776)	0.0039
LS Standard Error	1.4221	1.3641		

ASD=Acromegaly Symptoms Diary, EOT = week 24 if no rescue, otherwise EOT = last assessment prior to rescue, IRT = Interactive Response Technology, RC=randomized controlled.

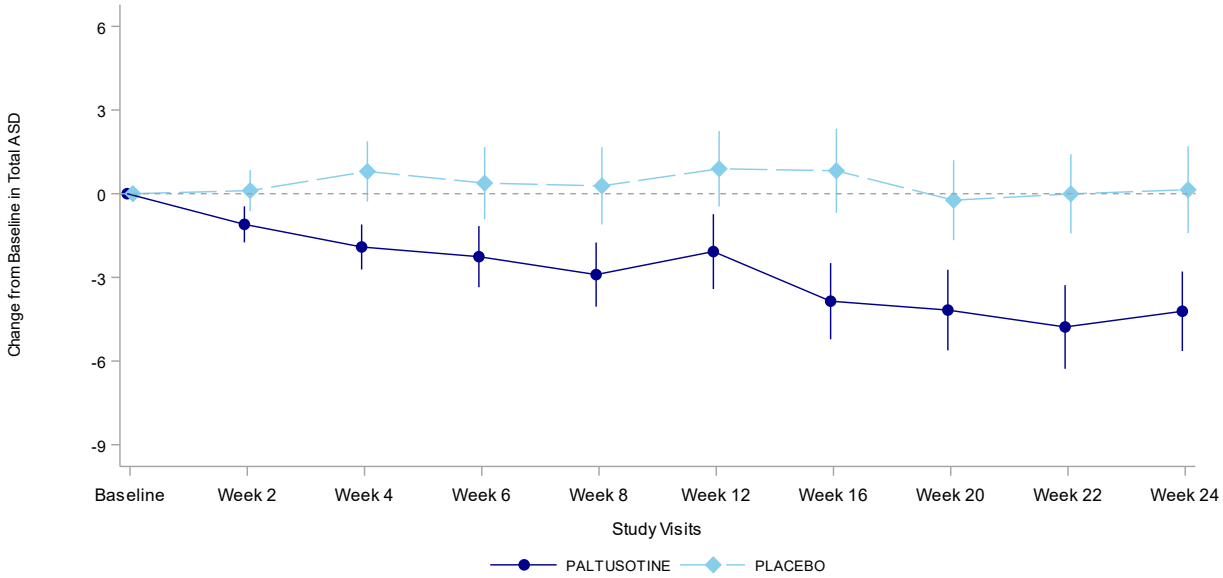
Baseline total ASD is the sum of the weekly average on or prior to Day 1, and post-baseline total ASD is the sum of the weekly average on or prior to the scheduled visit date, inclusive of the date of visit, for 7 items (headache, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling). Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, and prior treatment strata per IRT (medically naïve or previously treated versus washout), baseline total ASD score as a covariate.

Figure 16 presents the mean change from baseline in total ASD for participants without rescue or prior to rescue therapy at each visit by treatment group in the RC phase. ASD scores after rescue use were excluded.

For the paltusotine group, the mean total ASD score decreased by the first post-dose assessment at Week 2 and generally continued to decrease through Week 24 indicating improvement and/or

stabilization of symptoms. For the placebo group, the mean total ASD remained near Baseline for all visits through Week 24.

Figure 16 Mean (±SE) Total ASD Score Change from Baseline by Visit for All Participants Without /Prior to Rescue in RC Phase CRN00808-08 (Full Analysis Set)

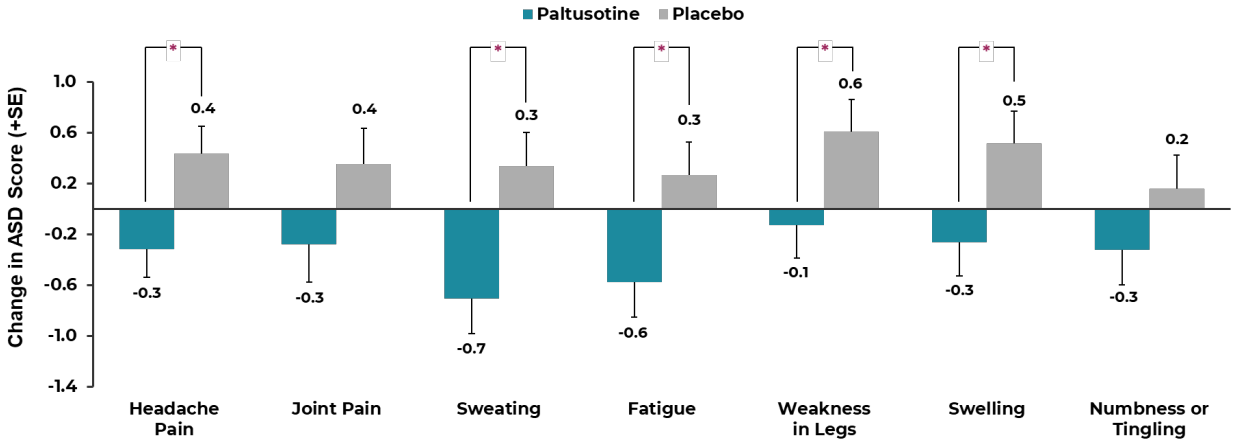


Paltusotine (n)	52	51	52	52	52	50	48	48	47	48
Placebo (n)	56	56	56	52	52	45	42	40	39	39

ASD=Acromegaly Symptoms Diary, RC=Randomized Controlled, SE=standard error
Note: Baseline total ASD is the sum of the weekly average on or prior to Day 1, and post-baseline total ASD is the sum of the weekly average on or prior to the scheduled visit date, inclusive of the date of visit, for 7 items (headache, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling).

When evaluating the ASD by individual item scores, all 7 items trended in favour of paltusotine, 5 of which were nominally significant (headache pain, sweating, fatigue, weakness in legs, swelling; nominal $p<0.05$). The overall total ASD score was not driven by a single item, indicating that there were improvement and stabilization across all acromegaly symptoms evaluated in the paltusotine group compared with the placebo group.

Figure 17 Change from Baseline to EOR in ASD Score by Item for All Participants Without or Prior to Rescue in RC Phase of Study CRN00808-08 (Full Analysis Set)



ASD=Acromegaly Symptoms Diary, EOR=End of Randomized Controlled, LS=least squares, RC=Randomized Controlled, SE=standard error
Note: LS mean is presented and estimated based on an analysis of covariance. ASD scores measured prior to rescue or discontinuation are used. Each symptom is on a 0 (no symptom) to 10 (worst symptom) scale.
*p<0.05. P-value is estimated based on an analysis of covariance.

The LS means (±SE) change from Baseline to EOT in most bothersome symptoms were **-0.553** (±0.4219) in the paltusotine group and **0.357** (±0.3770) in the placebo group, with a treatment difference of **-0.910** (95% CI: -1.976, 0.157) in favour of paltusotine (nominal **p=0.0935**).

Table 27 Change from Baseline to EOR in Most Bothersome Symptoms in RC Phase of Study CRN00808-08 (Full Analysis Set)

	Paltusotine (N=54)	Placebo (N=57)	Treatment Difference (95% CI)	P-value
Change from Baseline to EOT in Most Bothersome Symptom				
LS Mean	-0.553	0.357	-0.910 (-1.976, 0.157)	0.0935
LS Standard Error	0.4219	0.3770		

EOT = week 24 if no rescue, otherwise EOT=last assessment prior to rescue. IRT = Interactive Response Technology, RC=randomized controlled.
Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, prior treatment strata per IRT (medically naïve or previously treated versus washout) as fixed effects, baseline value as a covariate.

Main exploratory endpoints- RC phase

1) Change from Baseline to Week 22 in GH Level

The LS means (±SE) change from Baseline to EOT (**Week 22 if no rescue**, otherwise EOT was the last assessment prior to rescue) in GH level (ng/mL) were **-2.686** (±1.9109) for the paltusotine group and **1.636** (±1.2193) for the placebo group, with a treatment difference of **-4.322** (95% CI: -8.537, -0.0106).

2) Proportion of Participants Who Received Rescue Therapy

The proportion of participants who received rescue therapy was **3.7%** (2 of 54) in the paltusotine group and **22.8%** (13 of 57) in the placebo group affirming the treatment effect of paltusotine versus placebo.

3) Time from Randomization to Initial Response (IGF-1≤1.0×ULN)

The median (IQR) time to initial response was **44 days** (15.0 days, not estimable [NE]) for the paltusotine group and was not reached (NE, NE) for the placebo group.

4) Change from Baseline in Residual Tumour Volume at EOR

Pituitary tumour volume was evaluated by pituitary MRI and assessed by the Investigator for clinically significant safety findings and by an MRI central radiologist for tumor volume measurement/assessment.

At EOT, a clinically significant tumour volume reduction (as measured by >20% reduction in tumor volume) was observed in **4** (**11.8%**) participants in the Paltusotine group and in **0** (0.0%) participants in the placebo group. **Four** placebo participants had ≥**20%** increase in tumor volume compared to zero (0) Paltusotine participants. Paltusotine was associated with stable or reduced pituitary tumor size as measured by MRI.

4) Treatment Preference Questionnaire at EOR

In the paltusotine group (**N=54**), once daily oral medication was preferred by **42 participants** (**77.8**%), previous injections were preferred by **5 participants** (**9.3%**), 5 participants (9.3%) had no preference, and data were missing for 2 participants (3.7%).
In the placebo group (**N=57**), oral medication was preferred by **36 participants** (**63.2%**), previous injections were preferred by **6 participants** (**10.5%**), **9 participants** (**15.8%**) had no preference, and data were missing for **6 participants** (**10.5%**).

5) Summary of AcroQoL, EQ-5D-5L, PGI-S, PGI-I
- The LS means (±SE) for the change from Baseline to EOR in the **EQ-5D-5L** health index score were **0.001** (±0.0251) for the paltusotine group and **-0.102** (±0.0256) for the placebo group, with a treatment difference of **0.103** (95% CI: 0.038, 0.168) (nominal **p=0.0023**).
The LS means (±SE) for the change from Baseline to EOR in the EQ VAS score were **-0.120** (±2.2489) for the paltusotine group and **-5.573** (±2.3049) for the placebo group, with a treatment difference of **5.453** (95% CI: -0.413, 11.319) (nominal **p=0.0681**).

- **PGI-I at EOR (EOT at Week 24):** the LS means (±SE) for the **PGI-I** at EOT were **-1.488** (±0.1792) for the paltusotine group and **-1.040** (±0.1964) for the placebo group, with a treatment difference of **-1.040** (95% CI: -1.536, -0.544) (nominal **p<0.0001**).

- **Change from Baseline to EOR (EOT at Week 24) in the PGI-S**: The LS means (±SE) change from Baseline to EOT in **PGI-S** were **0.030** (±0.1078) for the paltusotine group and **0.181** (±0.1004) for the placebo group, with a treatment difference of **-0.151** (95% CI: -0.424, 0.122) (nominal **p=0.275**).

- Change from Baseline to EOR (EOT at Week 24) in AcroQoL composite scores and standardized scores: The LS means (±SE) for the change from Baseline to EOR in the AcroQoL total score using composite scores were **-0.506** (±2.0731) for the paltusotine group and **-4.327** (±2.0543) for the placebo group, with a treatment difference of **3.821** (95% CI: -1.639, 9.281) (nominal **p=0.1676**).

The LS means (±SE) for the change from Baseline to EOR in the AcroQoL total score using standardized scores were **-0.575** (±2.3558) for the paltusotine group and **-4.917** (±2.3344) for the placebo group, with a treatment difference of 4.343 (95% CI: -1.862, 10.547) (nominal **p=0.1676**).
Main exploratory endpoints-OLE Phase
Eligible participants who directly entered the OLE following screening initiated the study at Week 24 for the OLE Phase. OLE Baseline was defined as the last non-missing assessment prior to the first dose of study drug in OLE Phase.

1) Proportion of Participants with IGF-1 ≤1.0 × ULN and <1.3×ULN at each Visit in the OLE Phase

Table 28 presents the proportion of participants with IGF-1 level ≤1.0×ULN and IGF-1 level ≤1.3×ULN by visit in the OLE Phase of Study CRN00808-08. The starting dose of paltusotine in the OLE phase was 20 mg QD, and most participants who were receiving 40 mg QD or 60 mg QD at the end of the RC phase were anticipated to up-titrate to 40 mg QD or 60 mg QD during the OLE phase.

The proportion of participants who achieved IGF-1 level ≤1.0×ULN ranged from **51.3% to 100%** from Week 36 to Week 144 for the overall population (**51.0% to 100%** for the prior paltusotine group and **37.0% to 100%** for the prior placebo group) and ranged from 50.0% to 80.0% for the directly enrolled group from Week 36 to Week 120.

The proportion of participants who achieved IGF-1 level <1.3×ULN ranged from **69.9% to 100%** from Week 36 to Week 144 for the overall population (**68.6% to 100%** for the prior paltusotine group and **65.4% to 100%** for the prior placebo group) and was 100% from Week 36 to Week 120 for the directly enrolled group.

The starting paltusotine dose for the OLE was **20 mg** resulting in a temporary down titration for prior paltusotine participants from final dose in the RC Phase for most participants **and a subsequent increase in IGF-1 levels at Week 26**. Most participants who were responders in the RC phase continued to be responders in the OLE phase.

Table 28 Summary of Proportion of Participants with IGF-1 ⩽1.0×ULN and <1.3×ULN by Visit in OLE Phase of Study CRN00808-08 (OLE Safety Analysis Set)

	Paltusotine in RC (N=51) n (%)	Placebo in RC (N=52) n (%)	OLE Directly (N=11) n (%)	Total (N=114) n (%)
Week 26	50	52	11	113
IGF-1 <= 1.0×ULN	17 (34.0)	22 (42.3)	6 (54.5)	45 (39.8)
IGF-1 < 1.3×ULN	30 (60.0)	30 (57.7)	11 (100)	71 (62.8)
Week 36	51	52	10	113
IGF-1 <= 1.0×ULN	26 (51.0)	25 (48.1)	7 (70.0)	58 (51.3)
IGF-1 < 1.3×ULN	35 (68.6)	34 (65.4)	10 (100)	79 (69.9)
Week 48	49	49	10	108
IGF-1 <= 1.0×ULN	28 (57.1)	26 (53.1)	8 (80.0)	62 (57.4)
IGF-1 < 1.3×ULN	36 (73.5)	34 (69.4)	10 (100)	80 (74.1)
Week 60	48	47	10	105
IGF-1 <= 1.0×ULN	29 (60.4)	23 (48.9)	8 (80.0)	60 (57.1)
IGF-1 < 1.3×ULN	36 (75.0)	32 (68.1)	10 (100)	78 (74.3)
Week 72	43	45	10	98
IGF-1 <= 1.0×ULN	28 (65.1)	28 (62.2)	8 (80.0)	64 (65.3)
IGF-1 < 1.3×ULN	37 (86.0)	37 (82.2)	10 (100)	84 (85.7)
Week 84	40	38	10	88
IGF-1 <= 1.0×ULN	30 (75.0)	21 (55.3)	7 (70.0)	58 (65.9)
IGF-1 < 1.3×ULN	36 (90.0)	34 (89.5)	10 (100)	80 (90.9)
Week 96	36	33	9	78
IGF-1 <= 1.0×ULN	26 (72.2)	19 (57.6)	7 (77.8)	52 (66.7)
IGF-1 < 1.3×ULN	31 (86.1)	29 (87.9)	9 (100)	69 (88.5)
Week 108	30	27	9	66
IGF-1 <= 1.0×ULN	26 (86.7)	10 (37.0)	6 (66.7)	42 (63.6)
IGF-1 < 1.3×ULN	29 (96.7)	22 (81.5)	9 (100)	60 (90.9)
Week 120	16	16	4	36
IGF-1 <= 1.0×ULN	13 (81.3)	8 (50.0)	2 (50.0)	23 (63.9)
IGF-1 < 1.3×ULN	15 (93.8)	14 (87.5)	4 (100)	33 (91.7)
Week 132	8	10	0	18
IGF-1 <= 1.0×ULN	6 (75.0)	5 (50.0)	0	11 (61.1)
IGF-1 < 1.3×ULN	7 (87.5)	7 (70.0)	0	14 (77.8)
Week 144	1	1	0	2
IGF-1 <= 1.0×ULN	1 (100)	1 (100)	0	2 (100)
IGF-1 < 1.3×ULN	1 (100)	1 (100)	0	2 (100)

IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; ULN=upper limit of normal
Notes: Percentages are calculated based on the number of participants at each visit. Only visits with at least 1 participant are included in the table. OLE Baseline is Week 24.
Data snapshot date: 31 August 2025

- **Medically naïve patients**

Table 29 presents the proportion of participants with IGF-1 ≤1.0×ULN and IGF-1 ≤1.3×ULN by visit in the OLE phase for the medically naïve group. Results are presented based on the final paltusotine dose in the RC phase. Three medically naïve participants in the prior paltusotine group were receiving paltusotine 40 mg QD as their final dose in the RC phase; at Week 96, all 3 participants had IGF-1 ≤1.0×ULN at Week 96 during the OLE phase. Eighteen participants in the prior paltusotine group received paltusotine 60 mg QD as their final dose in the RC phase. Four of these participants had IGF-1 ≤1.0×ULN at Week 60 and Week 108.

Table 29 Summary of Proportion of Participants in Medically Naïve Group with IGF-1 ⩽ 1.0×ULN and <1.3×ULN by Visit in OLE Phase of Study CRN00808-08 (OLE Safety Analysis Set)

Medically naive					
	Paltusotine in RC (N=21)				
	20 mg (N=0)	40 mg (N=3)	60 mg (N=18)	Placebo in RC (N=23)	Total (N=44)
Week 26	0	3	18	23	44
IGF-1 <= 1.0×ULN	0	2 (66.7)	2 (11.1)	8 (34.8)	12 (27.3)
IGF-1 < 1.3×ULN	0	3 (100)	3 (16.7)	10 (43.5)	16 (36.4)
Week 36	0	3	18	23	44
IGF-1 <= 1.0×ULN	0	2 (66.7)	3 (16.7)	6 (26.1)	11 (25.0)
IGF-1 < 1.3×ULN	0	3 (100)	5 (27.8)	12 (52.2)	20 (45.5)
Week 48	0	3	18	20	41
IGF-1 <= 1.0×ULN	0	3 (100)	2 (11.1)	7 (35.0)	12 (29.3)
IGF-1 < 1.3×ULN	0	3 (100)	9 (50.0)	11 (55.0)	23 (56.1)
Week 60	0	3	18	18	39
IGF-1 <= 1.0×ULN	0	3 (100)	4 (22.2)	6 (33.3)	13 (33.3)
IGF-1 < 1.3×ULN	0	3 (100)	7 (38.9)	10 (55.6)	20 (51.3)
Week 72	0	3	13	18	34
IGF-1 <= 1.0×ULN	0	3 (100)	4 (30.8)	7 (38.9)	14 (41.2)
IGF-1 < 1.3×ULN	0	3 (100)	8 (61.5)	13 (72.2)	24 (70.6)
Week 84	0	3	11	14	28
IGF-1 <= 1.0×ULN	0	3 (100)	3 (27.3)	4 (28.6)	10 (35.7)
IGF-1 < 1.3×ULN	0	3 (100)	7 (63.6)	11 (78.6)	21 (75.0)
Week 96	0	3	8	8	19
IGF-1 <= 1.0×ULN	0	3 (100)	2 (25.0)	4 (50.0)	9 (47.4)
IGF-1 < 1.3×ULN	0	3 (100)	4 (50.0)	7 (87.5)	14 (73.7)
Week 108	0	2	7	7	16
IGF-1 <= 1.0×ULN	0	2 (100)	4 (57.1)	1 (14.3)	7 (43.8)
IGF-1 < 1.3×ULN	0	2 (100)	6 (85.7)	6 (85.7)	14 (87.5)
Week 120	0	1	3	2	6
IGF-1 <= 1.0×ULN	0	1 (100)	1 (33.3)	0	2 (33.3)
IGF-1 < 1.3×ULN	0	1 (100)	3 (100)	1 (50.0)	5 (83.3)

IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; ULN=upper limit of normal
Notes: Percentages are calculated based on the number of participants at each visit. 20 mg, 40 mg, and 60 mg refers to the final dose in the RC Phase. Only visits with at least 1 participant are included in the table.
Data snapshot date: 21 May 2025

The proportion of medically naïve patients with IGF-1 levels ≤ ULN increased over time from **25%** (11/44) at W36 to **35.7%** (10/28) at W84. Likewise, the proportion of participants wih IGF-1 < 1.3x ULN from **45.5%** (20/44) at week 36 to **75%** (21/28) at W84.

During the OLE phase, after starting at paltusotine 20 mg QD at Week 24, the majority of participants in the prior paltusotine group (**81.0%,** 17 of 21) and the prior placebo group (**61.1%,** 11 of 18) up-

titrated to paltusotine 60 mg QD by Week 48. The majority of participants continued to receive paltusotine 60 mg QD at subsequent timepoints in the OLE phase. Of note, participants in the medically naïve group had higher baseline IGF-1 levels compared to the previously treated and washout groups. These patients may require a longer treatment duration to achieve biochemical control.

- **Previously treated patients**

During the OLE phase, after starting at paltusotine 20 mg QD at Week 24, the majority of participants (**66.7%,** 10 of 15) in the prior paltusotine group up-titrated to paltusotine 40 mg QD by Week 36. The majority of participants continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE Phase. One participant was on paltusotine 20 mg QD at Week 96.

In the prior placebo group, after starting at paltusotine 20 mg QD at Week 24, the majority of participants (**58.8%,** 10 of 17) up-titrated to 60 mg QD by Week 60. The majority of participants in the prior placebo group continued to receive paltusotine 60 mg QD at subsequent timepoints in the OLE Phase. Two participants in the prior placebo group were receiving paltusotine 20 mg QD at Week 108 and 1 participant at Week 120.

Table 30 presents the proportion of participants with IGF-1 ≤1.0×ULN and IGF-1 ≤1.3×ULN by visit in the OLE phase for the previously treated group. Results are presented based on the final paltusotine dose in the RC phase. Seven participants in the prior paltusotine group who were receiving paltusotine 40 mg QD as their final dose in the RC phase had IGF-1 ≤1.0×ULN at Week 84, and those who continued to be followed up to Week 120 had IGF-1 ≤1.0×ULN. Nine participants in the prior paltusotine group received paltusotine 60 mg QD as their final dose in the RC phase. At Week 60, 5 of 7 (71.4%) of participants who received paltusotine 60 mg QD as their final dose in the RC phase had IGF-1 ≤1.0×ULN, with the majority of participants who were followed at subsequent weeks achieving IGF-1 level ≤1.0×ULN.

In the OLE phase, the proportion of previously treated participants with IGF-1 levels ≤ ULN increased over time from **55.9%** (19/34) at W36 to **73.1%** (19/26) at W84. Likewise, the proportion of participants with IGF-1 levels < 1.3xULN from **73.5%** (25/34) at W36 to **96.2%** (25/26) at W84.

Table 30 Summary of Proportion of Participants in Previously Treated Group with IGF-1 ⩽1.0×ULN and <1.3×ULN by Visit in OLE Phase of Study CRN00808-08 (OLE Safety Analysis Set)

Previously treated					
	Paltusotine in RC (N=16)				
	20 mg (N=0)	40 mg (N=7)	60 mg (N=9)	Placebo in RC (N=18)	Total (N=34)
Week 26	0	6	9	18	33
IGF-1 <= 1.0×ULN	0	5 (83.3)	2 (22.2)	7 (38.9)	14 (42.4)
IGF-1 < 1.3×ULN	0	6 (100)	5 (55.6)	10 (55.6)	21 (63.6)
Week 36	0	7	9	18	34
IGF-1 <= 1.0×ULN	0	6 (85.7)	4 (44.4)	9 (50.0)	19 (55.9)
IGF-1 < 1.3×ULN	0	7 (100)	7 (77.8)	11 (61.1)	25 (73.5)
Week 48	0	7	8	18	33
IGF-1 <= 1.0×ULN	0	6 (85.7)	4 (50.0)	9 (50.0)	19 (57.6)
IGF-1 < 1.3×ULN	0	6 (85.7)	5 (62.5)	12 (66.7)	23 (69.7)

Previously treated					
	Paltusotine in RC (N=16)				
	20 mg (N=0)	40 mg (N=7)	60 mg (N=9)	Placebo in RC (N=18)	Total (N=34)
Week 60	0	7	7	18	32
IGF-1 <= 1.0×ULN	0	7 (100)	5 (71.4)	8 (44.4)	20 (62.5)
IGF-1 < 1.3×ULN	0	7 (100)	6 (85.7)	11 (61.1)	24 (75.0)
Week 72	0	7	7	16	30
IGF-1 <= 1.0×ULN	0	7 (100)	4 (57.1)	10 (62.5)	21 (70.0)
IGF-1 < 1.3×ULN	0	7 (100)	6 (85.7)	13 (81.3)	26 (86.7)
Week 84	0	7	6	13	26
IGF-1 <= 1.0×ULN	0	7 (100)	4 (66.7)	8 (61.5)	19 (73.1)
IGF-1 < 1.3×ULN	0	7 (100)	6 (100)	12 (92.3)	25 (96.2)
Week 96	0	4	4	9	17
IGF-1 <= 1.0×ULN	0	4 (100)	4 (100)	5 (55.6)	13 (76.5)
IGF-1 < 1.3×ULN	0	4 (100)	4 (100)	8 (88.9)	16 (94.1)
Week 108	0	3	1	5	9
IGF-1 <= 1.0×ULN	0	3 (100)	1 (100)	3 (60.0)	7 (77.8)
IGF-1 < 1.3×ULN	0	3 (100)	1 (100)	4 (80.0)	8 (88.9)
Week 120	0	1	1	5	7
IGF-1 <= 1.0×ULN	0	1 (100)	1 (100)	3 (60.0)	5 (71.4)
IGF-1 < 1.3×ULN	0	1 (100)	1 (100)	5 (100)	7 (100)
Week 132	0	0	1	0	1
IGF-1 <= 1.0×ULN	0	0	1 (100)	0	1 (100)
IGF-1 < 1.3×ULN	0	0	1 (100)	0	1 (100)

IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; ULN=upper limit of normal
Notes: Percentages are calculated based on the number of participants at each visit. 20 mg, 40 mg, and 60 mg refers to the final dose in the RC Phase. Only visits with at least 1 participant are included in the table.
Data snapshot date: 21 May 2025

- **Washout patients**

Table 31 presents the proportion of participants with IGF-1 ≤1.0×ULN and IGF-1 ≤1.3×ULN by visit in the OLE phase for the washout group. Results are presented based on the final paltusotine dose in the RC phase. Four participants in the prior paltusotine group who were receiving paltusotine 40 mg QD as their final dose in the RC phase had IGF-1 ≤1.0×ULN through Week 84, and those who continued to be followed up to Week 96 had IGF-1 ≤1.0×ULN. Nine participants in the prior paltusotine group received paltusotine 60 mg QD as their final dose in the RC phase. At Week 60, 5 of 8 (62.5%) of participants who received paltusotine 60 mg QD as their final dose in the RC phase had IGF-1 ≤1.0×ULN, with the majority of participants who were followed at subsequent visits achieving IGF-1 level ≤1.0×ULN. One participant who received 20 mg QD as their final dose in the RC phase had IGF-1 ≤1.0×ULN at Week

96. Among the 36 washout participants, the majority of participants (84.6%, 11 of 13) in the prior paltusotine group up titrated to paltusotine 40 mg QD by Week 36. The majority of participants in the prior paltusotine group continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE phase. In the prior placebo group, after starting at paltusotine 20 mg QD at Week 24, the majority of participants (90.9%, 10 of 11) up-titrated to 40 mg QD by Week 36. The majority of participants in the prior placebo group continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE phase.

In the OLE phase, the proportion of the washout participants with IGF-1 levels ≤ULN increased over time from **80%** (28/35) at W36 to **85.3%** (29/34) at W84. Likewise, the proportion of participants with IGF-1 levels < 1.3xULN increased from **97.1%** (34/35) at W36 to **100%** (34/34) at W84.

Table 31 Summary of Proportion of Participants in the Washout Group with IGF-1 ⩽1.0 ×ULN and <1.3×ULN by Visit and Dose in OLE Phase of Study CRN00808-08 (OLE Safety Analysis Set)

Washout						
	Paltusotine in RC (N=14)					
	20 mg (N=1)	40 mg (N=4)	60 mg (N=9)	Placebo in RC (N=11)	OLE Directly (N=11)	Total (N=36)
Week 26	1	4	9	11	11	36
IGF-1 <= 1.0×ULN	1 (100)	2 (50.0)	3 (33.3)	7 (63.6)	6 (54.5)	19 (52.8)
IGF-1 < 1.3×ULN	1 (100)	4 (100)	8 (88.9)	10 (90.9)	11 (100)	34 (94.4)
Week 36	1	4	9	11	10	35
IGF-1 <= 1.0×ULN	1 (100)	4 (100)	6 (66.7)	10 (90.9)	7 (70.0)	28 (80.0)
IGF-1 < 1.3×ULN	1 (100)	4 (100)	8 (88.9)	11 (100)	10 (100)	34 (97.1)
Week 48	1	4	8	11	10	34
IGF-1 <= 1.0×ULN	1 (100)	4 (100)	8 (100)	10 (90.9)	8 (80.0)	31 (91.2)
IGF-1 < 1.3×ULN	1 (100)	4 (100)	8 (100)	11 (100)	10 (100)	34 (100)
Week 60	1	4	8	11	10	34
IGF-1 <= 1.0×ULN	1 (100)	4 (100)	5 (62.5)	9 (81.8)	8 (80.0)	27 (79.4)
IGF-1 < 1.3×ULN	1 (100)	4 (100)	8 (100)	11 (100)	10 (100)	34 (100)
Week 72	1	4	8	11	10	34
IGF-1 <= 1.0×ULN	1 (100)	4 (100)	5 (62.5)	11 (100)	8 (80.0)	29 (85.3)
IGF-1 < 1.3×ULN	1 (100)	4 (100)	8 (100)	11 (100)	10 (100)	34 (100)
Week 84	1	4	8	11	10	34
IGF-1 <= 1.0×ULN	1 (100)	4 (100)	8 (100)	9 (81.8)	7 (70.0)	29 (85.3)
IGF-1 < 1.3×ULN	1 (100)	4 (100)	8 (100)	11 (100)	10 (100)	34 (100)
Week 96	1	2	4	7	9	23
IGF-1 <= 1.0×ULN	1 (100)	2 (100)	3 (75.0)	4 (57.1)	7 (77.8)	17 (73.9)
IGF-1 < 1.3×ULN	1 (100)	2 (100)	4 (100)	7 (100)	9 (100)	23 (100)
Week 108	0	0	1	2	1	4
IGF-1 <= 1.0×ULN	0	0	1 (100)	1 (50.0)	1 (100)	3 (75.0)

Washout						
	Paltusotine in RC (N=14)					
	20 mg (N=1)	40 mg (N=4)	60 mg (N=9)	Placebo in RC (N=11)	OLE Directly (N=11)	Total (N=36)
IGF-1 < 1.3×ULN	0	0	1 (100)	2 (100)	1 (100)	4 (100)
Week 120	0	0	1	1	0	2
IGF-1 <= 1.0×ULN	0	0	1 (100)	1 (100)	0	2 (100)
IGF-1 < 1.3×ULN	0	0	1 (100)	1 (100)	0	2 (100)

IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; ULN=upper limit of normal
Notes: Percentages are calculated based on the number of participants at each visit. 20mg, 40mg and 60mg refers to the final dose in the RC Phase. Only visits with at least 1 participant are included in the table.
Data snapshot date: 21 May 2025

The applicant provided the proportion of patients who used adjunctive therapies (cabergoline, bromocriptine) from W48 in the OLE phase of study CRN00808-08 in each subgroup as recommended in the protocol.

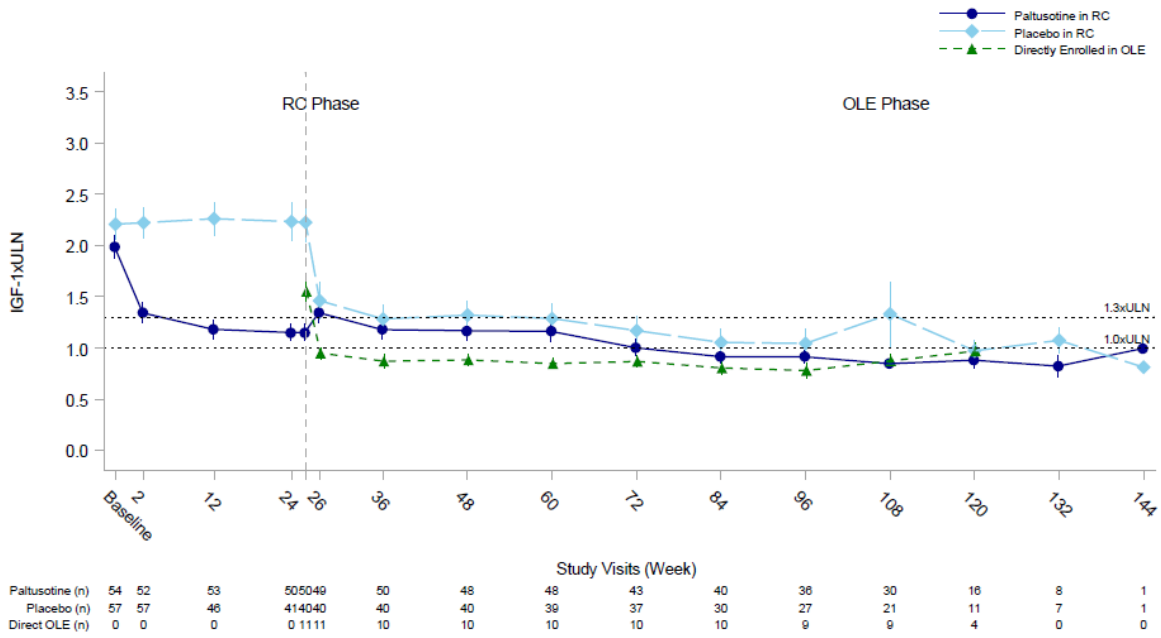
As of the data snapshot date of 21 May 2025 and also at the data snapshot date of 31 August 2025 (as no additional participant need adjunctive therapies from 21 May 2025), the need for adjunctive therapies in study CRN00808-08 was very limited, with 18 of 114 (**15.8%**) participants. The use of adjunctive therapies was observed more frequently in participants receiving prior placebo (**23.1%;** 12 of 52 participants) than in participants receiving prior paltusotine (**11.8%;** 6 of 51 participants) and no participants in the directly enrolled group. Overall, 12 participants (10.5%) received cabergoline, 6 participants (5.3%) received bromocriptine mesylate, and 1 participant received bromocriptine (0.9%).

When the 18 participants who received adjunctive therapies in study CRN00808-08 were excluded from the response analyses, the proportion of participants without adjunctive therapy who had IGF-1 ≤ 1.0 x ULN were similar to the proportion of participants with IGF-1 ≤ 1.0 x ULN in the overall group (**62.0% without adjunctive vs 54.7%** overall at Week 60; **74.3% without adjunctive vs 63.6%** overall at Week 72; **73.8% without adjunctive vs 65.4%** overall at Week 84). Similar trends continued up through Week 120. The proportion of participants with IGF-1 ≤ 1.3 x ULN were also similar between the 2 groups at these visits.

2) Change from OLE Baseline in IGF-1×ULN to the Visits in the OLE Phase

Figure 18 presents mean IGF-1 levels (×ULN) by visit for participants in the RC phase and OLE phase of study CRN00808-08. Continued maintenance and durability of mean IGF-1 levels were observed in participants in the prior paltusotine group up to Week 144. From W36 to W144, there was a constant decrease of the IGF-1 levels with a negative change from baseline at each visit highlighting a reduction of the IGF-1 levels over time.
In the prior placebo and directly enrolled groups, decreases in mean IGF-1 levels were observed over the initial 2 weeks with paltusotine in the OLE phase, which were consistent with the onset and magnitude of reduction in IGF-1 levels in the paltusotine group in the RC phase, and were maintained throughout the OLE phase.

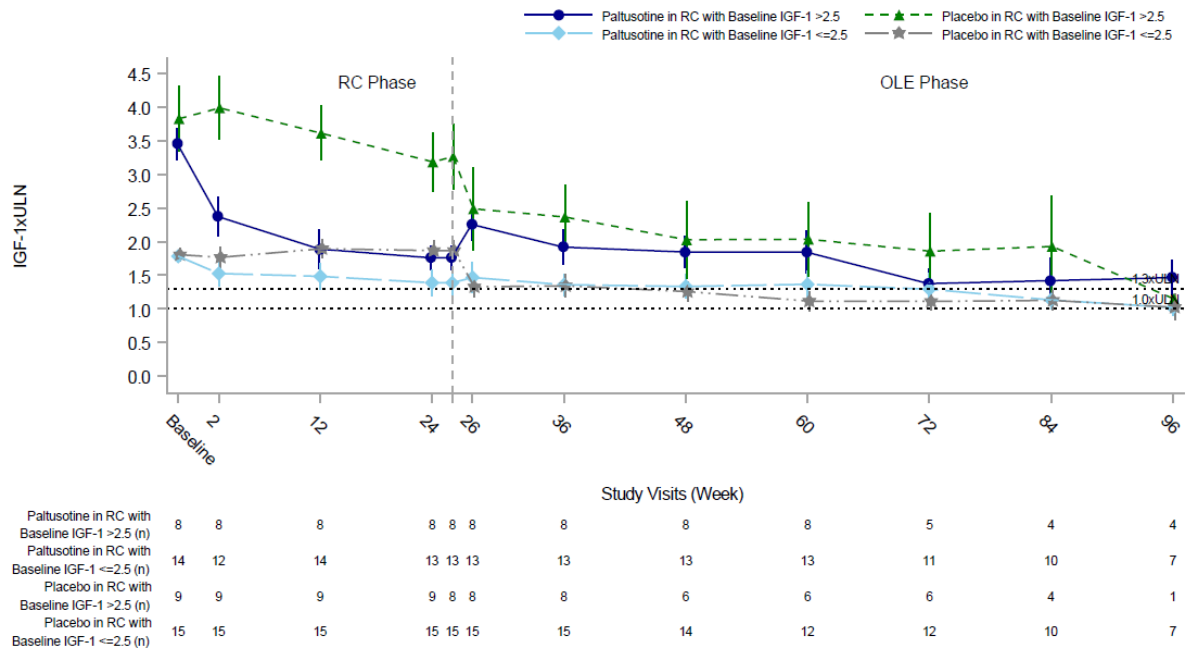
Figure 18 Mean (±SE) IGF-1 Level (×ULN) by Visit for Participants in RC Phase and OLE Phase of Study CRN00808-08 (Full Analysis Set and OLE Safety Analysis Set)



IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error; ULN=upper limit of normal
Note: Includes participants in the RC Phase and the OLE Phase without/or prior to rescue in the RC Phase.
Data snapshot date: 31 August 2025

After the dose titration period of the OLE phase, the results show that despite having high baseline IGF-1 levels, participants in the medically naïve group showed clinically meaningful reductions in IGF-1 levels, and with a longer treatment duration, these participants were able to achieve meaningful treatment benefits with paltusotine as evidenced by the further decreases in IGF-1 levels during the OLE phase.

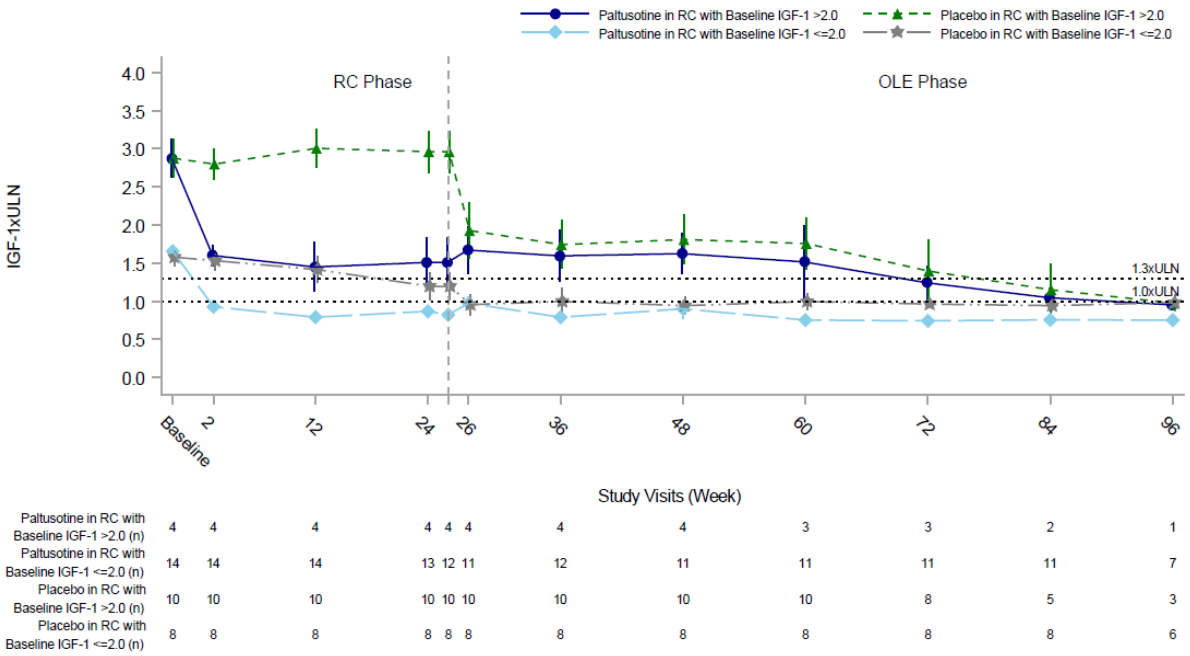
Figure 19 Mean (±SE) IGF-1 Level (×ULN) by Visit for Participants in the Medically Naïve Group in RC Phase and OLE Phase of Study CRN00808-08 by Baseline IGF-1 Level (Full Analysis Set)



IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error; ULN=upper limit of normal
Data snapshot date: 21 May 2025

In the previously treated group, in participants in the paltusotine group with mean baseline IGF-1 levels >2.0×ULN, a rapid and substantial reduction in mean IGF-1 level was observed during the first 2 weeks of paltusotine treatment, and mean IGF-1 levels were maintained with paltusotine treatment during the RC phase.

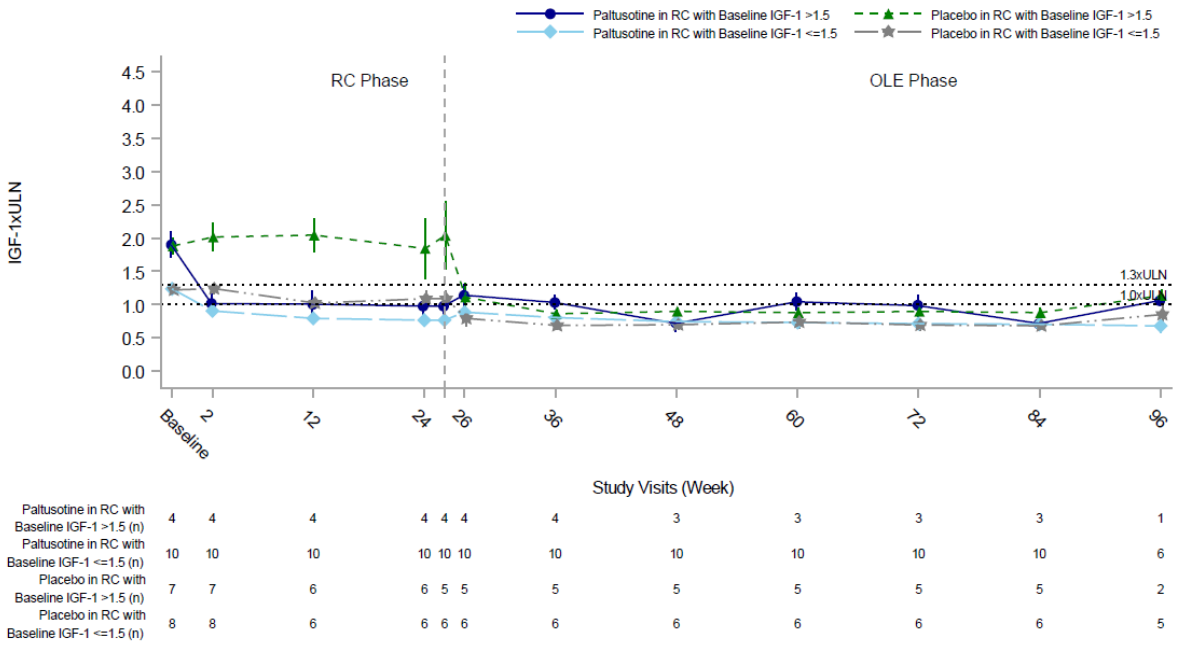
Figure 20 Mean (±SE) IGF-1 Level (×ULN) by Visit for Participants in the Previously Treated Group in RC Phase and OLE Phase of Study CRN00808-08 by Baseline IGF-1 Level (Full Analysis Set)



IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error; ULN=upper limit of normal
Data snapshot date: 21 May 2025

In the washout group, for participants in the paltusotine group with mean baseline IGF-1 level >1.5×ULN, a rapid reduction in mean IGF-1 level was observed during the first 2 weeks of paltusotine treatment, and mean IGF-1 levels were maintained during the RC phase and following the dose titration period in the OLE phase.

Figure 21 Mean (±SE) IGF-1 Level (×ULN) by Visit for Participants in the Washout Group in RC Phase and OLE Phase of Study CRN00808-08 by Baseline IGF-1 Level (Full Analysis Set)

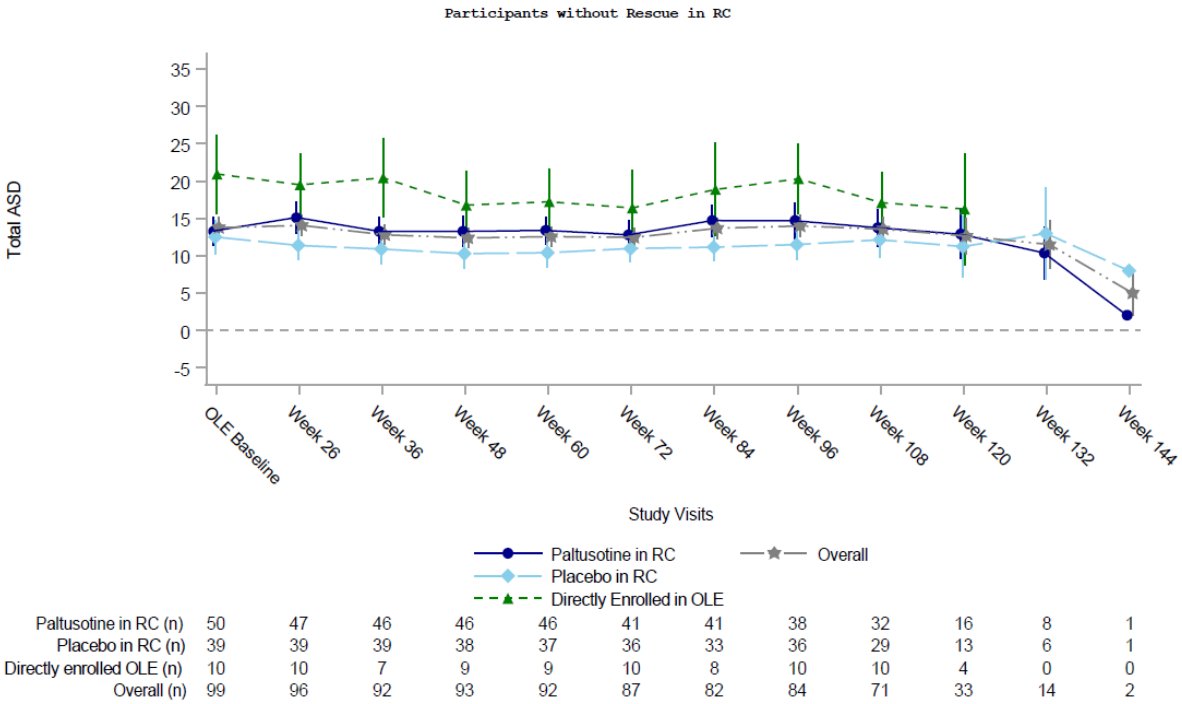


IGF-1=insulin-like growth factor-1; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error; ULN=upper limit of normal
Data snapshot date: 21 May 2025

3) Change from OLE Baseline in Total ASD Score to Visits in the OLE Phase

Figure 22 presents the mean ASD Total Score by visit for participants in the OLE phase of study CRN00808-08. Mean ASD Total Scores generally remained stable throughout the OLE phase. In the OLE phase, ASD scores were collected only once at quarterly study visits. Because the ASD was designed for daily administration, sparse data collections would be expected to result in some degree of visit-to-visit variability, reflecting sporadic variations over the course of a single day prior to the data collection date.

Figure 22 Mean (±SE) ASD Total Score by Visit in OLE Phase of Study CRN00808 08 (OLE Safety Analysis Set)



Paltusotine in RC (n)	50	47	46	46	46	41	41	38	32	16	8	1
Placebo in RC (n)	39	39	39	38	37	36	33	36	29	13	6	1
Directly enrolled OLE (n)	10	10	7	9	9	10	8	10	10	4	0	0
Overall (n)	99	96	92	93	92	87	82	84	71	33	14	2

ASD=Acromegaly Symptoms Diary; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error
Note: OLE Baseline is Week 24.
Data cutoff date: 31 August 2025

A *post hoc* analysis of the RC phase data from study CRN00808-08 was performed to evaluate the mean change from baseline at the end of treatment in ASD scores for the most bothersome symptoms (headache, joint pain, sweating, fatigue, weakness in legs, swelling, numbness or tingling, difficulty sleeping, and difficulty with short-term memory), as reported by participants across the three subgroups - medically naïve, previously treated, and washout participants.

An analysis of covariance (ANCOVA) model was used and all analyses were performed using the Full Analysis Set (FAS). Among participants who were medically naïve, the least squares (LS) mean changes in ASD scores for the most bothersome symptoms from baseline to the end of treatment showed a numerical improvement with paltusotine compared to placebo (0.206 [n=57] with paltusotine versus +0.284 with placebo [n=54]), resulting in a between treatment group difference of -0.490 (95% confidence interval [CI]: -2.161 to 1.180) . The findings were similar among the previously treated and washout subgroups, with numerical improvements observed in participants who received paltusotine compared with those who received placebo

In summary, this analysis demonstrates that ASD scores for the most bothersome symptoms were improved in the medically naïve population in line with the other participants with uncontrolled acromegaly, regardless of clinical status and baseline characteristics but the difference was not significant for any subgroup of patients.

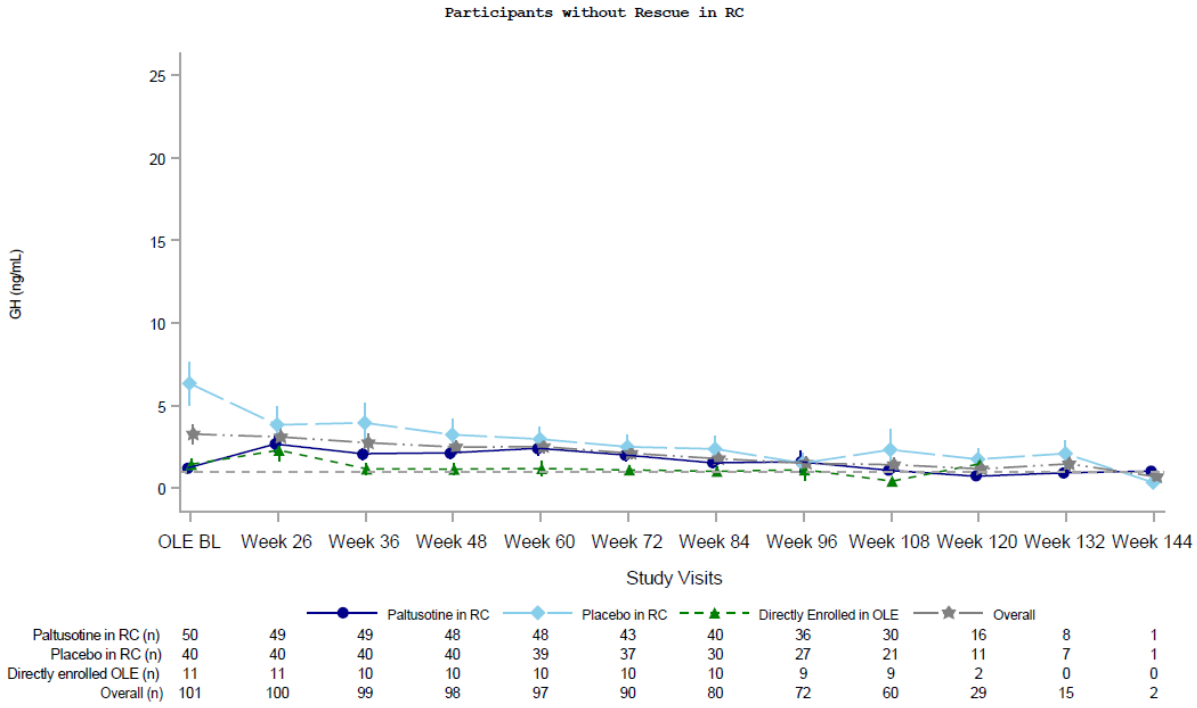
4) Change from OLE Baseline in GH at Each Visit in the OLE Phase

Figure 23 presents mean GH levels (ng/mL) by visit for participants in the OLE phase of study CRN00808-08.

Continued maintenance and durability of mean GH levels (ng/mL) were observed from OLE Baseline up to Week 144 in participants in the prior paltusotine group and up to Week 120 in the directly enrolled group.

Participants in the prior placebo group showed a decrease in mean GH level by Week 26 that remained stable through Week 144.

Figure 23 Mean (±SE) GH Levels (ng/mL) by Visit in OLE Phase of Study CRN00808 08 (OLE Safety Analysis Set)



Paltusotine in RC (n)	50	49	49	48	48	43	40	36	30	16	8	1
Placebo in RC (n)	40	40	40	40	39	37	30	27	21	11	7	1
Directly enrolled OLE (n)	11	11	10	10	10	10	10	9	9	2	0	0
Overall (n)	101	100	99	98	97	90	80	72	60	29	15	2

GH=growth hormone; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error; ULN=upper limit of normal
Note: OLE Baseline is Week 24. GH level at OLE Baseline was based on the average of fasting integrated GH measurements at the Week 22 visit for participants enrolled from the RC Phase and the average of all measurements taken from fasting integrated GH at the screening visit for participants enrolled directly in OLE Phase. All subsequent GH measurements in OLE Phase were based on single random samples at the visit.
Data cutoff date: 31 August 2025

5) Change from OLE Baseline in Residual Tumor Volume at Each Visit in the OLE Phase

No clinically significant changes (>25% increases or decreases in tumour volume) were observed in pituitary tumour size in 20 participants at Week 48 as measured by MRI for either prior paltusotine group or prior placebo group.

Pre-defined subgroup analyses

Subgroup analyses were conducted on the FAS for the primary endpoint for the following subgroups: sex, age, screening IGF-1 group, prior treatment (strata), BMI groups, weight groups, ethnicity, race, use of H2 blockers, and geographic region. Age was dichotomized to less than 65 years old and greater than or equal to 65 years old. Race was broken down to White and non-White.

Table 32 Subgroup Summary of Primary Efficacy Analysis: IGF-1⩽1.0×ULN at EOR in RC Phase of CRN00808-08 (Full Analysis Set)

Subgroup	Paltusotine (N=54) n	Paltusotine (N=54) m (%)	Placebo (N=57) n	Placebo (N=57) m (%)
Sex – n (%)				
Male	28	16 (57.1)	24	1 (4.2)
Female	26	14 (53.8)	33	2 (6.1)
Age – n (%)				
< 65 years	47	25 (53.2)	54	3 (5.6)
>=65 years	7	5 (71.4)	3	0
Screening IGF-1 Group – n (%)				
< Median (1.78xULN)	29	22 (75.9)	26	3 (11.5)
>= Median (1.78xULN)	25	8 (32.0)	31	0
Baseline Prior Treatment per IRT – n (%)				
Medically Naïve or Previously Treated	40	17 (42.5)	42	1 (2.4)
Medically Naïve	22	5 (22.7)	24	1 (4.2)
Previously Treated	18	12 (66.7)	18	0
Washout	14	13 (92.9)	15	2 (13.3)
Baseline Body Mass Index Group – n (%)				
< 30 kg/m^2	32	18 (56.3)	34	1 (2.9)
>= 30 kg/m^2	22	12 (54.5)	23	2 (8.7)
Baseline Weight Group – n (%)				
< Median (82.3 kg)	24	12 (50.0)	31	2 (6.5)
>= Median (82.3 kg)	30	18 (60.0)	26	1 (3.8)
Ethnicity – n (%)				
Hispanic or Latino	18	12 (66.7)	18	2 (11.1)
Not Hispanic or Latino	31	16 (51.6)	36	1 (2.8)
Not Reported	0	0	1	0
Unknown	5	2 (40.0)	2	0
Race – n (%)				
White	28	22 (78.6)	30	2 (6.7)
Non-White	23	6 (26.1)	24	1 (4.2)
Unknown	3	2 (66.7)	3	0
Use of H2 Blockers – n (%)				
Yes	2	1 (50.0)	1	0
No	52	29 (55.8)	56	3 (5.4)
Geographic Region – n (%)				
US	6	4 (66.7)	3	0
Europe	14	11 (78.6)	17	0
Rest of the World	34	15 (44.1)	37	3 (8.1)

EOR=end of Randomized Controlled Phase; IGF-1=insulin-like growth factor-1; IRT = Interactive Response Technology; n=number of participants in each subgroup; m=number of responders; RC=randomized controlled; ULN=Upper limit of normal; US=United States.

IGF-1 at EOR is based on the average of the last 2 measurements of IGF-1 collected at Weeks 22 and 24. When one of the two last IGF-1 measurements is missing a single value is used. Percentages are calculated based on the number of participants in each subgroup (n).

No notable subgroup effects were observed for any subgroup, showing that the paltusotine treatment effect was consistent across subgroups.

For the subgroups of unknown ethnicity, use of H2-blockers, and medically naïve participants, the 95% CI for the treatment difference included zero. However, the sample size for these subgroups was small, and the treatment differences were greater than zero and directionally favoured paltusotine.

Pre-defined sensitivity analyses

1) Sensitivity Analyses of the primary endpoint

To assess the robustness of the primary endpoint analysis, the following prespecified sensitivity analyses were performed on the primary efficacy endpoint. Results of these sensitivity analyses are summarized for the paltusotine and placebo groups in Table 33.

In Stratum 1 (medically naïve or previously treated), the proportion of patients with IGF-1 level ≤1.0× ULN was **42.5%** (17 of 40) in the paltusotine group compared with **2.4%** (1 of 42) in the placebo group.

In Stratum 2 (washout), the proportion of patients with IGF-1 level ≤1.0×ULN was **92.9%** (13 of 14) in the paltusotine group compared with **13.3%** (2 of 15) in the placebo group. Within Stratum 1, the proportion of patients with IGF-1 level ≤1.0×ULN was **22.7%** (5 of 22) in the paltusotine group compared with **4.2%** (1 of 24) in the placebo group among medically naïve participants and was **66.7%** (12 of 18) in the Paltusotine group compared with **0%** (0 of 18) in the placebo group among previously treated participants.

Table 33 Sensitivity Analyses on Primary Efficacy Endpoint: Proportion of Participants with IGF-1 ⩽1.0 x ULN at Week 22 (EOR) in Study CRN00808-08

Primary Endpoint **Analysis Set** **Stratum** **Group**	**Paltusotine (N=54)**	**Placebo (N=57)**	**P-value**
Proportion of subjects who achieved biological response in IGF-1 level at EOR (≤1.0×ULN)			
Sensitivity Analysis #1: Completers Analysis, % (n/N) [a]	60.0% (30/50)	7.3% (3/41)	<0.0001
Sensitivity Analysis #2: Per-protocol Analysis Set, % (n/N) [a]	57.7% (30/52)	5.7% (3/53)	<0.0001
Sensitivity Analysis #3: Dose Titration Not Nonresponder, % (n/N) [a]	55.6% (30/54)	5.3% (3/57)	<0.0001
Sensitivity Analysis #4: No Stratum in Model			
Stratum 1: Medically Naïve (Group 1) or Previously Treated (Group 2), % (n/N) [b]	42.5% (17/40)	2.4% (1/42)	<0.0001
Medically Naïve (Group 1), % (n/N) [b]	22.7% (5/22)	4.2% (1/24)	0.1509
Previously Treated (Group 2), % (n/N) [b]	66.7% (12/18)	0% (0/18)	<0.0001
Stratum 2: Washout (Group 3), % (n/N) [b]	92.9% (13/14)	13.3% (2/15)	<0.0001

CI=confidence interval, EOR=End of Randomized Controlled, IGF-1=insulin-like growth factor-1, IRT=interactive response technology, ULN=upper limit of normal
Note: Percentages are calculated based on the number of participants in each analysis population set.
[a] P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT. For the odds ratio, placebo participants are the reference group.
[b] Participants were stratified by prior treatment (medically naïve or previously treated versus washout). P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor. For the odds ratio, placebo participants are the reference group.

- Medically naïve patients

46 patients were medically naïve:

Among the **22 medically naïve patients** who were treated with paltusotine:

- there were **1/22 (4.5%) patient treated with paltusotine 20 mg**, **3/22 (13.6%) patients treated with paltusotine 40 mg** and **18/22 (81.8%) patients treated with paltusotine 60 mg**.

- only 5/22 (**22.7%**) patients were responders: 0 responder at dose of paltusotine 20 mg, 3/5 (**60%)** responders at the dose of paltusotine 40 mg and 2/5 (**40%)** responders at the dose of paltusotine 60 mg. (3/3) **100%** of the patients treated with paltusotine 40 mg and 2/18 (**11.1%**) of the patients treated with paltusotine 60 mg were responders.

In the **24 medically naïve patients** who were treated with placebo: only 1/24 (**4.2%**) patient was responder.

- Patients previously treated

36 patients previously treated with other SRLs:

Among the **18 patients** previously treated with other SRLs were treated with paltusotine:

- there were 1/18 **(5.6%)** patient treated with paltusotine 20 mg, 8/18 **(44.5%)** patients treated with paltusotine 40 mg and 9/18 **(50%)** patients treated with paltusotine 60 mg.

- **12/18 patients** (66.7%) were responders: no patient treated with paltusotine 20 mg was responder, 6/12 (**50%**) patients treated with paltusotine 40 mg and 6/12 (**50%**) patients treated with paltusotine 60 mg. 6/8 (**75%**) of the patients treated with paltusotine 40 mg and 6/9 (**66.7%**) of the patients treated with paltusotine 60 mg were responders.

In the 18 patients treated with placebo, 0 were responders.

- 1 patient treated with paltusotine 40 mg and 1 patient treated with paltusotine 60 mg received rescue therapy and **4 patients** in the group of placebo.

- 1 patient treated with paltusotine 20 mg, 1 patient treated with paltusotine 40 mg, 1 patient treated with paltusotine 60 mg and **4 patients** on placebo have discontinued the treatment.

- washout patients

There were **29 washout patients**

Among the **14 washout patients** who were treated with paltusotine:

- There were 1 patient treated with paltusotine 20 mg, 4 patients treated with paltusotine 40 mg, and 9 patients treated with paltusotine 60 mg.

- 13/14 were responders (**92.9%**): 1/13 (**7.7%**) patient treated with paltusotine 20 mg, 4/13 (**30.7%**) patients treated with paltusotine 40 mg, and 8/13 (**6.15%**) patients treated with paltusotine 60 mg

were responders. 1/1 (100%) of the patients treated with paltusotine 20 mg, 4/4 of the patients treated with paltusotine 40 mg and 8/9 (88.9%) of the patients treated with paltusotine 60 mg were responders.

In the **15 washout patients** who were treated with placebo, 2 were responders (**13.3%**).

No patient received rescue therapy in the group of patients treated with paltusotine versus **3 patients** in the group on placebo.

6 patients have discontinued the treatment in the group on placebo.

2) Sensitivity analysis was performed using a multiple imputation approach

For the key secondary endpoint of change from Baseline to EOR in IGF-1 x ULN, a sensitivity analysis was performed using a multiple imputation approach for missing data. In this analysis, missing IGF-1 results and all assessments following rescue therapy were imputed by multiple imputation using on-treatment intermediate values from the placebo group, which took into consideration the variability from natural disease course prior to medical intervention.

For this sensitivity analysis, the LS mean (±SE) changes from Baseline to EOT in IGF-1×ULN were **-0.827** (±0.0823) for the paltusotine group and **0.124** (±0.0855) for the placebo group, with a treatment difference of **-0.950** (95% CI: -1.166, -0.735) (nominal **p<0.0001**). This result was consistent with the primary analysis of change from Baseline to EOR in IGF-1xULN.

3) Sensitivity Analyses of Key Secondary Endpoint by Stratum

- **In Stratum 1**, the LS mean (±SE) changes from Baseline to EOT in IGF-1×ULN were **-0.887 (±0.0903)** for the paltusotine group and **0.070 (±0.0881)** for the placebo group, with a treatment difference **of -0.957** (95% CI: -1.210, -0.705) (nominal **p<0.0001**).

- **In Stratum 2**, the LS mean (±SE) change from Baseline to EOT in IGF-1×ULN were **-0.600** (±0.1044) for the paltusotine group and **0.152** (±0.1008) for the placebo group, with a treatment difference of **-0.752** (95% CI: -1.052, -0.453) (nominal **p<0.0001**).

Table 34 Sensitivity Analysis of Secondary Efficacy Endpoint: Change from Baseline to EOT in IGF-1 (×ULN) in RC Phase of Study CRN00808-08 by IRT Stratification Factor (Full Analysis Set)

	Paltusotine (N=54)	Placebo (N=57)	Treatment Difference (95% Confidence Interval)	P-value
Medically Naïve				
IGF-1xULN Change from Baseline to EOT				
LS Mean	-0.829	0.046	-0.875 (-1.254, -0.495)	<0.0001
LS Standard Error	0.1357	0.1299		
Previously Treated				
IGF-1xULN Change from Baseline to EOT				
LS Mean	-0.964	0.108	-1.072 (-1.408, -0.736)	<0.0001
LS Standard Error	0.1151	0.1151		
Medically Naïve or Previously Treated (Stratum 1)				
IGF-1xULN Change from Baseline to EOT				
LS Mean	-0.887	0.070	-0.957 (-1.210, -0.705)	<0.0001
LS Standard Error	0.0903	0.0881		
Washout (Stratum 2)				

	Paltusotine (N=54)	Placebo (N=57)	Treatment Difference (95% Confidence Interval)	P-value
IGF-1xULN Change from Baseline to EOT				
LS Mean	-0.600	0.152	-0.752 (-1.052, -0.453)	<0.0001
LS Standard Error	0.1044	0.1008		

EOT = the average of week 22 and week 24 if no rescue therapy, otherwise EOT= last assessment prior to rescue; IGF-1=insulin-like growth factor-1, IRT = Interactive Response Technology, ULN=upper limit of normal.

Baseline IGF-1 is the average of the measurements taken on Day 1 on or prior to first dose of study drug and the last IGF-1 value measured just prior to this day. Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group as fixed effects, baseline IGF-1xULN as a covariate.

4) Sensitivity Analysis: Proportion of Participants with IGF-1 <1.3×ULN at EOR by IRT Stratification Factor

Table 35 Sensitivity Analysis of Secondary Efficacy Endpoint: Proportion of Participants with IGF-1 ⩽1.3 x ULN at Week 22 (EOR) in Study CRN00808-08 by Stratification Factor (Full Analysis Set)

Primary Endpoint Analysis Set Stratum Group	Paltusotine (N=54)	Placebo (N=57)	P-Value
Proportion of subjects who achieved biological response in IGF-1 level at EOR (≤1.3×ULN)			
Sensitivity Analysis: No Stratum in Model			
Stratum 1: Medically Naïve (Group 1) or Previously Treated (Group 2), % (n/N) [b]	55.0% (22/40)	9.5% (4/42)	<0.0001
Medically Naïve (Group 1), % (n/N) [b]	36.4% (8/22)	8.3% (2/24)	0.0495
Previously Treated (Group 2), % (n/N) [b]	77.8%(14/18)	11.1% (2/18)	0.0001
Stratum 2: Washout (Group 3), % (n/N) [b]	100% (140/14)	26.7% (4/15)	<0.0001

EOR=End of Randomized Controlled, IGF-1=insulin-like growth factor-1, IRT=interactive response technology, ULN=upper limit of normal

Note: Percentages are calculated based on the number of participants in each analysis population set.

[a] P-value, are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT.

[b] Participants were stratified by prior treatment (medically naïve or previously treated versus washout).

5) Sensitivity Analysis: Proportion of Participants with GH<1.0 ng/mL at Week 22 by Stratification Factor

Table 36 Sensitivity Analysis of Secondary Efficacy Endpoint: Proportion of Participants with GH<1.0 ng/mL at Week 22 (EOR) in Study CRN00808-08 by Stratification Factor (Full Analysis Set)

Primary Endpoint Analysis Set Stratum Group	Paltusotine (N=54)	Placebo (N=57)	P-Value
Proportion of subjects who achieved biological response in GH level < 1.0 ng/mL at Week 22)			
Sensitivity Analysis #4: No Stratum in Model			
Stratum 1: Medically Naïve (Group 1) or Previously Treated (Group 2), % (n/N) [b]	52.5% (21/40)	7.1% (3/42)	<0.0001

Primary Endpoint Analysis Set Stratum Group	Paltusotine (N=54)	Placebo (N=57)	P-Value
Medically Naïve (Group 1), % (n/N) [b]	36.4% (8/22)	4.2% (1/24)	0.0148
Previously Treated (Group 2), % (n/N) [b]	72.2% (13/18)	11.1% (2/18)	0.0005
Stratum 2: Washout (Group 3), % (n/N) [b]	71.4% (10/14)	46.7% (7/15)	0.3297

EOR=End of Randomized Controlled, GH=growth hormone, IRT=interactive response technology, ULN=upper limit of normal

Note: Percentages are calculated based on the number of participants in each analysis population set.

[a] P-value is from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT.

[b] Participants were stratified by prior treatment (medically naïve or previously treated versus washout).

6) Sensitivity Analysis: Change Baseline to EOR in Total ASD Score by IRT Stratification Factor

Table 37 Secondary Efficacy Endpoint: Change from Baseline to EOT in Total ASD in Study CRN00808-08 by IRT Stratification Factor (Full Analysis Set)

	Paltusotine (N=54)	Placebo (N=57)	Treatment Difference (95% Confidence Interval)	P-value
Medically Naïve				
Total ASD Change from Baseline to EOT				
LS Mean	**-3.189**	**2.669**	**-5.858 (-11.336, -0.380)**	**0.0367**
LS Standard Error	**1.9761**	**1.8476**		
Previously Treated				
Total ASD Change from Baseline to EOT				
LS Mean	**-5.344**	**-3.381**	**-1.963 (-9.444, 5.518)**	**0.5967**
LS Standard Error	**2.5467**	**2.6213**		
Medically Naïve or Previously Treated				
Total ASD Change from Baseline to EOT				
LS Mean	**-4.187**	**0.163**	**-4.349 (-8.831, 0.132)**	**0.0570**
LS Standard Error	**1.6047**	**1.5647**		
Washout				
Total ASD Change from Baseline to EOT				
LS Mean	**-1.610**	**5.777**	**-7.387 (-13.638, -1.137)**	**0.0224**
LS Standard Error	**2.2087**	**2.0544**		

ASD=Acromegaly Symptoms Diary, EOT = week 24 if no rescue, otherwise EOT = last assessment prior to rescue, IRT = Interactive Response Technology.

Baseline total ASD is the sum of the weekly average on or prior to Day 1, and post-baseline total ASD is the sum of the weekly average on or prior to the scheduled visit date, inclusive of the date of visit, for 7 items (headache, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling). Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, and baseline total ASD score as a covariate.

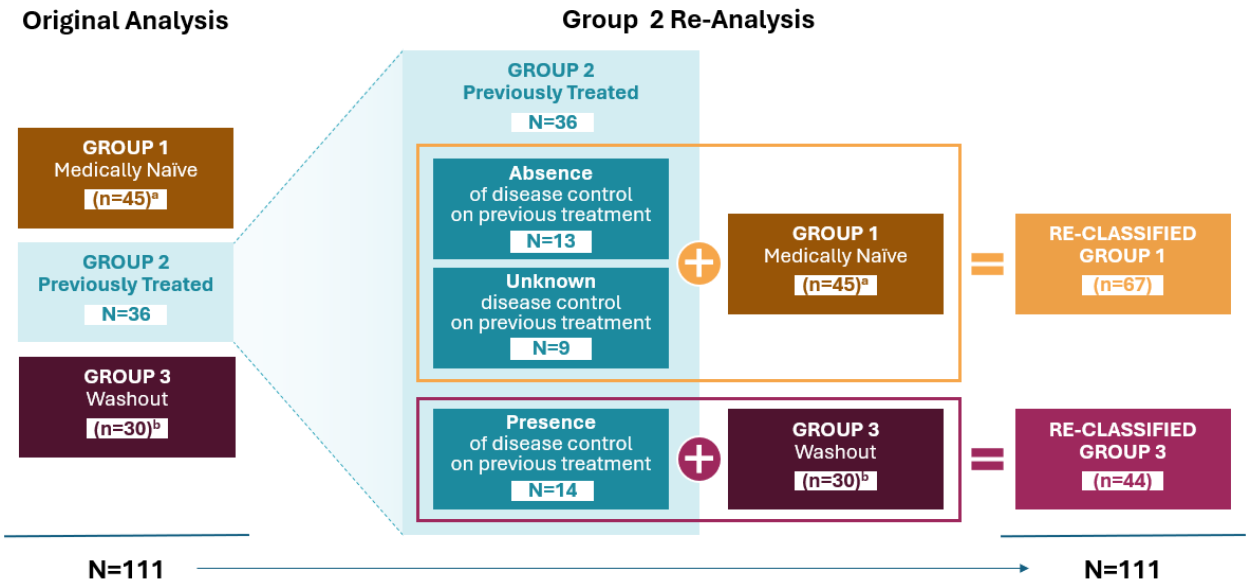
Ancillary analyses

1) Group 2 Post Hoc Analyses

Post hoc analyses were conducted to further characterize Group 2 (previously treated) participants in study CRN00808-08, including supplemental data collection of historical data and a retrospective reclassification and efficacy analyses based on disease control on previous treatment.

A retrospective re-classification based on detailed historical data allowed for a more informative grouping of participants who were medically naïve or not successfully treated (Stratum 1) or Stratum 2 with recently washed out or had an extended washout following a response. **Stratum 1 was reconfigured inclusive of participants who were medically naïve, previously uncontrolled, and with status unknown relative to disease control.**

Figure 24 Post-hoc Re-analysis of Group 2 Participants Based on Prior History of Biochemical Control



[a] BR014-0815 was incorrectly assigned to the medically naive group (Group 1) but was previously treated. This participant had presence of disease control after previous treatment and was reassigned to the previously treated group (Group 3).
[b] US031-08001 was incorrectly assigned to the previously treated group (Group 2) but was washed out of previous SRL treatment. This participant is now included in the re-classified Group 3.

A *post-hoc* analysis of the primary efficacy endpoint (IGF-1 ≤1×ULN at the End of the Randomized Control Phase), and all secondary endpoints were performed after conducting this re-classification of Group 2 (previously treated) based on the presence or absence of disease control on previous acromegaly treatment(s).

IGF-1 Response in Participants Who Received Any Prior Medical Therapy

Prior response data from the **36 participants** enrolled in Group 2 ("previously treated") who received any previous treatment, **14** had presence of disease control and **13** had absence of disease control while on previous acromegaly medication(s). In **9 participants**, the response to previous medical therapy was unknown, either because IGF-1 was not performed or because the results were not available and these participants were classified as medically naïve.

Results from the post-hoc analysis with the re-classified Groups 1 and 2 in Stratum 1 and Expanded Group 3 in Stratum 2 are summarized in Table 38.

Table 38 Primary Efficacy Analysis for Group 1 and Group 3: IGF-1 ⩽1.0×ULN at EOR Based on Re-classification of Group 2 (Any Prior Treatment)

	Paltusotine (N=54) % (n/N)	Placebo (N=57) % (n/N)	p-Value
Group 1 Re-analysis			
Medically Naïve + Absence of disease control + Unknown	34.4% (11/32)	2.9% (1/35)	0.0016
Absence disease control on any Tx	57.1% (4/7)	0% (0/6)	0.049
Unknown	66.7% (2/3)	0% (0/6)	0.0833
Group 3 Re-analysis			
Washout + Presence of disease control	86.4% (19/22)	9.1% (2/22)	<0.0001
Presence of disease control on any Tx	75% (6/8)	0% (0/6)	0.0093

Tx=treatment

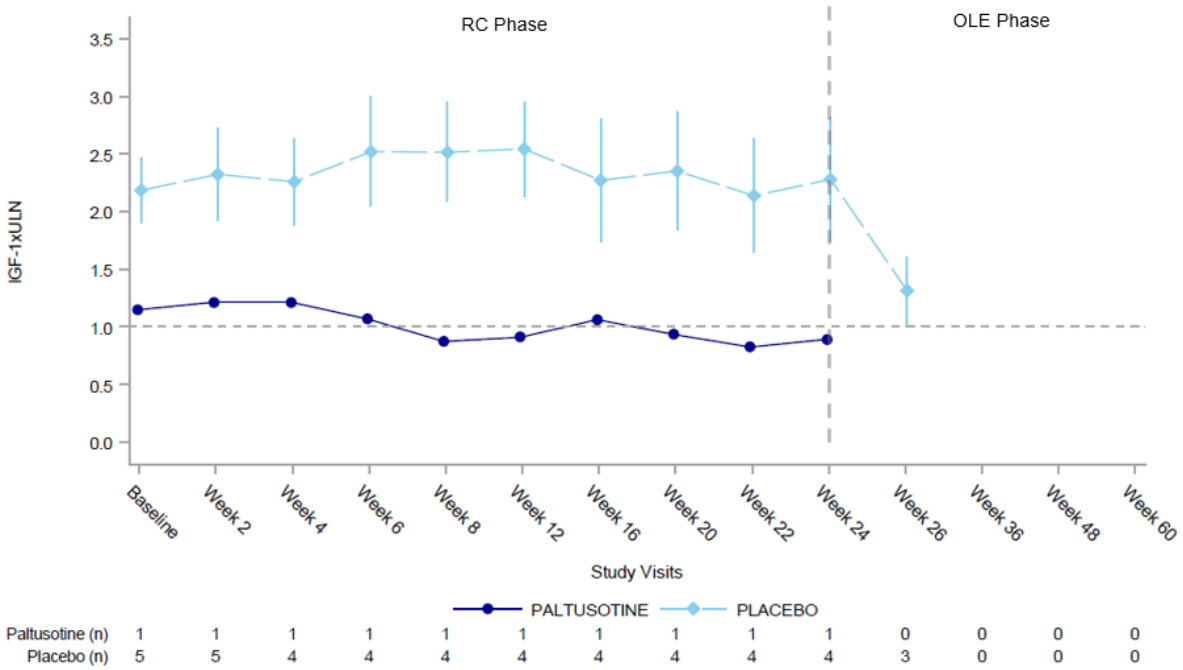
2) A post-hoc analysis was performed to evaluate the data for participants without prior surgery in study CRN00808-08

Study participants without prior pituitary surgery were slightly older than the overall population (median age **59.5 years** versus **46.0 years**). Participants without prior surgery had a longer median time since acromegaly diagnosis compared to the overall study population (105.3 months versus 72.2 months; CSR CRN00808-08 RC Phase.

No other notable differences were observed in Baseline demographic characteristics between participants without prior pituitary surgery and the overall study population. Baseline disease characteristics, including IGF-1 levels and time since acromegaly diagnosis, were also generally consistent between participants without prior pituitary surgery and the overall population. Of note, all the medically naïve patients had prior pituitary surgery.

Figure 25 presents the mean IGF-1 levels (×ULN) by visit for participants without prior pituitary surgery in the RC Phase and OLE Phase of the study.

Figure 25 Mean (±SE) IGF-1×ULN by Visit for Participants Without Prior Pituitary Surgery in RC Phase and OLE Phase of Study CRN00808-08 (Full Analysis Set)



IGF-1=insulin-like growth factor-1, OLE=open-label extension, RC=randomized controlled, SE=standard error, ULN=upper limit of normal
Notes: Figure reflects available IGF-1 assessments up to the data cut-off date (20 January 2024).

Table 39 presents a summary of the reasons why participants did not undergo prior pituitary surgery in studies CRN00808-08 and CRN00808-09. The most frequently reported reason was "Participant unwilling to undergo surgery" in 9 of 14 participants (64.3%). Other reasons were "medical decision" for 2 participants (14.3%) and "contraindication to surgery" for 1 participant (7.1%). The reason for not having surgery was unknown for 2 participants (14.3%) (1 for each study) who terminated the studies before data collection for this request, so it was not possible obtain the reason for not receiving prior surgery for these participants.

Table 39 Reasons for Participants Not Undergoing Prior Pituitary Surgery in Studies CRN00808-08 and CRN00808-09

Reason Participant Did Not Undergo Prior Pituitary Surgery	Study CRN00808-08 (n=5)	Study CRN00808-09 (n=7)	Total Participants (n=14)
Participant unwilling to undergo surgery	3	6	9
Contraindication to surgery	1	0	1
Medical decision	1	1	2
Unknown [a]	1	1	2

[a] Two participants (1 for each study) terminated the studies before data collection for this request.

5.3.2.2. Study CRN00808-09

5.3.2.2.1. Study title

PATHFNDR-1: Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen

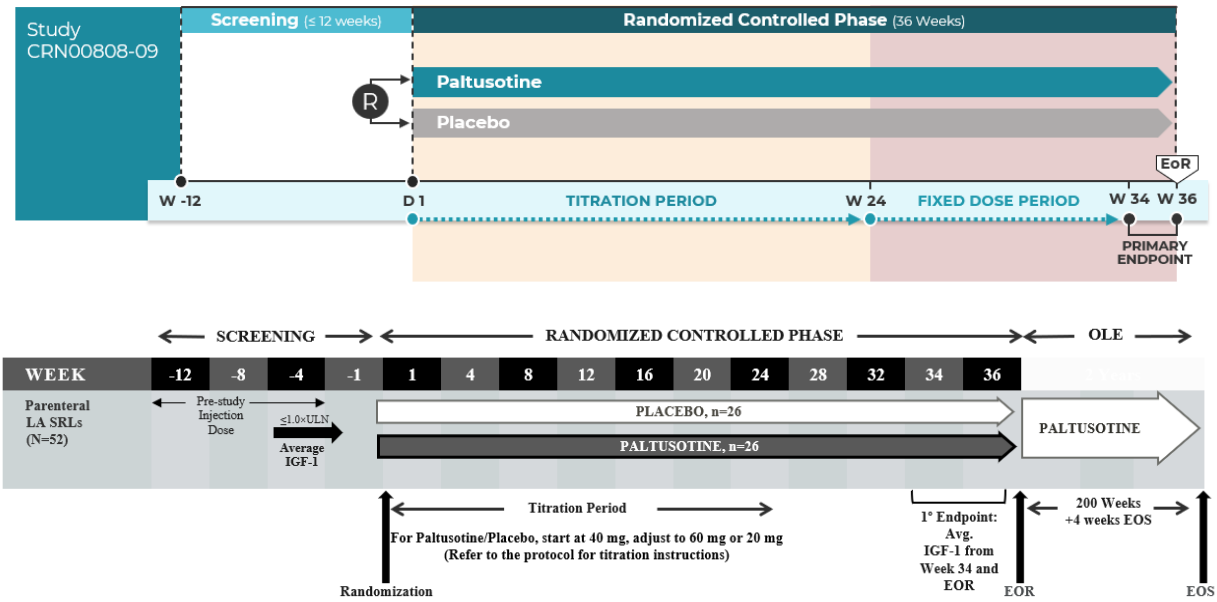
5.3.2.2.2. Study design

This is a phase 3, randomized, placebo-controlled, multicentre study designed to evaluate the efficacy and safety of paltusotine in participants with acromegaly who were switched from monotherapy with injected long-acting octreotide or lanreotide. In the Randomized Controlled (RC) Phase, eligible participants were randomized (1:1 ratio) to daily oral administration of paltusotine or placebo when their next dose of octreotide/lanreotide was due to begin, for a Treatment Period of **up to 36 weeks**.

Participants who completed the RC phase could be eligible to enrol and receive paltusotine in the Open-label Extension (OLE) Phase **for up to 200 weeks**. The RC phase is completed. This report describes results from RC Phase. The OLE phase is on-going.
The study design was aimed at maintaining participants in their baseline biochemical status and optimizing their dose while minimizing the period in which their IGF-1 level was above Baseline.

This study was conducted at 30 sites in 13 countries: Argentina, Belgium, Brazil, Bulgaria, France, Hungary, Israel, Italy, Peru, Poland, Serbia, United Kingdom (UK), and United States (US).

Figure 26 CRN00808-09 Study schema



Average IGF-1=average of all (up to 3) study assessments taken during Screening, EOR=end of RC Phase (end of treatment), EOS=End of Study, IGF-1=insulin-like growth factor-1, LA SRL=long-acting somatostatin receptor ligand (octreotide/lanreotide only), OLE=Open-label Extension, RC=Randomized Controlled, ULN=upper limit of normal
EOR was defined as the end of the RC Phase at Week 36.
EOS is defined as the day final study data are collected and should occur 4 weeks after the last dose of study drug. The end of Week 240/EOS Visit (Follow-up Visit for the OLE Phase) is the last planned visit of the study, but the EOS Visit could occur at Week 40 (Follow-up Visit for the RC Phase) in participants who did not enter the OLE Phase.

The study consisted of 3 periods:

- **Screening Period**: the Screening Period consisted of 2 to 3 visits **over 4 to 12 weeks**. The last pre-randomization long-acting SRL (octreotide/lanreotide) injection was to be administered before or during Screening to maintain the dosing interval between octreotide/lanreotide and the first dose of study drug, ie, the first dose of study drug was to be administered when the next dose of lanreotide/octreotide would have been due, provided the screening period did not exceed 12 weeks. As such, the last octreotide/lanreotide injection was the key temporal event during screening.
- **Treatment Period** (Randomized Controlled Phase):

Participants meeting all eligibility criteria were randomized (1:1) to paltusotine or placebo during the RC Phase, which lasted approximately 36 weeks. **Randomization was stratified by mean Screening IGF-1 level (<0.86×ULN, ≥0.86×ULN) and prior treatment (lanreotide, octreotide).** Scheduled study visits occurred approximately every 4 weeks.

- **Open-label Extension (OLE) Phase (cut-off date: 21 May 2025)**

Participants who completed the 36-week RC Phase or who met rescue criteria and completed the 36-week RC Phase with rescue treatment could continue participation in the OLE Phase if the participant was willing to participate and, in the opinion of the investigator, the participant could benefit from continued or initiated treatment with paltusotine.

Treatment

RC Phase

The starting dose was **40 mg** (2×20 mg tablets of active paltusotine or matching placebo) QD for oral self-administration. During the RC Phase, the dose of study drug could be increased from 40 mg (2×20 mg tablets) QD to 60 mg (3×20 mg tablets) QD **through Week 24** if the participant's most recent IGF-1 result was >0.9×ULN and tolerability at the current dose was acceptable, as evaluated by the investigator.

It was anticipated that the study drug dose would be stable, and titration would be completed, **prior to or at Week 24**, with no dose titrations/adjustments **after Week 24**. Participants who required dose up-titration after Week 24 were considered non-responders.

Dose down-titration was allowed at any time during the study if the dose was not tolerable in the judgement of the investigator.

If tolerability improved following the dose reduction, the dose could be increased in 20 mg increments up to a maximum dose of 60 mg. If study drug was not tolerated, treatment could be interrupted for a total of 14 days per year, but no more than 7 consecutive days per year during the study, followed by resumption of study drug at the same or at a reduced dose, as appropriate

Rescue criteria were provided for participants who required resumption of standard acromegaly treatment during the RC Phase.

Table 40 Dose Titration Options for Study CRN00808-09

Dose Titration/Adjustment	IGF-1 Criteria	Tolerability Criteria
40 mg→60 mg	Participant's most recent IGF-1 result on 40 mg was >0.9×ULN	Increase allowed due to acceptable tolerability on 40 mg
40 mg→20 mg	--	Dose reduction required due to unacceptable tolerability on 40 mg
20 mg→40 mg	Participant's most recent IGF-1 result on 20 mg was >0.9×ULN	Tolerability was acceptable on 20 mg

Dose Titration/Adjustment	IGF-1 Criteria	Tolerability Criteria
60 mg→40 mg	--	Dose reduction required due to unacceptable tolerability on 60 mg

IGF-1=insulin-like growth factor-1, ULN=upper limit of normal

OLE Phase

The starting dose for participants in the OLE phase was paltusotine **40 mg QD**, dispensed in an open-label manner. The first dose of the OLE phase was administered **at the Week 36/EOR Visit**. Participants were given bottles of paltusotine containing 36×20 mg tablets and were instructed to take 2 tablets daily until their next visit.

Dose escalation in the OLE phase could occur once the first IGF-1 result was available. At that time, the investigator could determine whether the dose **could be up-titrated to 60 mg**. Scheduled visits for the OLE phase occur approximately every 12 weeks. The OLE treatment period is 204 weeks.

Dose down-titration was allowed if the dose was not tolerable in the judgement of the investigator. Study medication could be held for up to a total of 14 days, but no more than 7 consecutive days per year in the OLE.

Concomitant medications

Prohibited Medications

- Oral estrogen, except for monophasic estrogen-progestin oral contraception
- Strong inducers of the drug metabolizing enzyme CYP3A4, including but not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort (because these medicines could decrease the concentration of paltusotine in the systemic circulation).
- Any standard acromegaly drug that was not used as a rescue medication during the RC Phase or an allowed adjunctive medication in the OLE Phase
- Any other investigational drug, unless approved by the Medical Monitor (e.g. coronavirus disease 2019 [COVID-19] therapies)

Rescue therapy

RC Phase

- During the RC Phase, acromegaly treatments other than study drug were prohibited, unless the participant met criteria for rescue therapy. Octreotide LAR or lanreotide depot monotherapy (approved SRLs) were the only rescue therapies permitted during the study.

Criteria for rescue therapy consisted of the following:

Significant worsening of 1 or more acromegaly symptoms or the development of a new acromegaly symptom, **at the highest dose (60 mg) for at least 2 weeks**, as assessed by the investigator. Symptoms needed to be attributed to uncontrolled acromegaly in the opinion of the investigator and could include but were not limited to the following: headache, arthralgia, fatigue, hyperhidrosis, or soft tissue swelling.

Significant worsening was defined as symptoms requiring a substantial increase in level of clinical care (e.g. significant intervention needed to avert hospitalization or a clinically notable increase in frequency or intensity of patient contact required) or substantial clinical deterioration (e.g. worsening from a mild to severe AE or the onset of an SAE would meet these criteria).

AND

IGF-1 value ≥1.3×ULN at the highest dose (60 mg) measured at 2 successive planned visits or at an unscheduled visit if an earlier result was needed (as evaluated by the investigator).
If rescue therapy was required during the RC phase, paltusotine or placebo **were to be discontinued** before rescue therapy was initiated. Study participants receiving rescue therapy were asked to continue study visits for surveillance for the remainder of the 36-week RC phase.
Participants who discontinued from study drug early by meeting protocol criteria for rescue therapy with approved SRLs and who completed the 36-week RC phase **could be eligible** for participation in the OLE Phase of the study, if the participant was willing and, in the opinion of the investigator, the participant could benefit from continued or initiated paltusotine treatment.

OLE Phase

At 6 months, if there was evidence of paltusotine efficacy but participants had not reached therapeutic target goals, **adjunctive treatment could be initiated** if clinically appropriate beginning **at Week 60**. If these criteria were met, non-SRL acromegaly treatments, such as cabergoline or the GH receptor antagonist pegvisomant, were permitted and could be initiated as an adjunctive treatment when a participant experienced at least 2 consecutive elevated IGF-1 (≥1.3×ULN) measurements at the highest paltusotine dose level (60 mg) or was otherwise not at the participant's therapeutic target in the judgement of the investigator.

Short- and long-acting somatostatin receptor agonists (other than paltusotine) remained prohibited therapies during the OLE Phase. If these treatments were needed, participants were to be discontinued from the study, and an ET Visit was to be scheduled prior to resuming these treatments.

Randomisation

Participants were randomized to study treatment using interactive response technology (IRT).
Randomization was performed using a fixed-block randomization scheme. The randomization scheme was generated prior to the initiation of the study by an independent statistician/programmer.
Investigators and the study team were not aware of the block size of the randomization scheme. **Randomization was stratified by IGF-1 level** (<0.86×ULN, ≥0.86×ULN) **and prior treatment** (lanreotide or octreotide).

Blinding

The Sponsor, contract research organizations (CROs), investigators, study site personnel, and study participants were blinded to treatment assignment during the RC phase. The randomization schedule was kept strictly confidential and accessible only to authorized persons. The randomization schedule was made available for unblinding and analysis only after the RC phase was completed, the protocol deviations were determined, and the study database was locked.
The IRT system was programmed with blind-breaking instructions in case of an emergency for participant safety and for expedited reporting of SAEs to regulatory agencies, when required.

Patient population

Main inclusion criteria
(also see other similar inclusion criteria in study **CRN00808-08**)

- Adults ≥18 years of age with medically stable, confirmed-active acromegaly and on an approved, stable monotherapy dose of long-acting octreotide or lanreotide, for at least 12 weeks prior to Screening. Continuous treatment with octreotide or lanreotide must be at least 24 weeks prior to Screening.

The following prior treatment regimens were allowed for inclusion into this study: long-acting octreotide: 10, 20, 30, 40 mg every 4 weeks or long-acting lanreotide: 60, 90, 120 mg every 4 weeks or 120 mg every 6 or 8 weeks.
- Previous diagnosis of acromegaly confirmed by the Investigator and approved by the Medical Monitor. This requires evaluable documentation of a pituitary tumour diagnosed by pituitary imaging or histopathologic confirmation of a pituitary adenoma **at least 24 weeks** prior to screening.
- For subjects who have had pituitary surgery, there must be documentation of IGF-1 concentration ≥ 1.3×ULN at least 12 weeks after last pituitary surgery. The surgery must have been performed ≥24 weeks prior to screening. Subjects who have not had pituitary surgery must have documentation of IGF-1 concentration ≥1.3×ULN performed ≥24 weeks prior to screening.
- **Screening average IGF-1 levels of ≤1.0×ULN**. The upper limit for eligibility is mean IGF-1 of 1.04 (rounded to 2 decimal places) and will be based on 2 or 3 separate measurements in consultation with the Medical Monitor.
- Willing and able to undergo biliary/gallbladder ultrasound procedure and pituitary MRI during screening and during the study.

Main exclusion criteria

Similar exclusion criteria to study **CRN00808-08.** In addition, treatment-naïve or treatment-withdrawn acromegaly subjects should be excluded.
- Treatment-naïve or treatment-withdrawn acromegaly subjects.
- Use of the following medications as outlined:
. Pasireotide LAR (within 24 weeks prior to screening),
. Pegvisomant (within 12 weeks before screening),
. Dopamine agonists (within 12 weeks before screening), or
. Short acting somatostatin analogues (SA-SSAs) within last 12 weeks before the first dose of study drug.
Note: Withdrawal of these medications should be part of the subject's medical care plan prior to screening; entry into the study should not be the sole reason for withdrawal of a prior medication.

5.3.2.2.3. Objectives and estimands

Primary objective

The primary objective of the RC phase was to evaluate the efficacy of paltusotine versus placebo on IGF-1 response in participants with acromegaly treated with long-acting SRLs.

Table 41 Efficacy Endpoint Definitions and Statistical Analysis Methods for RC Phase of Study CRN00808-09

Efficacy Endpoint	Definition	Statistical Test	Sensitivity Analyses
Primary Efficacy Endpoint			

Efficacy Endpoint	Definition	Statistical Test	Sensitivity Analyses
Proportion of participants who maintained biochemical response in IGF-1 (≤1.0× ULN) at EOR	IGF-1 response was defined as IGF-1 level ≤1.0×ULN based on the average of the last 2 measurements prior to EOR (Weeks 34 and 36), rounded to 2 significant figures. If only 1 measurement was available at Weeks 34 and 36, this 1 measurement was used to define response. Nonresponse was defined as IGF-1 level >1.0×ULN based on the average of the last 2 measurements or with IGF-1 missing at both Week 34 and Week 36. Participants who discontinued treatment for any reason prior to EOR, received prohibited standard acromegaly treatment, received rescue therapy with criteria met, or titrated up in dose after Week 24 were also considered nonresponders.	Analyzed on the FAS using an exact logistic regression model with covariates of Screening IGF-1 groups (<0.86×ULN, ≥0.86×ULN) and Baseline prior treatment groups (lanreotide, octreotide). For the odds ratio, placebo participants were the reference group. Subgroup analysis was performed on the FAS for the primary endpoint and included sex, age group (<65 years old and ≥65 years old), Screening IGF-1 group (<0.86×ULN, ≥0.86×ULN), prior treatment (octreotide, lanreotide), BMI groups (<30 and ≥30 kg/m^2), weight groups (split by median values), ethnicity, race (White and non-White), use H2 blockers, and geographic region (US sites and non-US sites).	The prespecified sensitivity analyses were performed on the primary efficacy endpoint: 1) completers analysis, which included only FAS participants who completed at least 34 weeks of treatment, 2) where participants were not considered nonresponders for up-titrating in dose after Week 24, and 3) on the PPS.

Efficacy Endpoint	Definition	Statistical Test	Sensitivity Analyses
Secondary Efficacy Endpoint			
Change from Baseline in IGF-1, in units of ULN, to EOR	For the change from Baseline to EOR in IGF-1×ULN, EOR was EOT at Week 36 if there was no rescue therapy administered or was based on the last available IGF-1 assessment prior to rescue.	Analyzed on the FAS using an ANCOVA model including fixed effects for treatment group, Screening IGF-1×ULN group (<0.86×ULN, ≥0.86×ULN), and Baseline prior treatment group (lanreotide, octreotide) and Baseline IGF-1 level	A sensitivity analysis was performed using a multiple imputation approach for missing data. IGF-1 results for all assessments following the first occurrence of intercurrent events, such as dropouts (ie, participants who discontinued the study prior to Week 36), taking rescue therapy or prohibited medications, or up titration in dose after Week 24, were evaluated as missing data.

		included as a covariate.	The missing measurement was imputed by a multiple imputation procedure using on-treatment intermediate values from the placebo group, which took into consideration the variability from the natural disease course prior to medical intervention.
Proportion of participants with GH <1 ng/mL at Week 34, out of those who had GH <1.0 at Baseline	GH level at Week 34 was based on the mean of GH values (ng/mL) collected from integrated samples at Week 34. Nonresponse was defined as GH level ≥1.0 ng/mL at Week 34. Participants who discontinued treatment for any reason prior to Week 34, took prohibited medication or rescue medication, or up-titrated in dose after Week 24 were also considered nonresponders.	Analyzed on the FAS using an exact logistic regression model with covariates of Screening IGF-1 groups (<0.86×ULN, ≥0.86×ULN) and Baseline prior treatment groups (lanreotide, octreotide). For the odds ratio, placebo participants were the reference group.	NA

Efficacy Endpoint	**Definition**	**Statistical Test**	**Sensitivity Analyses**
Change from Baseline in total ASD score to EOR	Change from Baseline to EOR in total ASD score was analyzed for the FAS, where EOR was EOT at Week 36 if there was no rescue or was based on the last available assessment prior to rescue.	Analyzed on the FAS using an ANCOVA model including fixed effects of Screening IGF-1×ULN group (<0.86×ULN, ≥0.86×ULN) and Baseline prior treatment group (lanreotide, octreotide) as fixed effects and baseline total ASD score as a covariate.	N/A

ANCOVA=analysis of covariance, ASD=acromegaly symptoms diary, BMI=body mass index, EOR=end of Randomized Controlled Phase, EOT=end of treatment, FAS=Full Analysis Set, GH=growth hormone, IGF-1=insulin-like growth factor-1, PPS=Per Protocol Set, ULN=upper limit of normal, US=United States

Estimands for the primary objective

Table 42 Estimands for primary objective

Population	Patients with acromegaly (previously treated with somatostatin receptor ligands) who would encounter the intercurrent event of discontinuation, rescue medication, prohibited medication, or dose up-titration after Week 24 if assigned to either paltusotine or placebo.
Treatment conditions	Assignment to paltusotine, regardless of discontinuation and use of rescue medication, compared to assignment to placebo, regardless of discontinuation and use of rescue medication.
Endpoint (variable)	Proportion of participants maintaining IGF-1 ≤ 1.0×ULN at end of randomised treatment (EOR), based on the average of Weeks 34 and 36. If only one value is available, that single result (rounded to two significant figures) is used.
Population-level summary	Proportion of responders in each treatment group; comparison via odds ratio using exact logistic regression with adjustment for baseline IGF-1 group and prior treatment (lanreotide or octreotide). If the model fails to converge, Firth logistic regression is applied.
Intercurrent events and strategy to handle them	
Discontinuation of treatment	Composite: to reflect treatment failure
Rescue medication use	Composite: to reflect treatment failure
Use of prohibited medication	Composite: to reflect treatment failure
Up-titration after Week 24	Composite: to reflect treatment failure

The primary estimand assesses the effect of paltusotine versus placebo on maintenance of biochemical control in acromegaly, defined as sustaining IGF-1 ≤ 1.0×ULN at Week 36 (based on the average of Weeks 34 and 36, or a single value if only one is available). Participants who discontinued treatment, received rescue or prohibited medication, or had dose up-titration after Week 24 were considered non-responders. These intercurrent events were handled using a composite strategy, reflecting clinical failure.

Statistical methods for estimation and sensitivity analysis on primary estimands

The primary efficacy analysis was based on the Full Analysis Set (FAS). The estimand targeted the proportion of participants with IGF-1 ⩽1.0×ULN at End of Randomisation (EOR), defined as the average of Weeks 34 and 36 (rounded to two significant figures). Participants with missing IGF-1 values at both visits or with intercurrent events (treatment discontinuation, rescue/prohibited medications, or dose titration after Week 24) were considered non-responders.

The primary analysis used an exact logistic regression model adjusting for baseline IGF-1 level and prior treatment strata; Firth logistic regression was prespecified as a fallback. Multiplicity was controlled through a hierarchical testing procedure. Sensitivity analyses explored variations in the estimand, including per-protocol, completers, and alternate handling of intercurrent events (e.g. up-titration not

considered treatment failure).

Secondary objectives

Secondary objectives were to evaluate the effects of paltusotine versus placebo on IGF-1 level, GH response, and acromegaly symptoms.
The objective of the OLE phase is to evaluate the long-term safety and efficacy of paltusotine.

Secondary Efficacy Endpoints
The secondary efficacy endpoints of the RC Phase were as follows:
- Change from Baseline in IGF-1, in units of ULN, to EOR
- Proportion of participants with GH<1.0 ng/mL at Week 34, out of those who had GH <1.0 ng/mL at Baseline
- Change from Baseline in total Acromegaly Symptom Diary (ASD) score to EOR.

Table 43 Estimands for the secondary objectives

Population	Patients with acromegaly previously treated with lanreotide or octreotide who would encounter the intercurrent event of discontinuation, rescue medication, prohibited medication, or dose up-titration after Week 24 if assigned to either paltusotine or placebo.
Treatment condition<s>	Assignment to paltusotine, regardless of discontinuation and use of rescue medication, compared to assignment to placebo, regardless of discontinuation and use of rescue medication.
Endpoint (variable)	Change from baseline to end of randomised treatment (Week 36) in IGF-1×ULN. EOR is defined as the average of IGF-1 values at Weeks 34 and 36. If only one value is available, that value is used. If neither is available, the last value prior to rescue, prohibited medication use, discontinuation, or up-titration is used.
Population-level summary	Treatment group difference in adjusted means based on ANCOVA model, including baseline IGF-1×ULN, screening IGF-1 strata (<0.86×ULN / ≥0.86×ULN), and prior treatment (lanreotide, octreotide) as fixed effects. Least squares means, standard errors, 95% confidence intervals and p-values are reported.
Intercurrent events and strategy to handle them	
Discontinuation of treatment	While-on-treatment: last value prior to event carried forward
Rescue medication use	While-on-treatment: last value prior to event carried forward
Use of prohibited medication	While-on-treatment: last value prior to event carried forward
Up-titration after Week 24	While-on-treatment: last value prior to event carried forward

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The key secondary efficacy analysis was based on the Full Analysis Set (FAS) and evaluated change from baseline in IGF-1×ULN at End of Randomisation (EOR). The analysis used an ANCOVA model with treatment group, baseline IGF-1×ULN strata, and prior treatment group (lanreotide, octreotide) as fixed effects, and baseline IGF-1×ULN as a covariate.

Missing data following intercurrent events (rescue/prohibited medication, up-titration after Week 24, or dropout) were imputed using the last available pre-event value. A sensitivity analysis was conducted using multiple imputation, applying on-treatment intermediate values from the placebo group to reflect the natural course of the disease.

Exploratory objectives

The exploratory efficacy endpoints for the RC phase were as follows:
- Change from baseline to Week 34 in GH
- Proportion of participants who received rescue therapy
- Proportion of participants who achieved IGF-1<1.3×ULN at EOR
- Proportion of participants with GH<2.5 ng/mL at Week 34
- Change from baseline in residual tumor volume at EOR
- Time from randomization to the first IGF-1>1.0×ULN for 2 consecutive visits
- Time from randomization to the first IGF-1≥1.3×ULN for 2 consecutive visits
- Change from baseline to EOR in Acromegaly Quality of Life (AcroQoL) total score
- Treatment preference questionnaire (TPQ) at EOR
- Change from Baseline to EOR in EuroQol-5 Dimensions 5-Level (EQ-5D-5L) health index, EuroQol Visual Analogue Scale (EQ VAS), and dimension scores

5.3.2.2.4. Results

Participant flow and numbers analysed

Data cut-off date: 5 December 2023

Interim analysis: 21 May 2025

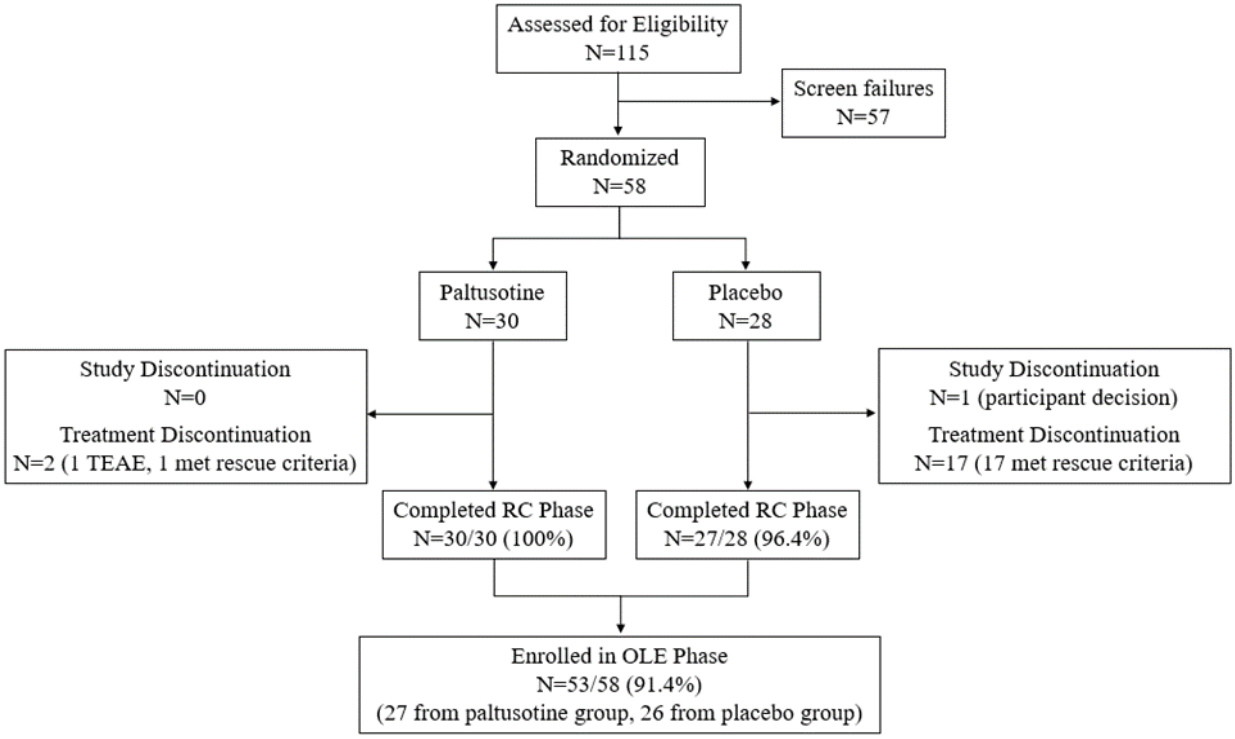
Interim analysis: 31 October 2025

RC phase

A total of **115 participants** were screened, of which **58 participants were randomized** (**30 participants in the total paltusotine group and 28 participants in the placebo group**) and included in the FAS) for the RC Phase of the study.

Treatment groups were balanced with respect to randomization stratification factors (Screening IGF-1 groups [<0.86×ULN, ≥0.86×ULN] and prior treatment [lanreotide, octreotide]).

Figure 27 Participant Disposition for RC Phase of Study CRN00808-09



OLE=Open-label Extension, RC=Randomized Controlled, RC=randomized controlled, TEAE=treatment-emergent adverse event

Treatment Discontinuation

In the paltusotine group, one treatment discontinuation due to an adverse event and one met the rscue criteria.

In the placebo group, 17 patients discontinued the treatment as they met the rescue criteria.

Rescue therapy

In the paltusotine group, **3 participants** received octreotide or lanreotide as rescue therapy during the RC Phase of the study.

A total of **17 participants** (**60.7%)** in the placebo group received octreotide or lanreotide as rescue therapy during the RC Phase.

Table 44 Participant Enrollment and Disposition in RC Phase of Study CRN00808-09 (All Participants)

	Paltusotine Final Dose				
	40 mg n (%)	60 mg n (%)	Total Paltusotine n (%)	Placebo n (%)	Overall n (%)
Total Participants Screened					115
Screen Failure Set					57
Randomized			30	28	58
Randomized and Not Treated			0	0	0
Safety Analysis Set	14 (100)	16 (100)	30 (100)	28 (100)	58 (100)
Full Analysis Set	14 (100)	16 (100)	30 (100)	28 (100)	58 (100)
Stratification Factors					
Screening IGF-1 < 0.86xULN and Lanreotide	4 (28.6)	2 (12.5)	6 (20.0)	5 (17.9)	11 (19.0)
Screening IGF-1 < 0.86xULN and Octreotide	7 (50.0)	1 (6.3)	8 (26.7)	8 (28.6)	16 (27.6)

	Paltusotine Final Dose				
	40 mg n (%)	60 mg n (%)	Total Paltusotine n (%)	Placebo n (%)	Overall n (%)
Screening IGF-1 >= 0.86xULN and Lanreotide	2 (14.3)	4 (25.0)	6 (20.0)	7 (25.0)	13 (22.4)
Screening IGF-1 >= 0.86xULN and Octreotide	1 (7.1)	9 (56.3)	10 (33.3)	8 (28.6)	18 (31.0)
Per-Protocol Analysis Set (PPS)	14 (100)	16 (100)	30 (100)	27 (96.4)	57 (98.3)
Reasons Excluded from PPS					
Randomization/Treatment Error	0	0	0	0	0
< 75% Compliance	0	0	0	0	0
Major Protocol Deviation (PD)	0	0	0	0	0
Did Not Complete the RC phase	0	0	0	1 (3.6)	1 (1.7)
Completed RC Phase	14 (100)	16 (100)	30 (100)	27 (96.4)	57 (98.3)
Treatment Discontinuation in RC Phase	0	2 (12.5)	2 (6.7)	17 (60.7)	19 (32.8)
Primary Reason					
Adverse Event	0	1 (6.3)	1 (3.3)	0	1 (1.7)
Rescue Therapy Required	0	1 (6.3)	1 (3.3)	17 (60.7)	18 (31.0)
Study Discontinuation in RC Phase	0	0	0	1 (3.6)	1 (1.7)
Primary Reason					
Other	0	0	0	1 (3.6)	1 (1.7)

	Paltusotine Final Dose				
	40 mg n (%)	60 mg n (%)	Total Paltusotine n (%)	Placebo n (%)	Overall n (%)
Enrolled in Open Label Extension (OLE) Phase	14 (100)	13 (81.3)	27 (90.0)	26 (92.9)	53 (91.4)
Completed Study Treatment in RC Phase	14 (100)	12 (75.0)	26 (86.7)	10 (35.7)	36 (62.1)
Did not Complete Study Treatment in RC Phase	0	1 (6.3)	1 (3.3)	16 (57.1)	17 (29.3)
Not Enrolled in OLE Phase	0	3 (18.8)	3 (10.0)	2 (7.1)	5 (8.6)
Reasons					
Subject's Decision	0	3 (18.8)	3 (10.0)	2 (7.1)	5 (8.6)

Percentages are calculated based on the number of participants in the Full Analysis Set.

OLE Phase

Of the **58 participants** randomized in this study, **53 participants** (**91.4%**) entered the OLE Phase. All of these participants received at least 1 dose of paltusotine and were included in the OLE Safety Analysis Set.

Of these 53 total participants, **27 participants** were from the paltusotine group, and **26 participants were from the placebo group** in the RC phase of the study. One participant discontinued study treatment and the study due to the inability to fulfil study requirements and procedures.

At the cut-off date of August/September 2024, 2 participants (both in the prior placebo group) had dose reductions from 40 mg to 20 mg due to a TEAEs. For both participants, the events were reported as resolved and disease control was maintained.

At the data snapshot date of 31 August 2025, eight participants (15.1%) overall discontinued the OLE phase of the study**: three participants in the prior paltusotine group and five participants in the prior placebo group.**

Deviations from study plan

Changes in the Conduct of the Study in relation to efficacy assessments

Table 45 Summary of Protocol Amendments and Clarification Letters for Study CRN00808-09

Protocol Version or Clarification Letter	**Summary of Key Changes**
Protocol Version 1.0	Initial protocol version
Protocol Version 2.0, dated 24 February 2021 (participants enrolled in study beginning with Protocol Version 2.0)	Removed Group 2 (IGF-1 level >1.0×ULN and ≤1.5×ULN) from the study population after discussion with Health Authority.
Protocol Version 3.0, dated 14 September 2021	Primary endpoint analysis was revised based on the average of last 2 measurements from Week 34 and Week 36 (EOR) instead of the last 3 measurements from Week 32, Week 34, and Week 36 after discussion with Health Authority. After discussion with Health Authority, clarified that it was anticipated that the study drug dose would be stable, and titration completed prior to or at Week 24, with no dose titrations/adjustments after Week 24. Clarified that up-titration after Week 24 should not occur; participants who required dose up-titration after Week 24 would be considered nonresponders. After discussion with Health Authority, clarified that participants who were rescued during the RC Phase of the study should remain in the study and complete the study assessments. Clarified that these participants could be eligible for enrollment into the OLE Phase of the study. Addition of exploratory endpoints for loss or response (time from randomization to first IGF-1 >1×ULN for 2 consecutive visits, time from randomization to first IGF-1 ≥1.3×ULN for 2 consecutive visits). Change in residual tumor volume changed from a safety endpoint to an exploratory efficacy endpoint at request of regulatory authorities. Addition of monthly pregnancy testing throughout the study.

Protocol Version or Clarification Letter	Summary of Key Changes
Protocol Clarification Letter 1 to Protocol Version 2.0 and Version 3.0, dated 09 December 2021 (Clarification letter applied to both Protocol Versions 2.0 and 3.0 because Protocol Version 3.0 was still under review in some countries.)	In SOA footnote, clarified that the screening fasting integrated GH at this timepoint was during Screening, and there was no study drug dosing during the Screening Period. The collection timeframe of the ASD was updated in Protocol Version 3.0 to 2 weeks prior to study drug dosing. This update was made in "1.2 Schedule of Activities: Randomized, Controlled Phase"; however, the corresponding body text was inadvertently not updated to match. Exclusion Criterion #23 (renal function) clarified to exclude creatinine level, as exclusion based on renal function already provided as Exclusion Criterion #18. Correction of PGI-I and PGI-S description in body of protocol (no change to scale used in protocol). Clarification to procedures for unblinding. The date and reason for breaking the blind was to be recorded in the source documentation but not recorded in the eCRF for the study. Inclusion criteria #5 (Screening average IGF-1 levels of ≤1.0×ULN) and average IGF-1 level for IGF-1 response revised to clarify only one rounding procedure to determine eligibility, ie, to 2 decimal places.
Protocol Clarification Letter 2 to Protocol Version 3.0, dated 29 November 2022	Clarified timing of pituitary MRI and biliary/gallbladder ultrasound in SOA and body of protocol. Clarified objective of OLE Phase (to evaluate long-term safety and efficacy of paltusotine).
Protocol Clarification Letter 3 to Protocol Version 3.0, dated 05 April 2023	Clarification that gallbladder ultrasounds could be performed at any time during the study if clinically indicated in the opinion of the Investigator.
Protocol Version 4.0, dated 21 November 2023	Extended the OLE Treatment Period by 2 years (ie, from 96 weeks to 200 weeks). Implemented ophthalmic monitoring in response to a Health Authority request to collect additional data to facilitate evaluation of the clinical relevance of a phototoxicity study in rodents. Ophthalmic assessments added as a safety endpoint to OLE Phase. Harmonized protocol to align with protocol clarification letters as described above.

ASD=Acromegaly Symptom Diary, EOR=end of Randomized Controlled Phase; IGF-1=insulin-like growth factor-1, GH=growth hormone, MRI=magnetic resonance imaging, OLE=Open-label Extension, PGI-I=Patient Global Impression of Improvement, PGI-S=Patient Global Improvement of Severity, RC=Randomized Controlled, SOA=Schedule of Activities, ULN=upper limit of normal

Protocol deviations

RC phase

Important protocol deviations (PDs) were reported for 8 participants (**13.8%**) in the FAS; all of which pertained to ASD questionnaires not being completed during screening. No major protocol deviations were reported. One participant in the placebo group had a protocol deviation due to COVID-19. The majority of PDs were administrative, and none of the PDs were deemed to have a significant impact on study efficacy or safety.

OLE Phase

No important or major protocol deviations were reported during the OLE phase. The majority of protocol deviations were administrative, and none of the protocol deviations were deemed to have a significant impact on study safety or efficacy.

Baseline data

Table 46 presents a summary of demographic and other baseline characteristics for the FAS.

Most demographic and other baseline characteristics were consistent between treatment groups. The median age for all participants was **55.0 years**, ranging from 29 to 84 years, higher percentage of participants overall were receiving octreotide compared with lanreotide (58.6% versus 41.4%) as their long-acting SRL therapy prior to study enrolment, with most participants receiving mid and high doses of both SRLs (mid doses: lanreotide 90 mg/month or 120 mg/6 weeks or octreotide 20 mg/month; high doses: lanreotide 120 mg/month or octreotide 30 mg/month).

A higher percentage of participants in the paltusotine group were male compared with the placebo group (**50.0%** versus **39.3%**), and the paltusotine group had a higher mean weight (**83.7 kg** versus **73.2** kg) and BMI (**29.9** kg/m2 versus **27.6** kg/m2) compared with the placebo group. A higher percentage of participants in the paltusotine group had screening HbA1c level ≥6.5% compared with the placebo group (**23.3%** versus **7.1%**).

Table 46 Demographic and Other Baseline Characteristics for RC Phase of Study CRN00808-09 (Full Analysis Set)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Sex - n (%)					
Male	7 (50.0)	8 (50.0)	15 (50.0)	11 (39.3)	26 (44.8)
Female	7 (50.0)	8 (50.0)	15 (50.0)	17 (60.7)	32 (55.2)
Age at Informed Consent (years)					
N	14	16	30	28	58
Mean	54.9	56.8	55.9	53.9	54.9
SD, SE	13.82, 3.69	15.59, 3.90	14.57, 2.66	12.89, 2.44	13.70, 1.80
Median	57.5	58.0	58.0	53.5	55.0
Min, Max	29, 73	35, 84	29, 84	31, 80	29, 84
Age Group - n (%)					
< 65 years	10 (71.4)	10 (62.5)	20 (66.7)	22 (78.6)	42 (72.4)
>=65 years	4 (28.6)	6 (37.5)	10 (33.3)	6 (21.4)	16 (27.6)
65 to <=74 years	4 (28.6)	4 (25.0)	8 (26.7)	4 (14.3)	12 (20.7)
>74 to <=84 years	0	2 (12.5)	2 (6.7)	2 (7.1)	4 (6.9)
> 84 years	0	0	0	0	0
Geographic Region - n (%)					
United States (US)	4 (28.6)	2 (12.5)	6 (20.0)	5 (17.9)	11 (19.0)
Non-US	10 (71.4)	14 (87.5)	24 (80.0)	23 (82.1)	47 (81.0)
European Union	3 (21.4)	5 (31.3)	8 (26.7)	9 (32.1)	17 (29.3)
Rest of the World	7 (50.0)	9 (56.3)	16 (53.3)	14 (50.0)	30 (51.7)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Ethnicity - n (%)					
Hispanic or Latino	4 (28.6)	7 (43.8)	11 (36.7)	8 (28.6)	19 (32.8)
Not Hispanic or Latino	10 (71.4)	7 (43.8)	17 (56.7)	18 (64.3)	35 (60.3)
Not Reported	0	0	0	0	0
Unknown	0	2 (12.5)	2 (6.7)	2 (7.1)	4 (6.9)
Race - n (%)					
White	13 (92.9)	10 (62.5)	23 (76.7)	19 (67.9)	42 (72.4)
All Other Races	1 (7.1)	4 (25.0)	5 (16.7)	7 (25.0)	12 (20.7)
Asian	0	0	0	2 (7.1)	2 (3.4)
Black or African American	1 (7.1)	1 (6.3)	2 (6.7)	1 (3.6)	3 (5.2)
Multiple/Other	0	3 (18.8)	3 (10.0)	4 (14.3)	7 (12.1)
Unknown	0	2 (12.5)	2 (6.7)	2 (7.1)	4 (6.9)
Height (cm)					
n	14	16	30	28	58
Mean	166.119	167.744	166.986	163.116	165.118
SD, SE	11.2925, 3.0180	8.1269, 2.0317	9.5920, 1.7512	12.0677, 2.2806	10.9360, 1.4360
Median	162.500	165.900	165.000	163.500	165.000
Min, Max	156.00, 190.50	156.00, 183.00	156.00, 190.50	129.54, 180.50	129.54, 190.50
Weight (kg)					
n	14	16	30	28	58
Mean	83.761	83.552	83.650	73.193	78.602
SD, SE	19.8505, 5.3053	18.1594, 4.5399	18.6338, 3.4021	16.0427, 3.0318	18.0651, 2.3721
Median	83.000	86.525	84.375	73.075	76.193
Min, Max	56.65, 127.19	55.00, 109.20	55.00, 127.19	45.00, 108.00	45.00, 127.19

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
BMI (kg/m^2)					
n	14	16	30	28	58
Mean	30.160	29.586	29.854	27.577	28.755
SD, SE	5.6828, 1.5188	5.7190, 1.4298	5.6106, 1.0244	5.9052, 1.1160	5.8181, 0.7640
Median	30.572	29.852	29.997	26.668	28.333
Min, Max	22.81, 45.95	20.20, 41.24	20.20, 45.95	18.73, 45.52	18.73, 45.95
BMI Groups - n (%)					
< 30 kg/m^2	6 (42.9)	9 (56.3)	15 (50.0)	21 (75.0)	36 (62.1)
>= 30 kg/m^2	8 (57.1)	7 (43.8)	15 (50.0)	7 (25.0)	22 (37.9)
US Ring Size					
n	14	16	30	28	58
Mean	10.54	11.16	10.87	9.43	10.17
SD, SE	2.613, 0.698	3.515, 0.879	3.090, 0.564	3.633, 0.687	3.411, 0.448
Median	10.00	11.00	10.50	8.75	9.25
Min, Max	7.0, 15.0	6.5, 17.5	6.5, 17.5	5.0, 19.5	5.0, 19.5
Hemoglobin Alc(%)(HbAlc)					
n	14	16	30	28	58
Mean	5.94	6.36	6.16	5.83	6.00

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
SD, SE	0.486, 0.130	0.794, 0.199	0.690, 0.126	0.478, 0.090	0.615, 0.081
Median	5.90	6.10	5.95	5.75	5.90
Min, Max	5.2, 6.9	5.4, 8.0	5.2, 8.0	4.9, 7.1	4.9, 8.0
HbAlc Groups - n (%)					
< 6.5%	12 (85.7)	11 (68.8)	23 (76.7)	26 (92.9)	49 (84.5)
>= 6.5%	2 (14.3)	5 (31.3)	7 (23.3)	2 (7.1)	9 (15.5)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Average Screening IGF-1xULN					
n	14	16	30	28	58
Mean	0.731	0.894	0.818	0.816	0.817
SD, SE	0.1187, 0.0317	0.1017, 0.0254	0.1363, 0.0249	0.1661, 0.0314	0.1501, 0.0197
Median	0.730	0.915	0.870	0.865	0.870
Min, Max	0.58, 0.90	0.59, 0.99	0.58, 0.99	0.39, 1.03	0.39, 1.03
Average Screening IGF-1xULN Groups - n (%)					
< 0.86	11 (78.6)	3 (18.8)	14 (46.7)	13 (46.4)	27 (46.6)
>= 0.86	3 (21.4)	13 (81.3)	16 (53.3)	15 (53.6)	31 (53.4)
Screening IGF-1xULN Groups from IRT - n (%)					
< 0.86	11 (78.6)	3 (18.8)	14 (46.7)	13 (46.4)	27 (46.6)
>= 0.86	3 (21.4)	13 (81.3)	16 (53.3)	15 (53.6)	31 (53.4)
UGT1A1 Genotype - n (%)					
*1/*1	5 (35.7)	6 (37.5)	11 (36.7)	12 (42.9)	23 (39.7)
*1/*80	6 (42.9)	8 (50.0)	14 (46.7)	12 (42.9)	26 (44.8)
*80/*80	2 (14.3)	2 (12.5)	4 (13.3)	1 (3.6)	5 (8.6)
Missing	1 (7.1)	0	1 (3.3)	3 (10.7)	4 (6.9)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Baseline SRL and Dose* - n (%)					
Octreotide	8 (57.1)	10 (62.5)	18 (60.0)	16 (57.1)	34 (58.6)
Low	1 (7.1)	0	1 (3.3)	2 (7.1)	3 (5.2)
Mid	5 (35.7)	2 (12.5)	7 (23.3)	11 (39.3)	18 (31.0)
High	2 (14.3)	8 (50.0)	10 (33.3)	3 (10.7)	13 (22.4)
Lanreotide	6 (42.9)	6 (37.5)	12 (40.0)	12 (42.9)	24 (41.4)
Low	2 (14.3)	0	2 (6.7)	1 (3.6)	3 (5.2)
Mid	1 (7.1)	3 (18.8)	4 (13.3)	5 (17.9)	9 (15.5)
High	3 (21.4)	3 (18.8)	6 (20.0)	6 (21.4)	12 (20.7)
Use of Proton Pump Inhibitor - n (%)					
Yes	3 (21.4)	2 (12.5)	5 (16.7)	2 (7.1)	7 (12.1)
No	11 (78.6)	14 (87.5)	25 (83.3)	26 (92.9)	51 (87.9)
Use of H2 Blockers - n (%)					
Yes	1 (7.1)	0	1 (3.3)	0	1 (1.7)
No	13 (92.9)	16 (100)	29 (96.7)	28 (100)	57 (98.3)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)

*Low: 60mg/month or 120mg/8 weeks lanreotide or 10mg/month octreotide; Mid: 90mg/month or 120mg/6 weeks lanreotide or 20mg/month octreotide; High: 120 mg/month lanreotide or =30 mg/month octreotide. Percentages are calculated based on the number of participants in the Full Analysis Set. SRL = somatostatin receptor ligand. Screening IGF-1 value is defined as the average of the IGF-1 values from all the Screening Visits.

Disease Characteristics

Most disease characteristics were consistent between the paltusotine and placebo groups, including Baseline mean (SD) IGF-1×ULN levels (**0.828** [0.144] and **0.822** [0.159], respectively) and Baseline mean (SD) GH (ng/mL) levels (**0.916** [1.023] and **0.886** [0.831], respectively).

Study participants overall had long-standing disease prior to enrolment, with a higher mean (SD) duration since acromegaly diagnosis in the paltusotine group compared with the placebo group (**186.6** [88.3] months versus **120.8** [81.9] months).

The majority of participants overall (**86.2%**) had prior pituitary surgery, with a higher mean (SD) duration since pituitary surgery in the paltusotine group compared with the placebo group (**171.8** [89.4] months versus **102.4** [65.0] months).

Table 47 Baseline Acromegaly Disease Characteristics for RC Phase of Study CRN00808-09 (Full Analysis Set)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Duration (months) since acromegaly diagnosis					
n	14	16	30	28	58
Mean	186.840	186.333	186.569	120.810	154.823
SD, SE	88.8422, 23.7441	90.7497, 22.6874	88.3064, 16.1225	81.8550, 15.4691	90.7742, 11.9192
Median	163.088	171.778	171.778	104.509	138.661
Min, Max	78.82, 428.68	54.18, 349.67	54.18, 428.68	21.13, 377.00	21.13, 428.68
Duration since acromegaly diagnosis groups - n (%)					
< 10 years	2 (14.3)	3 (18.8)	5 (16.7)	15 (53.6)	20 (34.5)
>= 10 to < 20 years	10 (71.4)	9 (56.3)	19 (63.3)	11 (39.3)	30 (51.7)
>= 20 years	2 (14.3)	4 (25.0)	6 (20.0)	2 (7.1)	8 (13.8)
Acromegaly diagnosis based on testing - n (%)					
Elevated IGF-1 prior to pituitary surgery	10 (71.4)	11 (68.8)	21 (70.0)	22 (78.6)	43 (74.1)
Confirmed pituitary tumor	14 (100)	16 (100)	30 (100)	28 (100)	58 (100)
Growth Hormone level after oral glucose load	5 (35.7)	8 (50.0)	13 (43.3)	11 (39.3)	24 (41.4)
Other	2 (14.3)	1 (6.3)	3 (10.0)	2 (7.1)	5 (8.6)
IGF-1xULN prior to pituitary surgery					
n	9	11	20	20	40
Mean	3.220	3.160	3.187	3.486	3.336
SD, SE	1.6396, 0.5465	0.8746, 0.2637	1.2391, 0.2771	1.5642, 0.3498	1.4010, 0.2215

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Median	2.702	2.997	2.926	3.128	2.989
Min, Max	1.38, 6.58	1.73, 4.13	1.38, 6.58	1.40, 6.84	1.38, 6.84

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
IGF-1xULN prior to pituitary surgery					
>= 2.0xULN - n (%)	8 (57.1)	9 (56.3)	17 (56.7)	17 (60.7)	34 (58.6)
>=1.3xULN to < 2.0xULN - n (%)	1 (7.1)	2 (12.5)	3 (10.0)	3 (10.7)	6 (10.3)
>=1.0xULN to < 1.3xULN - n (%)	0	0	0	0	0
IGF-1 assay platform prior to pituitary surgery - n (%)					
IDS iSYS	1 (7.1)	0	1 (3.3)	0	1 (1.7)
Siemens IMMULITE 2000	1 (7.1)	4 (25.0)	5 (16.7)	6 (21.4)	11 (19.0)
Roche COBAS	1 (7.1)	1 (6.3)	2 (6.7)	2 (7.1)	4 (6.9)
Cisbio IGF1-RIACT	0	1 (6.3)	1 (3.3)	1 (3.6)	2 (3.4)
Other	5 (35.7)	4 (25.0)	9 (30.0)	7 (25.0)	16 (27.6)
Missing	6 (42.9)	6 (37.5)	12 (40.0)	12 (42.9)	24 (41.4)
Tumor size (mm) prior to first pituitary surgery					
n	10	12	22	22	44
Mean	11.70	17.77	15.01	21.65	18.33
SD, SE	4.547, 1.438	5.737, 1.656	5.972, 1.273	12.257, 2.613	10.103, 1.523
Median	11.00	17.60	14.00	17.50	16.00
Min, Max	6.0, 20.0	9.0, 28.0	6.0, 28.0	5.5, 45.0	5.5, 45.0
<=10 - n (%)	5 (35.7)	2 (12.5)	7 (23.3)	4 (14.3)	11 (19.0)
> 10 - n (%)	5 (35.7)	10 (62.5)	15 (50.0)	18 (64.3)	33 (56.9)
Tumor confirmed with - n (%)					
MRI	12 (85.7)	13 (81.3)	25 (83.3)	25 (89.3)	50 (86.2)
CT Scan	2 (14.3)	2 (12.5)	4 (13.3)	2 (7.1)	6 (10.3)
Surgical Pathology	5 (35.7)	3 (18.8)	8 (26.7)	11 (39.3)	19 (32.8)
Other	0	0	0	1 (3.6)	1 (1.7)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Pituitary surgery performed - n (%)					
Yes	12 (85.7)	14 (87.5)	26 (86.7)	24 (85.7)	50 (86.2)
No	2 (14.3)	2 (12.5)	4 (13.3)	4 (14.3)	8 (13.8)
Duration (months) since pituitary surgery					
n	12	14	26	24	50
Mean	177.235	167.082	171.768	102.383	138.463
SD, SE	97.2224, 28.0657	85.5784, 22.8718	89.4087, 17.5345	65.0493, 13.2781	85.3865, 12.0755
Median	143.277	156.632	154.316	96.772	129.840
Min, Max	80.76, 425.92	19.19, 332.39	19.19, 425.92	19.12, 327.06	19.12, 425.92
IGF-1xULN at least 3 months after surgery					
n	11	14	25	24	49

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Mean	1.856	2.703	2.330	2.790	2.556
SD, SE	0.6022, 0.1816	2.8546, 0.7629	2.1792, 0.4358	2.7546, 0.5623	2.4626, 0.3518
Median	1.558	1.867	1.689	1.672	1.683
Min, Max	1.29, 2.98	1.26, 12.24	1.26, 12.24	1.25, 13.33	1.25, 13.33
IGF-1 assay platform at least 3 months after surgery - n (%)					
IDS iSYS	1 (7.1)	1 (6.3)	2 (6.7)	0	2 (3.4)
DiaSorin Liaison XL	1 (7.1)	0	1 (3.3)	2 (7.1)	3 (5.2)
Siemens IMMULITE 2000	3 (21.4)	6 (37.5)	9 (30.0)	8 (28.6)	17 (29.3)
Roche COBAS	1 (7.1)	1 (6.3)	2 (6.7)	2 (7.1)	4 (6.9)
Cisbio IGF1-RIACT	0	1 (6.3)	1 (3.3)	1 (3.6)	2 (3.4)
Other	4 (28.6)	4 (25.0)	8 (26.7)	8 (28.6)	16 (27.6)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
GH (ng/mL) after oral glucose load post surgery					
n	5	7	12	11	23
Mean	9.668	38.586	26.537	31.556	28.937
SD, SE	8.4955, 3.7993	47.4520, 17.9352	38.4210, 11.0912	38.9773, 11.7521	37.8843, 7.8994
Median	10.240	21.900	16.300	13.200	13.200
Min, Max	1.59, 22.41	1.90, 141.00	1.59, 141.00	0.60, 118.00	0.60, 141.00
> 1.0 ng/mL	5 (35.7)	7 (43.8)	12 (40.0)	9 (32.1)	21 (36.2)
> 2.5 ng/mL	3 (21.4)	6 (37.5)	9 (30.0)	9 (32.1)	18 (31.0)
IGF-1xULN most recent prior to Screening					
n	14	16	30	26	56
Mean	0.779	0.875	0.830	0.840	0.834
SD, SE	0.4428, 0.1183	0.2814, 0.0703	0.3623, 0.0661	0.4532, 0.0889	0.4032, 0.0539
Median	0.691	0.847	0.745	0.712	0.735
Min, Max	0.48, 2.20	0.44, 1.57	0.44, 2.20	0.46, 2.34	0.44, 2.34
Duration (days) since most recent IGF-1 prior to Screening					
n	14	16	30	28	58
Mean	144.6	177.9	162.4	192.9	177.1
SD, SE	174.04, 46.51	186.39, 46.60	178.41, 32.57	170.53, 32.23	173.80, 22.82
Median	86.0	141.5	100.0	168.5	146.0
Min, Max	17, 664	13, 761	13, 761	-84, 717	-84, 761

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Baseline IGF-1xULN					
n	14	16	30	28	58
Mean	0.736	0.909	0.828	0.822	0.825
SD, SE	0.1161, 0.0310	0.1175, 0.0294	0.1444, 0.0264	0.1591, 0.0301	0.1504, 0.0197
Median	0.725	0.957	0.872	0.859	0.863
Min, Max	0.59, 0.92	0.55, 1.00	0.55, 1.00	0.39, 1.03	0.39, 1.03
Baseline GH (ng/mL)					

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
n	14	16	30	28	58
Mean	0.609	1.186	0.916	0.886	0.902
SD, SE	0.5964, 0.1594	1.2455, 0.3114	1.0234, 0.1869	0.8312, 0.1571	0.9276, 0.1218
Median	0.448	0.594	0.526	0.604	0.548
Min, Max	0.07, 2.12	0.18, 3.82	0.07, 3.82	0.11, 3.79	0.07, 3.82

Percentages are calculated based on the number of participants in the Full Analysis Set. Baseline IGF-1 value is defined as the average of the IGF-1 values from all the Screening Visits and Day 1. Baseline GH is defined as the average of all the measurements taken from fasting integrated GH samples at Screening Visit.

Extent of Exposure

RC Phase

Of the 30 participants in the paltusotine group, **14 participants (46.7%) received paltusotine 40 mg QD** and **16 participants (53.3%) received paltusotine 60 mg QD as their final dose**. No participants received 20 mg as their final dose in the RC phase.

Only 1 participant in the paltusotine 40 mg group had a dose reduction to 20 mg due to TEAEs, which were constipation, diarrhoea, soft faeces, flatulence, nausea, and fatigue.

Table 48 Extent of Exposure for RC Phase of Study CRN00808-09 (Safety Analysis Set)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Duration of Dose (days)[1]					
n	14	16	30	28	58
Mean	251.4	236.7	243.5	166.0	206.1
SD, SE	2.59, 0.69	42.62, 10.65	31.59, 5.77	77.38, 14.62	69.80, 9.17
Median	252.0	252.0	252.0	154.5	251.0
Min, Max	244, 254	113, 254	113, 254	56, 258	56, 258
>= 0 - < 3 Months - n (%)	0	0	0	6 (21.4)	6 (10.3)
>= 3 - < 6 Months - n (%)	0	2 (12.5)	2 (6.7)	8 (28.6)	10 (17.2)
>= 6 - <= 9 Months - n (%)	14 (100)	14 (87.5)	28 (93.3)	14 (50.0)	42 (72.4)
Duration of Dose (weeks)					
n	14	16	30	28	58
Mean	35.908	33.813	34.790	23.709	29.441
SD, SE	0.3700, 0.0989	6.0882, 1.5220	4.5127, 0.8239	11.0537, 2.0890	9.9719, 1.3094
Median	36.000	36.000	36.000	22.071	35.857
Min, Max	34.86, 36.29	16.14, 36.29	16.14, 36.29	8.00, 36.86	8.00, 36.86
Duration of Final Dose (days)[1]					
n	14	16	30	0	30
Mean	243.4	165.2	201.7		201.7
SD, SE	31.82, 8.50	44.87, 11.22	55.42, 10.12		55.42, 10.12
Median	252.0	179.0	209.0		209.0
Min, Max	133, 254	70, 216	70, 254		70, 254

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
>= 0 - < 3 Months - n (%)	0	1 (6.3)	1 (3.3)	0	1 (1.7)
>= 3 - < 6 Months - n (%)	1 (7.1)	4 (25.0)	5 (16.7)	0	5 (8.6)
>= 6 - <= 9 Months - n (%)	13 (92.9)	11 (68.8)	24 (80.0)	0	24 (41.4)

	Paltusotine Final Dose				
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)	Overall (N=58)
Days on Dose Holiday					
n	0	0	0	1	1
Mean				4.0	4.0
SD, SE				NE, NE	NE, NE
Median				4.0	4.0
Min, Max				4, 4	4, 4
Any Dosing Change due to AE - n (%)					
Dose Reduced	1 (7.1)	0	1 (3.3)	0	1 (1.7)
Drug Interrupted	0	0	0	1 (3.6)	1 (1.7)
Dose Increased	0	1 (6.3)	1 (3.3)	3 (10.7)	4 (6.9)
Drug Withdrawn	0	2 (12.5)	2 (6.7)	17 (60.7)	19 (32.8)
Percent Compliance[2]					
n	14	16	30	28	58
Mean	100.025	96.100	97.931	99.570	98.722
SD, SE	1.1464, 0.3064	5.2898, 1.3225	4.3623, 0.7964	2.5358, 0.4792	3.6619, 0.4808
Median	100.099	99.710	100.000	100.000	100.000
Min, Max	97.22, 101.80	83.04, 100.72	83.04, 101.80	88.89, 102.82	83.04, 102.82

Percentages are calculated based on the number of participants in the Safety Analysis Set. 1 Duration of study drug exposure calculated as date of last dose - date of first dose + 1. 2 Calculated as 100 x (total tablets taken/expected tablets to be taken).

OLE phase

At the data snapshot date of 31 August 2025, the median duration (range) of exposure to paltusotine in the OLE phase was 126.0 weeks (9.4 to 175.0 weeks) for the total population (127.1 weeks [24.3 to 175.0 weeks] for the prior paltusotine group and 124.9 weeks [9.4 to 158.7 weeks] for the prior placebo group.

At the snapshot date of **21 May 2025**, during the OLE phase, after starting at paltusotine 40 mg QD at Week 36, **61.5%** (16 of 26) participants in the prior paltusotine group remained on paltusotine 40 mg QD by Week 60 and **38.5%** (10 of 26) escalated to 60 mg QD. Approximately **one-half** of participants continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE Phase, while the other **one-half** of participants escalated to 60 mg QD.

In the prior placebo group, after starting at 40 mg QD at Week 36, approximately **70% to 80%** of participants continued to receive paltusotine 40 mg QD at subsequent timepoints in the OLE phase, while the remaining **20%** escalated to 60 mg QD.

Outcomes and estimation

1) Primary Efficacy Endpoint – RC Phase

The proportion of participants who maintained IGF-1 level ≤1.0×ULN was **83.3%** (25 of 30) in the paltusotine group compared with **3.6%** (1 of 28) in the placebo group. This study met statistical significance on the primary endpoint (**p<0.0001**) favouring paltusotine over placebo.

At EOR, **14 patients** were treated with paltusotine 40 mg, and **16 patients** were treated with paltusotine 60 mg. Among the **25/30 patients** who maintained IGF-1 levels ≤ ULN, 14/25 (**56%**) in the paltusotine 40 mg group and 11/16 (**44%**) in the paltusotine 60 mg group.

Of note, there was 5/16 (**31.3%**) of patients treated with 60 mg who are non-responders versus 0% of patients treated with 40 mg.

Table 49 Primary Efficacy Analysis: IGF-1 ⩽1.0xULN at EOR in Study CRN00808-09 (Full Analysis Set)

	Paltusotine Final Dose			
	40 mg (N=14)	60 mg (N=16)	Total Paltusotine (N=30)	Placebo (N=28)
IGF-1 <= 1.0xULN at EOR - n (%)				
Responder	14 (100)	11 (68.8)	25 (83.3)	1 (3.6)
Non-Responder	0	5 (31.3)	5 (16.7)	27 (96.4)
IGF-1 > 1.0xULN	0	4 (25.0)	4 (13.3)	10 (35.7)
Missing IGF-1 at Week 34 and Week 36	0	0	0	1 (3.6)
Prohibited acromegaly medication	0	0	0	0
Rescue medication	0	2 (12.5)	2 (6.7)	17 (60.7)
Dose up-titration after Week 24	0	0	0	0
Treatment Discontinuation	0	2 (12.5)	2 (6.7)	17 (60.7)
Odds ratio (Paltusotine/Placebo)			126.526	
95% CI for odds ratio			(13.733, >999.999)	
P-value			<0.0001	

EOR=end of Randomized Controlled Phase, IGF-1=insulin-like growth factor-1, ULN=upper limit of normal.

Percentages are calculated based on the number of participants in the Full Analysis Set. ULN is determined based on the participant's age and sex.

P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression adjusting for Screening IGF-1 groups (<0.86xULN, >=0.86xULN), and prior treatment with Lanreotide or Octreotide. For the odds ratio, placebo participants are the reference group.

Secondary Efficacy Endpoints

1) Change from Baseline to EOR in IGF-1×ULN

Table 50 presents results for the secondary efficacy endpoint of change from Baseline to EOR in IGF-1×ULN, where EOR was EOT at Week 36 if there was no rescue therapy administered or was based on the last available IGF-1 assessment prior to rescue. The LS means (±SE) for the change from Baseline to EOT in IGF-1×ULN were **0.042** (±0.093) for the paltusotine group and **0.833** (±0.096) for the placebo group, with a treatment difference of **-0.791** (95% CI: -1.057 to -0.525). This difference was statistically significant (**p<0.0001**).

Table 50 Secondary Efficacy Endpoint: Change from Baseline to EOT in IGF-1 (×ULN) in RC Phase of Study CRN00808-09 (Full Analysis Set)

	Paltusotine (N=30)	Placebo (N=28)	Treatment Difference (95% CI)	P-value
IGF-1xULN Change from Baseline to EOT – Primary Analysis				
LS Mean	0.042	0.833	-0.791 (-1.057, -0.525)	<0.0001
LS Standard Error	0.0932	0.0962		
IGF-1xULN Change from Baseline to EOT - Multiple Imputation Approach for Missing Data				
LS Mean	0.045	0.767	-0.722 (-1.373, -0.071)	0.0301
LS Standard Error	0.1081	0.3163		
IGF-1xULN Change from Baseline to EOT - Multiple Imputation Using All Observed Values				
LS Mean	0.041	0.783	-0.742 (-1.032, -0.453)	<0.0001
LS Standard Error	0.0889	0.1196		

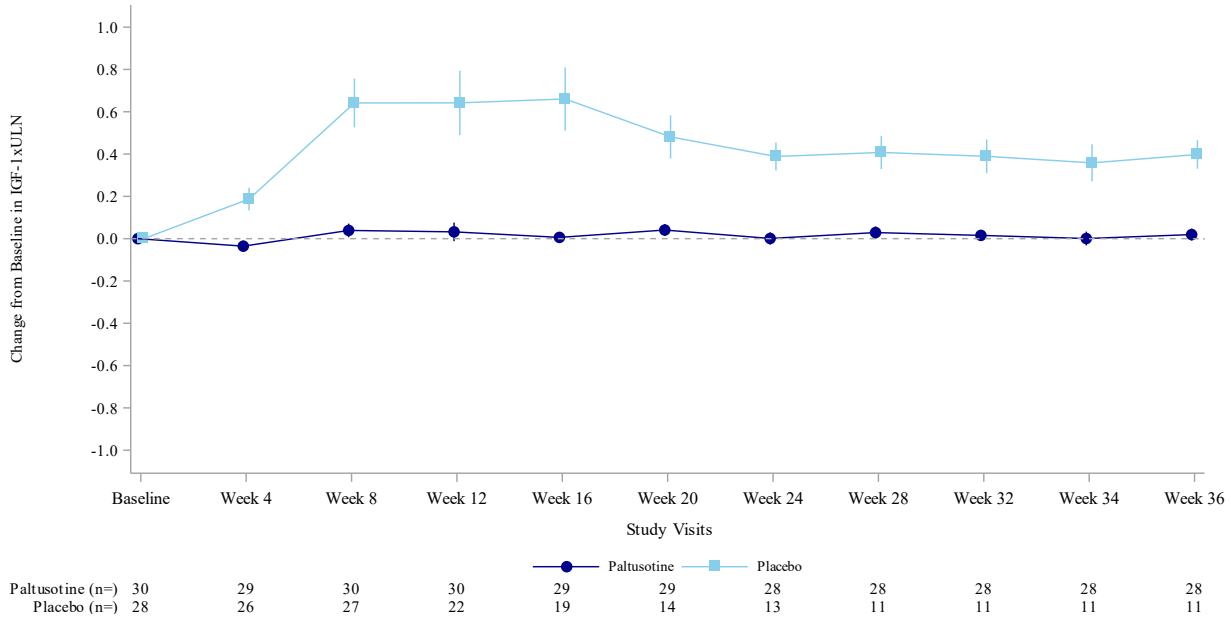
EOT = week 36 if no rescue, otherwise EOT= last assessment prior to rescue, IGF 1=insulin-like growth factor 1, ULN=upper limit of normal.

Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, Screening IGF-1xULN groups (<0.86xULN, >=0.86xULN) and prior treatment group with lanreotide or octreotide as fixed effects, Baseline IGF-1xULN as a covariate.

Figure 28 shows the mean change from Baseline in IGF-1 level (×ULN) for participants who did not receive rescue therapy at each visit by treatment group. IGF-1 values after rescue therapy use were excluded.

In the paltusotine group, mean IGF-1 levels were maintained at all scheduled visits from Baseline to Week 36, whereas in the placebo group, mean IGF-1 levels were increased at Week 4 through Week 36, by which time 17 participants in the placebo group had received rescue therapy.

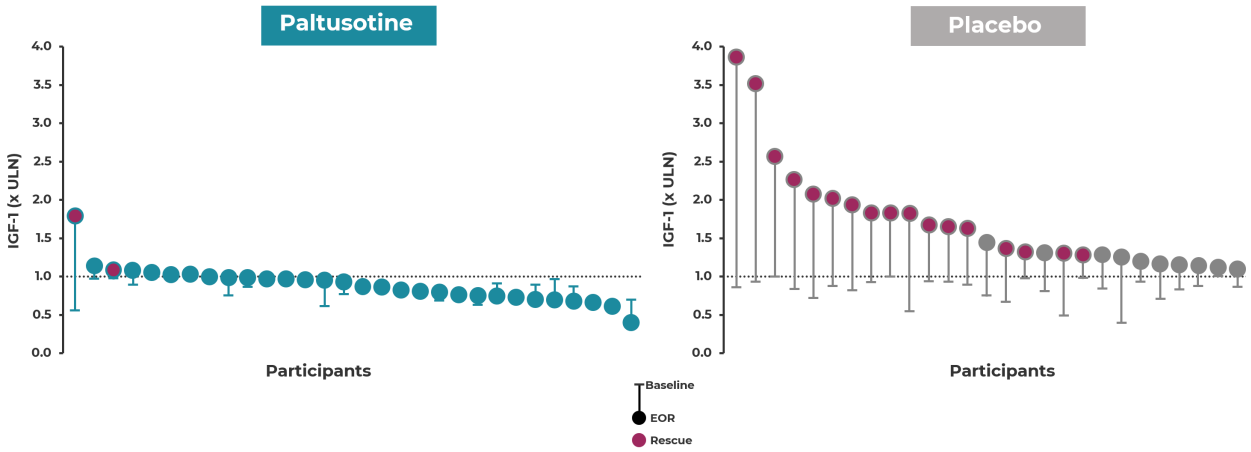
Figure 28 Mean (±SE) Change from Baseline IGF-1 (×ULN) Level by Visit for Participants Without/Prior to Rescue Therapy in RC Phase of Study CRN00808-09 (Full Analysis Set)



IGF-1=insulin-like growth factor-1; RC=randomized controlled, SE= standard error; ULN= upper limit of normal.
Note: Paltusotine group (bottom) and placebo group (top).

The majority of individual participants in the paltusotine group maintained IGF-1 levels ≤1.0 ×ULN compared to participants in the placebo group, which is consistent with the proportion of participants who maintained IGF-1 levels ≤1.0×ULN for the primary endpoint.

Figure 29 IGF-1 Level (×ULN) from Baseline to EOR by Participant in the RC Phase of Study CRN00808-09 (Full Analysis Set)



EOR: End of Randomized Control Phase. IGF-1 values measured prior to rescue or discontinuation are used.

EOT=end of treatment, IGF-1=insulin-like growth factor-1; RC=randomized controlled; SE= standard error; ULN= upper limit of normal. EOR = EOT at Week 36 if there was no rescue therapy administered or was based on the last available IGF-1 assessment prior to rescue.

2) Proportion of Participants with GH<1.0 ng/mL at Week 34

A total of **23 participants** in the paltusotine group and **18 participants** in the placebo group had GH level <1.0 ng/mL at Baseline. The proportion of participants who maintained GH level <1.0 ng/mL at Week 34 was **87.0%** (20 of 23) in the paltusotine group compared with **27.8%** (5 of 18) in the placebo group. This study met statistical significance on this endpoint (**p=0.0003**) favouring paltusotine over placebo.

Table 51 Secondary Efficacy Endpoint: Proportion of Participants with GH<1.0 ng/mL at EOR (W34 for GH level) in Study CRN00808-09 (Full Analysis Set)

	Paltusotine Final Dose			
	40 mg (N=12)	60 mg (N=11)	Total Paltusotine (N=23)	Placebo (N=18)
GH maintenance < 1.0 ng/mL at EOR – n (%)				
Responder	11 (91.7)	9 (81.8)	20 (87.0)	5 (27.8)
Non-Responder	1 (8.3)	2 (18.2)	3 (13.0)	13 (72.2)
GH >= 1.0 ng/mL	1 (8.3)	1 (9.1)	2 (8.7)	2 (11.1)
Missing GH Result at Week 34	0	0	0	1 (5.6)
Prohibited acromegaly medication	0	0	0	0
Rescue medication	0	2 (18.2)	2 (8.7)	12 (66.7)
Dose up-titration after Week 24	0	0	0	0
Treatment Discontinuation	0	2 (18.2)	2 (8.7)	12 (66.7)
Odds ratio (Paltusotine/Placebo)			16.609	
95% CI for odds ratio			(2.864, 181.355)	

	Paltusotine Final Dose			
	40 mg (N=12)	60 mg (N=11)	Total Paltusotine (N=23)	Placebo (N=18)
P-value			0.0003	

CI=confidence interval, EOR=end of Randomized Controlled Phase (Week 34 for GH level), GH=growth hormone.

Percentages are calculated based on the number of participants with Baseline GH < 1.0 ng/mL in the Full Analysis Set. P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression adjusting for Screening IGF-1 groups (<0.86xULN, >=0.86xULN), and prior treatment with lanreotide or octreotide. For the odds ratio, placebo participants are the reference group.

3) Change from Baseline to EOR in Total ASD Score

The LS means (±SE) for the change from Baseline to EOT in total ASD score were **-0.606** (±1.504) for the paltusotine group and **4.558** (±1.593) for the placebo group, indicating stabilization of symptoms for the paltusotine group and significant worsening of symptoms for the placebo group, with a treatment difference of **-5.164** (95% CI: -9.536 to -0.792). This study met statistical significance (**p=0.0216**) on this endpoint favouring paltusotine over placebo.

Table 52 Secondary Efficacy Endpoint: Change from Baseline to EOT in Total ASD Score in RC Phase of Study CRN00808-09 (Full Analysis Set)

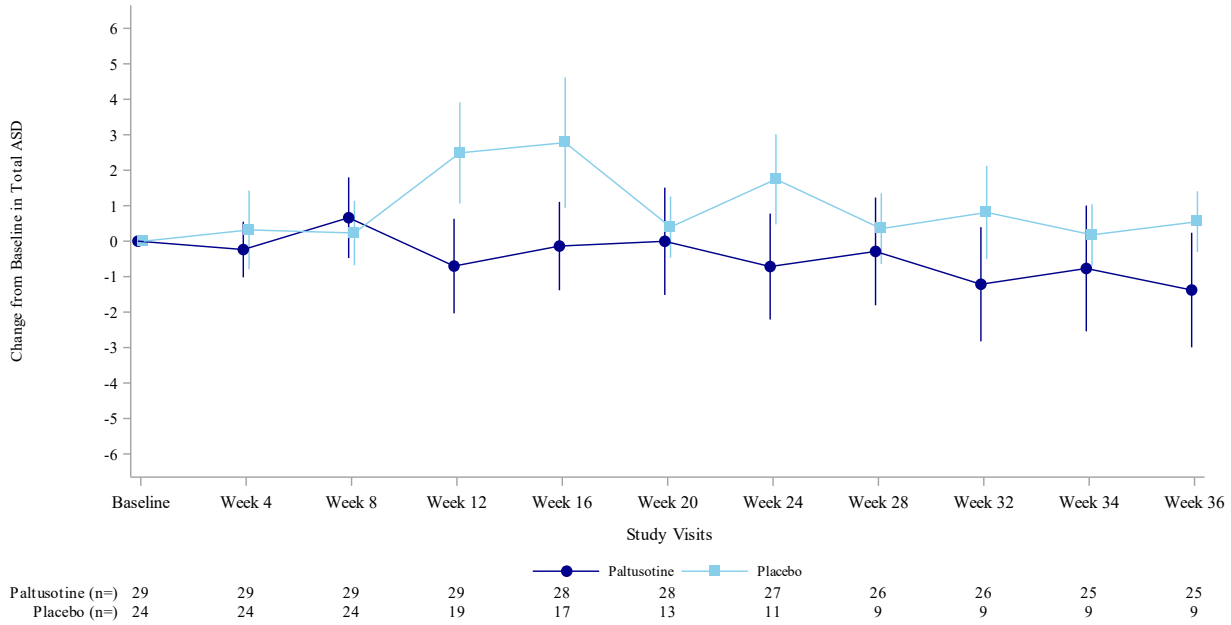
	Paltusotine (N=30)	Placebo (N=28)	Treatment Difference (95% CI)	P-value
Total ASD Change from Baseline to EOT				
LS Mean	-0.606	4.558	-5.164 (-9.536, -0.792)	0.0216
LS Standard Error	1.5044	1.5926		

ASD=Acromegaly Symptoms Diary, CI=confidence interval, EOT = week 36 if no rescue, otherwise EOT= last assessment prior to rescue, RC=randomized controlled, ULN= upper limit of normal.

Total ASD score is defined as the sum of the averages of the available 7 individual item scores (headache pain, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling) 7 days on or prior to EOT. Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, Screening IGF-1xULN groups (<0.86xULN, >=0.86xULN) and prior treatment group with lanreotide or octreotide as fixed effects, Baseline total ASD score as a covariate.

For the paltusotine group, stabilized acromegaly symptom scores were sustained and maintained throughout the RC phase, demonstrating persistence of effects for paltusotine. In comparison, symptoms were significantly worsened in the placebo group up to being rescued. Subjects who were not rescued showed a mild worsening of the symptoms burden from baseline.

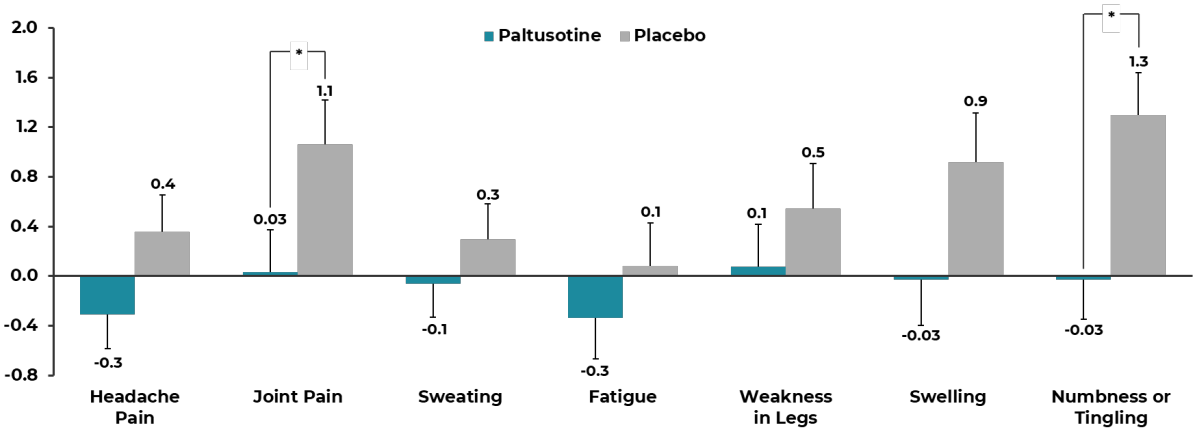
Figure 30 Mean (±SE) Change from Baseline in Total ASD Scores by Visit in All Participants Without/Prior to Rescue in RC Phase of Study CRN00808-09 (Full Analysis Set)



ASD=Acromegaly Symptoms Diary, SE=standard error, RC=randomized controlled
Note: Total ASD score is defined as the average of the available scores seven days on or prior to the scheduled visit date.

The LS means for the change from Baseline to EOT for all individual ASD items were lower in the paltusotine group compared with the placebo group, and the differences in the change from Baseline to EOT for joint pain and numbness or tingling were nominally significant between treatment groups. The overall total ASD score was not driven by a single item, indicating that there were improvement and stabilization across all acromegaly symptoms evaluated in the paltusotine group compared with the placebo group.

Figure 31 Mean Change from Baseline to EOR in ASD Scores by Item in RC Phase of Study CRN00808-09 (Full Analysis Set)



ASD=Acromegaly Symptoms Diary, EOR= end of RC Phase, LS=least square, RC=randomized controlled
Note: LS mean is presented and estimated based on an analysis of covariance. ASD scores measured prior to rescue or discontinuation are used. Each symptom is on a 0 (no symptom) to 10 (worst symptom) scale.
*Nominal $p<0.05$. P-value is estimated based on an analysis of covariance.

The LS means (±SE) for the change from Baseline to EOT in most bothersome symptoms were **-0.530** (±0.360) for the paltusotine group and **0.617** (±0.381) for the placebo group, with a treatment difference of **-1.147** (95% CI: -2.199 to -0.094) (nominal p=**0.0335**).

Table 53 Change from Baseline to EOT in Most Bothersome Symptoms in RC Phase of Study CRN00808-09 (Full Analysis Set)

	Paltusotine (N=30)	Placebo (N=28)	Treatment Difference (95% CI)	P-value
Change from Baseline to EOT in Most Bothersome Symptom				
LS Mean	-0.530	0.617	-1.147 (-2.199, -0.094)	0.0335
LS Standard Error	0.3596	0.3808		

ASD=Acromegaly Symptoms Diary, EOT = week 36 if no rescue, otherwise EOT= last assessment prior to rescue, IGF-1=insulin-like growth factor-1, RC=randomized controlled, ULN=upper limit of normal.

ASD score is defined as the average of the available scores seven days on or prior to EOT. Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, Screening IGF-1xULN groups (<0.86xULN, >=0.86xULN) and prior treatment group with lanreotide or octreotide as fixed effects.

Main exploratory Efficacy Endpoints – RC Phase

1) Proportion of Participants Who Received Rescue Therapy

The proportion of participants who received rescue therapy was **6.7%** (**2 of 30**) in the paltusotine group and **60.7%** (**17 of 28**) in the placebo group (nominal **p<0.0001**) affirming the treatment effect of paltusotine versus placebo.

2) Proportion of Participants Who Achieved IGF-1 <1.3×ULN at EOR

The proportion of participants who maintained IGF-1 level <1.3×ULN was **93.3%** (28 of 30) in the paltusotine group compared with **28.6%** (8 of 28) in the placebo group (nominal **p<0.0001**).

3) Change from Baseline to EOR in Residual Tumour Volume

No clinically significant decreases or increases (as measured by >25% reduction or increase in tumour volume) were observed in the change from Baseline to EOR in residual tumour volume.

4) Time from Randomization to First IGF-1>1.0×ULN for 2 Consecutive Visits

Participants needed to be on a dose of 60 mg QD (paltusotine or placebo) for at least 2 weeks in order to be considered as having an event.

The Kaplan-Meier analyses were performed using 2 different methods:

1) participants who discontinued treatment prior to having the event were counted as having the event at the time of treatment discontinuation: the median (IQR) time to loss of biochemical control was not reached (IQR: 141.0 days, not estimable [NE]) for the Paltusotine group and was **83.0 days** (IQR: 57.0, 85.0) for the placebo group.

2) participants who discontinued treatment prior to reaching IGF-1>1.0×ULN were censored at the time of the last assessment prior to discontinuation of treatment: The median (IQR) time to loss of biochemical control was not reached (IQR: 141.0 days, NE) for the Paltusotine group and was **84.0 days** (IQR: 58.0, 85.0) for the placebo group.

5) Treatment Preference Questionnaire at EOR

In the paltusotine group (N=30), oral medication was preferred by **18 participants** (**60.0%**), previous injections were preferred by **6 participants** (**20.0%), 4 participants** (**13.3%)** had no preference, and data were missing for **2 participants** (**6.7%).** In the placebo group (N=28), oral medication was preferred by **17 participants** (**60.7%**), previous injections were preferred by **5 participants** (**17.9%**), **3 participants** (**10.7%**) had no preference, and data were missing for **3 participants** (**10.7%**).

6) Summary for AcroQoL, EQ-5D-5L, PGI-S, PGI-I

- Acro-QoL: The LS means (±SE) for the change from Baseline to EOR in the AcroQoL total score using composite scores were **0.268** (±2.480) for the paltusotine group and **3.557** (±3.676) for the placebo group, with a treatment difference of **-3.289** (95% CI: -13.220 to 6.643) (nominal **p=0.4844**). The LS means (±SE) for the change from Baseline to EOR in the AcroQoL total score using standardized scores were **0.304** (±2.818) for the paltusotine group and **4.041** (±4.178) for the placebo group, with a treatment difference of **-3.737** (95% CI: -15.023 to 7.548) (nominal **p=0.4844**).

- **EQ-5D-5L health index, EQ VAS:** The LS means (±SE) for the change from Baseline to EOR in the EQ-5D-5L health index score were **-0.152** (±0.037) for the paltusotine group and -0.037 (±0.051) for the placebo group, with a treatment difference of -0.114 (95% CI: 0.255 to 0.026) (nominal **p=0.0951**).

The LS means (±SE) for the change from Baseline to EOR in the EQ VAS score were **-11.073** (±4.230) for the Paltusotine group and **2.498** (±6.048) for the placebo group, with a treatment difference of **-13.571** (95% CI: -30.132 to 2.989) (nominal **p=0.0938**).

- **PGI-I at EOR (EOT at week 36):** The LS means (±SE) for the PGI-I at EOT were **-0.933** (±0.272) for the paltusotine group and **-0.058** (±0.438) for the placebo group, with a treatment difference of -0.875 (95% CI: -1.922 to 0.172) (nominal **p=0.0984**).

Main exploratory Efficacy Endpoints – OLE Phase

Although the sample sizes for subsequent timepoints (e.g. Weeks 156 to 204) were small, results are also presented in the source tables for subsequent timepoints per the scheduled efficacy assessments specified.

1) Proportion of Participants with IGF-1 ≤ 1.0×ULN and < 1.3×ULN at Each Visit

The starting dose of paltusotine in the OLE phase was 40 mg QD day, and most participants who were receiving 60 mg/day at the end of the RC phase were anticipated to up-titrate to 60 mg/day during the OLE phase.

The proportion of participants who achieved IGF-1 level ≤1.0×ULN ranged from **74.5% to 93.3%** from Week 48 to Week 180 for the overall population (**50.0% to 96.0%** for the prior paltusotine group and **77.3% to 100%** for the prior placebo group). (Note: Only 1 participant reached the timepoints for Week 192 and Week 204 at the time of the data snapshot.)

The proportion of participants who achieved IGF-1 level <1.3×ULN ranged from **95.7% to 100%** from Week 48 to Week 180 for the overall population (**92.0% to 100%** for the prior paltusotine group and **92.9% to 100%** for the prior placebo group).

2) Change from OLE Baseline in IGF-1×ULN to the Visits in the OLE phase

A total of **53 participants** (27 in the prior paltusotine group and 26 in the prior placebo group) had IGF-1 results at OLE Baseline.

At the data snapshot date of 31 August 2025, continued maintenance and durability of mean IGF-1 levels ≤1.0×ULN were observed in participants in the prior paltusotine group up to Week 180, while a decrease in mean IGF-1 level was observed over the initial 2 weeks in the prior placebo group that was maintained to Week 180. (Note: Only 1 participant reached the timepoints for Week 192 and Week 204 at the time of the data snapshot.)

3) Proportion of Participants with GH <1.0 ng/mL at Each Visit in the OLE Phase Out of Those Who had GH <1.0 ng/mL at OLE Baseline

At the cut-off date of 5 December 2023, at Week 60, GH results were available for **37 participants** (**20 in the prior paltusotine group** and **17 participants in the prior placebo group**) who had GH<1.0 ng/mL at OLE Baseline.

The proportion of participants who maintained GH level <1.0 ng/mL **at Week 60** was **81.1%** (30 of 37) for the total population (**80.0%** [16 of 20] for the prior paltusotine group and **82.4%** [14 of 17] for the prior placebo group).

4) Change from OLE Baseline in Total ASD Score to Visits in the OLE Phase and mean ASD total score by visit in the OLE Phase

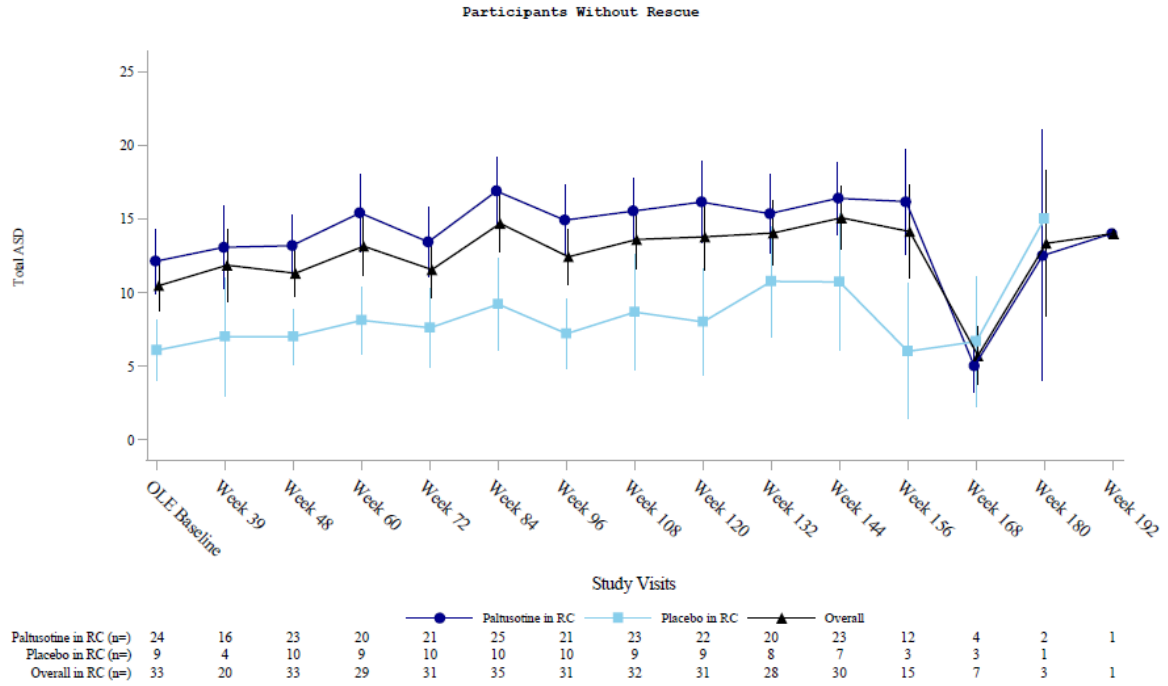
At the data cut-off of 5 December 2023, a total of **41 participants** (20 in the prior paltusotine group and 21 in the prior placebo group) had ASD score results at OLE Baseline and Week 60.

The mean change (±SE) in the total ASD score **from OLE Baseline to Week 39** was **-0.027** (±0.8273) for the total population (**1.004** [±0.1.1492] for the prior paltusotine group and **-1.403** [±1.1203] for the prior placebo group showing a decrease for the total population and the prior placebo group at Week 39.

The mean change (±SE) in the total ASD score from OLE Baseline to Week 60 was **2.642** (±1.1253) for the total population (**3.219** [±1.4986] for the prior paltusotine group and **2.092** [±1.6977] for the prior placebo group).

At the data snapshot date of 31 August 2025, mean ASD Total Scores generally remained stable throughout the OLE phase. In the OLE phase, ASD scores were collected only at quarterly study visits. Because the ASD was designed for daily administration, sparse data collections would be expected to result in some degree of visit-to-visit variability, reflecting sporadic variations over the course of a single day prior to the data collection date.

Figure 32 Mean (±SE) ASD Total Score by Visit in OLE Phase of Study CRN00808 09 (OLE Safety Analysis Set)



ASD=Acromegaly Symptoms Diary; OLE=Open-label Extension; RC=Randomized Controlled; SE=standard error
Data cut-off date: 31 August 2025

5) Change from OLE Baseline in GH to the Visits in the OLE Phase and mean GH levels (ng/mL) by visit for participants in the OLE Phase of Study CRN00808-09

At the data cut-off date of 5 December 2023, a total of **52 participants** (**27 participants** in the prior paltusotine group and **25 participants** in the prior placebo group) had GH results reported at OLE Baseline and **Week 60**.
For these participants, the mean (±SE) GH level (ng/mL) at OLE Baseline was **0.937** (±0.1398) for the total population (**0.938** [±0.2348] for the prior paltusotine group and **0.936** [±0.1480] for the prior placebo group).

The mean change (±SE) in GH (n/mL) from **OLE Baseline to Week 60** was **0.420** (±0.1686) for the total population (**0.357** [±0.1887] for the prior paltusotine group and **0.488** [±0.2891] for the prior placebo group) demonstrating a stable result for all participants that was maintained through **Week 84**.

Although the sample sizes after Week 60 were small, similar results were observed at Weeks 72, 84, 96, and Week 120.

At the data snapshot date of 31 August 2025, mean GH levels in the OLE phase showed long-term maintenance and durability from OLE Baseline through Week 180.

6) Change from OLE Baseline in Residual Tumour Volume to the Visits in the OLE Phase

At the data cut-off of 5 December 2023, a summary of the change in residual pituitary volume from OLE Baseline to **Week 84** was provided for **11 participants**. No clinically significant changes (>25% increases or decreases in tumour volume) were observed in pituitary tumour size as measured by MRI.

7) Proportion of Participants who Received Adjunctive Therapy in the OLE Phase

As of the data cut-off date of 5 December 2023, no participants received permitted adjunctive acromegaly treatment during the OLE Phase.

8) Summary of AcroQoL, EQ-5D-5L, PGI-S, PGI-I

At the data cut-off of 5 December 2023,

- ACRO-QoL and EQ-5D-5L health index, EQ VAS, and dimension scores: A total of **14 participants** (6 in the prior paltusotine group and 8 in the prior placebo group) had results reported for AcroQoL total scores at OLE Baseline and **Week 84**.

No significant changes from OLE baseline were highlighted.

- **PGI-S:** total of **43 participants** (20 in the prior paltusotine group and 23 in the prior placebo group) had PGI-S results at OLE Baseline and **Week 60.**

No significant changes from OLE baseline were highlighted.

Pre-defined subgroup analyses

Subgroup analyses were conducted on the FAS for the primary endpoint for the following subgroups: sex, age group, screening IGF-1 group, prior treatment, BMI groups, weight groups, race, ethnicity, use of PPI and H2 blockers, and geographic region.

No notable subgroup effects were observed for any subgroup, showing that the paltusotine treatment effect was consistent across subgroups. For the subgroups of unknown ethnicity and non-White and unknown race, the 95% CI for the treatment difference included zero. However, the sample size for these subgroups was small, and the treatment differences were greater than zero and directionally favoured paltusotine.

Pre-defined sensitivity analyses

1) Sensitivity Analyses of the primary endpoint

To assess the robustness of the primary endpoint analysis, the following prespecified sensitivity analyses were performed on the primary efficacy endpoint: 1) completers analysis, which included only FAS participants who completed at least 34 weeks of treatment, 2) where participants were not considered non-responders for up-titrating in dose after Week 24, and 3) on the PPS. The analyses were conducted using the same methodology for the primary endpoint.

For the completers analysis, **28 participants** in the paltusotine group and **11 participants** in the placebo group completed 34 weeks of randomized treatment. The proportion of participants who maintained IGF-1 level $\leq 1.0 \times$ ULN was **89.3%** (25 of 28) in the paltusotine group compared with **9.1%** (1 of 11) in the placebo group (nominal **p<0.0001**). These results were consistent with the results of the primary endpoint.

No participants up-titrated in dose after Week 24, so results of this sensitivity analysis were identical to the results of the primary endpoint analysis.

The PPS included **57 participants** (30 participants in the paltusotine group and 27 participants in the placebo group). One participant in the placebo group was excluded from the PPS for not completing the RC phase of the study. In the PPS, the proportion of participants who maintained IGF-1 level $\leq 1.0 \times$ ULN was **83.3%** (25 of 30) in the paltusotine group compared with **3.7%** (1 of 27) in the placebo group (nominal **p<0.0001**).

2) Sensitivity analysis using a multiple imputation approach

A sensitivity analysis was performed using a multiple imputation approach for missing data for the secondary efficacy endpoint of change from Baseline to EOR in IGF-1×ULN. In this analysis, IGF-1 results for all assessments following the first occurrence of intercurrent events, such as dropouts, taking rescue therapy or prohibited medications, or up titration in dose after Week 36, were evaluated as missing data.

The missing measurement was imputed by a multiple imputation procedure using on-treatment intermediate values from the placebo group, which took into consideration the variability from the natural disease course prior to medical intervention.

The imputation models included treatment group and stratification factors as fixed effects, along with by-visit IFG-1×ULN values as covariates.

However, there were a substantial amount of placebo participants (17 out of 28 participants) that went on rescue therapy. To overcome model convergence, treatment group, stratification factors, and baseline IGF-1×ULN values were excluded from the imputation model(s).

For this sensitivity analysis, the LS means (±SE) for the change from Baseline to Week 36 in IGF-1×ULN were **0.045** (±0.108) for the paltusotine group and **0.767** (±0.316) for the placebo group, with a treatment difference of **-0.722** (95% CI: -1.373 to -0.071; nominal **p=0.0301**).

Results of this sensitivity analysis were consistent with results of the primary analysis of the secondary efficacy endpoint.

In addition, missing data on IGF-1×ULN were imputed using a multiple imputation procedure that utilized all observed data from both treatment groups to overcome the convergence issue.

For this analysis, the LS means (±SE) for the change from Baseline to Week 36 in IGF-1×ULN were **0.041** (±0.089) for the paltusotine group and **0.783** (±0.120) for the placebo group, with a treatment difference of **-0.742** (95% CI: -1.032 to -0.453; nominal **p<0.0001**).

Ancillary analyses

A *post hoc* analysis was performed to evaluate the data for participants without prior surgery.

In the RC phase of **Study CRN00808-09**, **8 participants** (4 in the paltusotine group and 4 in the placebo group) had not undergone prior pituitary surgery.

Baseline demographic and disease characteristics were generally consistent between participants without prior pituitary surgery and the overall population, including age and mean IGF-1 level, except for time since acromegaly diagnosis (**median of 139 months** for overall and **177 months** for participants without prior pituitary surgery).

Seven of the 8 participants (**87.5%**) without prior pituitary surgery had microadenomas at the time of diagnosis. Tumour size at the time of diagnosis was missing for 1 participant.

Similar to the overall population, a higher percentage of participants were receiving octreotide compared with lanreotide (6/8 [75.0%] versus 2/8 [25.0%]) as their long-acting SRL therapy prior to study enrolment, with all participants receiving mid (n=3) and high doses (n=5) of their prior SRLs.

In the RC phase, of the 4 participants without prior pituitary surgery in the paltusotine group, the final paltusotine dose was 40 mg QD for 2 participants and 60 mg QD for the other 2 participants.

During the OLE phase, the final dose of paltusotine was 40 mg QD for 5 participants (2 paltusotine, 3 placebo), and 60 mg QD for 3 participants (2 paltusotine, 1 placebo) at the time of the data cut-off.

In the paltusotine group, mean IGF-1 levels <1.0×ULN were maintained at all scheduled visits from Baseline through Week 36, whereas in the placebo group, mean IGF-1 levels were increased at Week 8, by which time 1 of the **4 participants** in the placebo group had received rescue therapy.

Participants in the paltusotine group continued to maintain IGF-1 levels <1.0×ULN up through Week 96 in the OLE phase, although the numbers were small.

Participants in the placebo group showed a rapid decrease over the first two weeks in the OLE Phase that was maintained to Week 96.

Overall, all **8 participants without prior surgery** had IGF-1 levels <1.0×ULN at their last available IGF-1 assessment in the OLE Phase. These results showing consistent and durable maintenance of response to paltusotine are consistent with the overall population for the study.

In the RC phase, these 8 participants had stable pituitary tumour volume (evaluated by MRI by central reviewer) at EOR. In the OLE phase, pituitary tumour volume assessments were available for 3 participants, and all were stable.

5.3.3. Clinical studies in special populations

The efficacy of paltusotine was evaluated for selected subpopulations for each of the phase 3 studies.

No notable subgroup effects were observed for any subgroup in either study **CRN00808-08** or study **CRN00808-09**, showing that the paltusotine treatment effect was consistent across subgroups.

For both studies, the subgroups of unknown ethnicity and non-White and unknown race, the 95% CI for the treatment difference included zero. However, the sample size for these subgroups was small, and the treatment differences were greater than zero and directionally favoured Paltusotine.

By region

In the two pivotal registration trials (study **CRN00808-09** and study **CRN00808-08**), a total of **169** patients were treated. Of these, a total of **48 patients** (**28.4%**) were from Europe.

For study CRN00808-08, **8.1%** of participants were from the US and **64.0%** from Rest of World (RoW). In study CRN00808-09, **19.0%** were from the US and **51.7%** from RoW.

Clinically relevant decreases in IGF-1 were observed in all regional subgroups. Likewise, reduction in GH levels and proportion of participants who experienced clinically meaningful change was observed consistently across subgroups. Subgroup analyses did not reveal any significant differences in efficacy across regions.

By IGF-1 Baseline Levels, Age, Gender, and BMI

Reduction in IGF-1 from baseline was generally comparable, irrespectively of baseline IGF-1 (median <1.78 or ≥1.68 ng/mL or median< 0.86 ng/mL or ≥0.86 ng/mL).

Although the number of participants age ≥65 years was low, the observed treatment effects and disease control was similar to that observed in participants <65 years of age. Similarly, gender did not impact the observed treatment effect, with males and females experiencing similar effects.

BMI did not have any significant effect on the IGF-1 response to paltusotine, with participants with BMI ≥30 kg/m^2 experiencing comparable clinical effects as participants with BMI <30 kg/m^2. The observed treatment effect of paltusotine was comparable.

Participants Without Prior Pituitary Surgery

First-line therapy for acromegaly is pituitary tumour resection, typically by transsphenoidal surgery. However, for some patients, surgical removal is not an option, or they choose not to have surgery or may experience delays before a surgical appointment becomes available. For many others, surgical intervention does not achieve IGF-1 normalization and adequately resolve acromegaly symptoms, necessitating additional adjunctive pharmacotherapy.

In the paltusotine clinical studies, the majority of participants enrolled had undergone prior surgical intervention for their pituitary tumours.

However, a small subset of participants (**N=20**) across the acromegaly studies (6 participants in studies **CRN00808-08**, 8 participants in study **CRN00808-09**, and 6 participants in study **CRN00808-05**) were surgically naïve but had received pharmacological intervention prior to study enrolment.

A *post-hoc* analysis was performed to evaluate the data for participants without prior surgery (see more details in the section *Ancillary analyses*).

Although the small number of participants in this *post-hoc* analysis limits its use, the overall results demonstrate a consistent paltusotine treatment effect across a broad spectrum of acromegaly participants. In participants without prior pituitary surgery who received pharmacological therapy prior to enrolment in the phase 3 studies, paltusotine demonstrated a rapid, consistent, and durable treatment effect, as well as stable pituitary volume, consistent with the efficacy results with paltusotine in the overall population of the phase 3 studies.

5.3.4. Supportive studies

3 supportive phase 2 studies were provided: study **CRN00808-03**, **CRN00808-02** and **CRN00808-05**. All the details are in *Dose-response studies* of this report.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

Primary Efficacy Endpoint

The primary efficacy endpoint for both studies defined as IGF-1 level $\leq 1.0 \times$ ULN based on the average of the last 2 measurements collected at Week 22 and Week 24 (EOR) in Study **CRN00808-08** and at Week 34 and Week 36 (EOR) in study **CRN00808-09**. Both studies met statistical significance on the primary endpoint ($p<0.0001$) favouring paltusotine over placebo.

In study **CRN00808-08**, the proportion of participants who achieved IGF-1 level $\leq 1.0 \times$ ULN at EOR was **55.6%** (30 of 54) in the paltusotine group compared with **5.3%** (3 of 57) in the placebo group.

Study **CRN00808-09** the proportion of participants who maintained biochemical response (IGF-1 level $\leq 1.0 \times$ ULN) at EOR in the paltusotine group was **83.3%** (25 of 30) in the paltusotine group compared with **3.6%** (1 of 28) in the placebo group.

Results of prespecified sensitivity analyses to assess the robustness of the primary efficacy analyses for study **CRN00808-08** and study **CRN008008-09** were consistent with the primary efficacy endpoint results.

Table 54 Primary Efficacy Analysis: IGF-1 ⩽1.0xULN at EOR in Study CRN00808-08 (Week 24) and Study CRN00808-09 (Week 36)

	CRN00808-08		CRN00808-09	
	Total Paltusotine (N=54)	**Placebo (N=57)**	**Total Paltusotine (N=30)**	**Placebo (N=28)**
IGF-1 <= 1.0xULN at EOR - n (%)				
Responder	30 (55.6)	3 (5.3)	25 (83.3)	1 (3.6)
Non-Responder	24 (44.4)	54 (94.7)	5 (16.7)	27 (96.4)
IGF-1 > 1.0xULN	22 (40.7)	46 (80.7)	4 (13.3)	10 (35.7)
Missing IGF-1 at Week 22 and Week 24 (StudyCRN00808-08) or at Week 34 and Week 36 (Study CRN00808-09)	2 (3.7)	3 (5.3)	0	1 (3.6)
Prohibited acromegaly medication	0	0	0	0
Rescue medication	2 (3.7)	13 (22.8)	2 (6.7)	17 (60.7)
Dose up-titration after Week 12 (CRN00808-08) or Week 24 (CRN00808-09)	1 (1.9)	0	0	0
Treatment Discontinuation	4 (7.4)	16 (28.1)	2 (6.7)	17 (60.7)
Odds ratio (Paltusotine/Placebo)	42.806		126.526	
95% CI for odds ratio	(8.444, 455.821)		(13.733, >999.999)	
P-value	<0.0001		<0.0001	

CI=confidence interval, EOR=end of Randomized Controlled Phase, IGF-1= insulin-like growth factor-1, IRT = Interactive Response Technology, ULN= upper limit of normal.
Percentages are calculated based on the number of participants in the Full Analysis Set.
IGF-1 at EOR is based on the average of the last 2 measurements of IGF-1 collected at Weeks 22 and 24. When one of the two last IGF-1 measurements is missing a single value is used.
In CRN00808-08, p-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT (medically naïve or previously treated versus washout). For the odds ratio, placebo participants are the reference group. The primary endpoint was defined as the proportion of participants who achieved a biochemical response in IGF-1 (≤1.0×ULN) at EOR.
In CRN00808-09, p-value, odds ratio, and corresponding 95% CI are from an exact logistic regression adjusting for Screening IGF-1 groups (<0.86xULN, >=0.86xULN), and prior treatment with Lanreotide or Octreotide. For the odds ratio, placebo participants are the reference group. The primary endpoint was defined as the proportion of participants who maintained biochemical response in IGF-1 (≤1.0×ULN) at EOR.

Secondary Efficacy Endpoints

Similar secondary endpoints are summarized together for both phase 3 studies. Study CRN00808-08 has an additional secondary endpoint of the proportion of participants who achieved IGF-1 <1.3×ULN at EOR.

1) Change from Baseline in IGF-1×ULN to EOR, for Study CRN00808-08 (Week 24) and Study CRN00808-09 (Week 36)

Table 55 presents results for the secondary efficacy endpoint of change from Baseline to EOR in IGF-1×ULN, where EOR was Week 22 to Week 24 at EOT for **CRN00808-08** and EOT was Week 36 for **CRN00808-09** if there was no rescue therapy administered or was based on the last available IGF-1

assessment prior to rescue. Both studies met statistical significance on the secondary endpoint (p<0.0001) favouring paltusotine over placebo.

Table 55 Secondary Efficacy Endpoint: Change from Baseline to EOT in IGF-1 (×ULN) in the RC Phase of Study CRN00808-08 and Study CRN00808-09 (Full Analysis Set)

	CRN00808-08				CRN00808-09			
	Paltusotine (N=54)	**Placebo (N=57)**	**Treatment Difference (95% CI)**	**P-value**	**Paltusotine (N=30)**	**Placebo (N=28)**	**Treatment Difference (95% CI)**	**P-value**
IGF-1xULN Change from Baseline to EOT (Week 22 for CRN00808-08 and Week 36 for CRN00808-09)								
LS Mean	-0.819	0.087	-0.906 (-1.106, -0.706)	<0.0001	0.042	0.833	-0.791 (-1.057, -0.525)	<0.0001
LS Standard Error	0.0789	0.0751	-	-	0.0932	0.0962	-	-

For CRN00808-08 EOT = The average of Week 22 and Week 24 if no rescue therapy, otherwise EOT = last assessment prior to rescue; IRT = Interactive Response Technology; Baseline IGF-1 is the average of the measurements taken on Day 1 on or prior to first dose of study drug and the last IGF-1 value measured just prior to this day. Least squares (LS) means, standard error, difference in LS means, and associated 95% CI, and pretreatment p-value from an analysis of covariance with treatment group, prior treatment strata per IRT (medically naïve or previously treated versus washout) as fixed effects, baseline IGF-1xULN as a covariate.
For CRN00808-09 EOT = Week 36 if no rescue, otherwise EOT= last assessment prior to rescue.
Least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, Screening IGF-1xULN groups (<0.86xULN, >=0.86xULN) and prior treatment group with lanreotide or octreotide as fixed effects, Baseline IGF-1xULN as a covariate.

2) Proportion of Participants with GH level <1.0 ng/mL for Study CRN00808-08 and Study CRN00808-09

Table 56 presents results for the secondary efficacy endpoint of the proportion of participants with GH level <1.0 ng/mL for Study **CRN00808-08** at Week 22 and Study **CRN00808-09** at Week 34, out of those who had GH level <1.0 ng/mL at Baseline. Both studies met statistical significance on the secondary endpoint (p<0.0001 and p=0.0003, respectively) favouring paltusotine over placebo.

Table 56 Secondary Efficacy Endpoint: Proportion of Participants with GH<1.0 ng/mL at EOR in Study CRN00808-08 and Study CRN00808-09 (Full Analysis Set)

	CRN00808-08		CNR00808-09	
	Total Paltusotine (N=54)	**Placebo (N=57)**	**Total Paltusotine (N=23)**	**Placebo (N=18)**
GH maintenance < 1.0 ng/mL at EOR – n (%)				
Responder	31 (57.4)	10 (17.5)	20 (87.0)	5 (27.8)
Non-Responder	23 (42.6)	47 (82.5)	3 (13.0)	13 (72.2)
GH >= 1.0 ng/mL	20 (37.0)	39 (68.4)	2 (8.7)	2 (11.1)
Missing GH Result at Week 22 (CRN00808-08) or Week 34 (CRN00808-09)	2 (3.7)	4 (7.0)	0	1 (5.6)

	CRN00808-08		CNR00808-09	
	Total Paltusotine (N=54)	**Placebo (N=57)**	**Total Paltusotine (N=23)**	**Placebo (N=18)**
Prohibited acromegaly medication	0	0	0	0
Rescue medication	2 (3.7)	13 (22.8)	2 (8.7)	12 (66.7)
Dose up-titration after Week 12 (CRN00808-08) or Week 24 (CRN00808-09	1 (1.9)	0	0	0
Treatment Discontinuation	4 (7.4)	16 (28.1)	2 (8.7)	12 (66.7)
Odds ratio (Paltusotine/Placebo)	7.588		16.609	
95% CI for odds ratio	(2.776, 23.483)		(2.864, 181.355)	
P-value	<0.0001		0.0003	

In Study CRN00808-08: EOR = end of Randomized Controlled Phase (Week 22); IRT = Interactive Response Technology. In Study CRN00808-08, average from the integrated GH sampling at week 22 is used to determine response. Percentages are calculated based on the number of participants in the Full Analysis Set. P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression model with treatment group as a factor and a covariate for prior treatment strata per IRT (medically naïve or previously treated versus washout). For the odds ratio, placebo participants are the reference group.
In Study CRN00808-09: EOR=end of Randomized Controlled Phase (Week 34). Percentages are calculated based on the number of participants with Baseline GH < 1.0 ng/mL in the Full Analysis Set. P-value, odds ratio, and corresponding 95% CI are from an exact logistic regression adjusting for Screening IGF-1 groups (<0.86xULN, >=0.86xULN), and prior treatment with lanreotide or octreotide. For the odds ratio, placebo participants are the reference group.

3) Change from Baseline to EOR in Total ASD Score

Table 57 presents results if no rescue therapy was administered or was based on the last available assessment prior to rescue therapy. Both studies met statistical significance on the secondary endpoint favouring paltusotine over placebo.

In Study **CNR00808-08**, the LS mean (±SE) changes from Baseline to EOT in total ASD score were -2.669 (±1.4221) for the paltusotine group and 2.754 (±1.3641) for the placebo group, with a treatment difference of **-5.423** (95% CI: -9.070, -1.776) (**p=0.0039**).

In Study **CRN00808-09**, the LS means (±SE) for the change from Baseline to EOT in total ASD score were -0.606 (±1.5044) for the paltusotine group and 4.558 (±1.5926) for the placebo group, with a treatment difference of **-5.164** (95% CI: -9.536, -0.792) (**p=0.0216**).

Table 57 Secondary Efficacy Endpoint: Change from Baseline to EOT in Total ASD Score in RC Phase of Study CRN00808-08 (Week 24) and Study CRN00808- 09 (Week 36) (Full Analysis Set)

	CRN00808-08 (Week 24)				CRN00808-09 (Week 36)			
	Paltusotine (N=54)	**Placebo (N=57)**	**Treatment Difference (95% CI)**	**P-value**	**Paltusotine (N=30)**	**Placebo (N=28)**	**Treatment Difference (95% CI)**	**P-value**
LS Mean	-2.669	2.754	-5.423 (-9.070, -1.776)	0.0039	-0.606	4.558	-5.164 (-9.536, -0.792)	0.0216
LS Standard Error	1.4221	1.3641			1.5044	1.5926		

In Study CRN00808-08: EOT = Week 24 if no rescue, otherwise EOT = last assessment prior to rescue. In Study CRN000808-09: EOT = Week 36 if no rescue, otherwise EOT= last assessment prior to rescue.
Baseline total ASD is the sum of the weekly average on or prior to Day 1, and post-baseline total ASD is the sum of Tabe the weekly average on or prior to the scheduled visit date, inclusive of the date of visit, for 7 items (headache, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling).
In Study CRN00808-08 least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, and prior treatment strata per IRT (medically naïve or previously treated versus washout), baseline total ASD score as a covariate.
In Study CRN00808-09, least squares (LS) means, standard error, difference in least squares means and associated 95% confidence interval, and treatment p-value from an analysis of covariance with treatment group, Screening IGF-1xULN groups (<0.86xULN, >=0.86xULN) and prior treatment group with lanreotide or octreotide as fixed effects, Baseline total ASD score as a covariate.
ASD=Acromegaly Symptoms Diary, IRT=interactive response technology, ULN=upper limit of normal

5.3.6. Healthcare professional engagement

Input has been received from a healthcare professionals' organisation, **European Society of Endocrinology (ESE)** relating to paltusotine.

The ESE has highlighted that current medication is painful to administer, and it requires an HCP to give the injection. Patients are unable to administer the injection by themselves, and they complain about the hardened injection spot.

The wear-off effect is considered a big problem, several patients struggling until the next injection. A new medicine that mitigates this wear-off effect would be welcomed by most patients. The wear-off phase will be noticed by increased tiredness and increased joint problems and mostly occurs in the last week before the new injection.

Keeping the current medication cooled is inconvenient when travelling. Also, the need to find a HCP for giving the injection during a stay abroad is considered difficult.

The current medication can cause serious side effects, such as type 2 diabetes and, in some patients, the gallbladder needs to be removed.

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

The efficacy of paltusotine has been evaluated based mainly in the 2 pivotal phase 3 studies **"CRN00808-08** and **CRN08008-09" and also on** 2 phase 2 dose studies "**CRN00808-03** and **CRN00808-02" with a long-term extension of these studies "CRN00808-05**".

The dose selection was mainly based on 2 phase 2 dose studies "**CRN00808-03** and **CRN00808-02" with a long-term extension of these studies "CRN00808-05**".

Phase 2 studies

1) Phase 2 study **CRN00808-03** "**ACROBAT EDGE"** was **an open-label, dose blinded**, exploratory study designed to evaluate the efficacy, safety, and PK of 5 doses (5 mg, 10mg, 20 mg, 30 mg and 40 mg) of paltusotine in capsules **in participants with acromegaly treated with SRL-based treatment regimens.** In this study, subjects were to be switched from their current monthly depot regimen to a once-daily regimen of oral paltusotine **without a washout** to loss of IGF-1 control.

The starting dose of **10 mg** QD paltusotine was found to be the lowest dose that was maximally effective in suppressing IGF-1 in healthy volunteers at steady-state and this level of suppression mirrored that achieved by either octreotide or lanreotide.

The results showed a maintenance of the effects of the prior treatments with other SRLs but there are a lot of uncertainties in this study**:**

- these results of this study are mainly driven by the results of group 1 (n= 25/47) (partial responders previously treated with monotherapy of octreotide or lanreotide).

- most of the patients in group 1 were treated with paltusotine 40 mg. According to the applicant, these data can be consistent with lower doses of paltusotine (10 and 20 mg) being less suppressive of IGF-1 than the upper end of the dose range. Likewise, doses for most subjects in Groups 2 to 5 were titrated to 40 mg/day. However, most subjects were titrated to the 40 mg per dose of paltusotine, consistent with the upper end of the dose range used in this study (ie, 40 mg/day) being the effective dose for most subjects.

- the population is limited, and the interpretation of the results is very complicated all the more than due to COVID pandemic, some participants were up-titrated during specific study visits without availability of prior IGF-1 data.

- as there was not any washout between the previous SRLs treatment and the start of paltusotine, the possible carry-over effect of previous SRLs treatment (lanreotide) cannot be ruled-out due to the short duration of the study (13 weeks). However, Sensitivity analyses indicate that the wash out of both octreotide and lanreotide were adequate to measure IGF-1 and GH suppression associated with paltusotine treatment. Indeed, median residual concentrations of octreotide fell to the LLOQ of the octreotide assay by W7 (12 weeks after last depot injection). The residual concentrations of lanreotide had fallen by a median of 50.1% by W7 and by 77.3% at W13.

- the results of study show a maintenance of the effects of the prior treatments with other SRLs.

2) Phase 2 study **CRN00808-02** "**ACROBAT EVOLVE**" was a placebo-controlled, double-blind, **randomized withdrawal study** designed to evaluate the safety, efficacy, and PK of **4 different doses** of paltusotine in capsules (10 mg, 20 mg, 30 mg and 40 mg) in a sample of participants, with a confirmed acromegaly diagnosis that was controlled (mean of IGF-1≤ULN) values, on a stable approved dose of octreotide LAR or lanreotide depot. **Enrolment in this study was halted due to business reasons/considerations as of 31 March 2020, with 13 participants receiving paltusotine.**

The participants with acromegaly were responders to octreotide LAR or lanreotide depot. Of the randomized subjects (n=7), the percentage who met the responder criteria (IGF-1≤ULN) at Week 13 (Visit 13 and Visit 14) was greater in the paltusotine arm, (2 subjects [66.7%]) compared to placebo, (1 subject [25.0%]) with a treatment difference of **41.7%** (95% CI: -43.0%, 91.6%). The reduced sample size did not allow for meaningful statistical comparisons between treatments in the RWP.

However, no conclusion can be drawn from this study as this study was halted early and therefore the clinical data are too limited. No washout has been planned between the SRLs and the oral paltusotine. Thus, the carry-over of the effect of SRLs cannot be ruled out given the short duration of 13 weeks. The

comparison with patients on placebo cannot be taken into consideration. Moreover, in this study, as in the **CRN00808-03** study, the capsules of paltusotine were used while in the phase 3 studies, the SDD tablets are used. This change can have an impact on the dose and on the clinical data.

3) Eligible participants from studies **CRN00808-03** and **CRN00808-02** were invited to participate in the **on-going OLE study CRN00808-05 "ACROBAT ADVANCE"**, which provides long-term safety, tolerability, and efficacy data for 3 doses (10 mg, 20 mg and 30 mg) of paltusotine in tablets (patients were switched from capsules to tablets). Participants are permitted to remain on paltusotine treatment **up to 312 weeks** (6 years) as long as withdrawal criteria are not met. In summary, long-term paltusotine administration was evaluated **up to 272 weeks** as of the data cut-off (31 August 2025).

In this on-going study, the starting dose was 10 mg/day. If tolerated, the dose of study medication was to be increased to 20 mg QD at the Week 4 Visit **if the IGF-1 value measured was >ULN** range provided by the central laboratory. **At the Week 8** Visit, the dose of study medication was to be increased to a maximum of **40 mg QD** if IGF-1 remained >ULN and the participant was tolerating the study medication. After the switch from the capsules to the tablets, it was also possible to up-titrate the dose to **60 mg/day** if IGF-1 > ULN. Doses could be decreased from doses of 20 mg QD or above, to improve tolerability, as necessary, at any time during the study.

Adjunctive acromegaly treatments (ie, dopamine agonists and/or pegvisomant) were permitted to be initiated in combination with paltusotine if IGF-1 levels were still elevated after the participant had been taking paltusotine 40 mg QD (or maximally tolerated lower dose) for 2 to 4 weeks, if clinically appropriate.

The median duration (range) of exposure was 256.6 (15.0 to 287.7) weeks. Most participants (65.1%) 28/43 were being treated with paltusotine 60 mg QD, and 27.9% 12/43 were being treated with 40 mg QD with (6/11) 54.5% of participants from parent study CRN00808-02 and (24/32, 75%) of participants from parent study CRN00808-03 were receiving paltusotine 60 mg QD,

Most participants who received adjunctive therapy during the study were on a more intensive regimen (adjunctive therapy with cabergoline or pegvisomant; or on pasireotide) prior to entering the parent study CRN00808-03.

The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs) throughout the study.

At the first cut-off date of 5 December 2023, the overall proportion of participants with IGF-1 ≤ 1.0 x ULN **at Week 3** was **34.9%** (95% CI 21.01, 50.93), with highest rates of **42.5%** at **Week 23** (95% CI 27.04, 59.11) and **54.1%** at Weeks 64 and **W77** (95% CI 36.92, 70.51).

The main observations of the phase 2 studies are:

- the proportion of responders is higher in study **CRN00808-02** than in study **CRN00808-03** and especially in the group of patients treated with paltusotine alone in study **CRN00808-03.**

- they have only investigated the efficacy of paltusotine in patients already treated with other SRLs (octreotide, lanreotide, pasireotide) and for study **CRN00808-03**, the patients have also been treated with dopamine agonists (cabergoline or bromocriptine), and pegvisomant. The study duration of these studies is only 13 *weeks,* and this is too short to provide substantial evidence of the safety and effectiveness of paltusotine in the treatment of acromegaly due to the potential carry-over of the effects of the other SRLs treatments as no washout has been planned in both studies. In both studies, there were no medically naïve patients, thus the choice of the starting dose for these patients in the phase 3 studies is not based on the results of these studies.

- the duration of the effect "IGF-1 levels ≤ ULN" is longer among patients from study **CRN00808-02** than in study **CRN00808-03.**

- at the data snapshot date of 31 August 2025, at Week 15, **31.0%** of participants in the overall CRN00808-05 population achieved IGF-1 level ≤1.0xULN with a higher proportion of participants from parent study CN00808-02 (**63.6%)** than in participants from parent study CRN00808-03 (**19.4%)**.

- the proportion of IGF-1 responders (IGF-1 level ≤1.0xULN) increased over time and was generally maintained through Week 272 in the overall study population and within the subgroups by parent study.

- the proportion of participants with GH level <1.0 ng/mL ranged from **50.0% to 100.0%** from Week 23 to Week 272 in the overall study population.

- overall, based on the long-term results of study CRN00808-05, paltusotine in monotherapy was able to maintain IGF-1 levels similar to previous SRL-based therapy, and for participants who were treated with paltusotine and adjunctive therapy, additional treatment benefits were observed, as evidenced by the continued improvement in IGF-1 levels during the study.

Phase 3 studies

Study design

1) **CRN00808-08 "PATHFNDR-2: Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen"** was a multicentre, randomized, double-blind, placebo-controlled study where participants with non-pharmacologically treated acromegaly including participants with no prior medical therapy, participants who last received medical therapy at least 4 months prior to screening, and participants who were controlled on medical therapy for at least 3 months but agreed to wash out prior to beginning study treatment, were randomly allocated to receive either paltusotine or placebo **up to 24 weeks**.

After the Screening Period, all eligible participants were randomized in a 1:1 ratio to receive paltusotine or placebo, stratified by prior treatment (naïve or previously treated).

After the first 12 weeks of study treatment including dose titration in the RC phase, no further dose titration was permitted for the remaining 12 weeks of study treatment in the RC phase. This allowed for **an additional 12 weeks on a stable dose** of study treatment to adequately assess the effectiveness of paltusotine.

Participants who completed the 24-week RC phase or who met rescue criteria and completed the 24-week RC phase with rescue medication could continue participation in the OLE phase for **up to 200 weeks**. This OLE phase is still on-going. At the completion of study target enrolment for the RC phase, remaining participants in the washout group who had entered screening and met eligibility criteria were eligible to directly enrol into the OLE.

2) **Study CRN00808-09 "PATHFNDR-1"** was a randomized, placebo-controlled, multicentre study designed to evaluate the efficacy and safety of paltusotine in participants **with biochemically controlled acromegaly** (IGF-1 level ≤1.0×ULN) who were switched from monotherapy with injected long-acting octreotide or lanreotide. In the Randomized Controlled (RC) phase, eligible participants were randomized (1:1 ratio) to daily oral administration of paltusotine or placebo when their next dose of octreotide/lanreotide was due to begin, for a Treatment Period of **up to 36 weeks**. There were stratified by mean Screening IGF-1 level (<0.86×ULN, ≥0.86×ULN) and prior treatment (lanreotide, octreotide).

The study consisted of 3 periods. **The screening period** consisted of 2 to 3 visits over **4 to 12 weeks**, treatment period (**randomized controlled phase**) of **up to 36 weeks** with a possible up-titration of paltusotine **through week 24** and a fixed dose of paltusotine during the last 12 weeks.
Participants who completed the RC phase could be eligible to enrol and receive paltusotine in the **Open-label Extension** (OLE) phase **for up to 200 weeks**. The RC phase is completed. This report describes results from RC phase. The OLE phase is on-going.

The design of the phase 3 studies has been discussed with EMA and FDA. This design is in line with the line with the *Guidance for Acromegaly: Developing Drugs for Treatment (FDA 2023)*. The use of placebo was discouraged during the EMA SA, where the use of an active comparator as control arm in the setting of an open label study was suggested, in particular for the population that was already in treatment before enrolment: this, mainly, to prevent an overestimation of efficacy due to possible rebound effects after suspension of the previous treatment in patients enrolled in the placebo arm. However, the applicant has chosen placebo-controlled studies, since paltusotine is administered orally and no other oral drugs were approved at the time of the clinical trials; this was considered acceptable also since the main endpoint used was a biochemical measure (IGF-1 level) which is quite a robust marker. A double-dummy long-acting SRL active comparator was also not feasible with injectable forms of somatostatine or lanreotide, in particular patients are accustomed to injections of a viscous SRL solution and would be able to distinguish between an approved SRL injection and a placebo injection, thus breaking the blind; moreover, SRL injections require large-bore needles that can be painful and would place an undue burden on study participants.

Target population ("inclusion and exclusion criteria)

1) **Study CRN00808-08**

Main inclusion criteria:
≥18 years of age falling into 1 of the following 3 groups:

- Medically naïve group (Group 1), patients not previously treated with acromegaly medications (including LA-SRLs), with at screening IGF-1 ≥1.3×ULN (the lower limit for eligibility is IGF-1 of 1.25×ULN when rounded to 2 decimal places). This group subjects must have had at least 1 pituitary surgery at least 3 months prior to screening.
- Previously Treated group (Group 2) with other SRLs, but no treatment within previous 4 months, with IGF-1 ≥1.3×ULN.
- Washout group (Group 3), subjects with stable treatment at screening (no change in dose for 3 months) with octreotide or lanreotide monotherapy, with IGF-1 ≤1.0×ULN. Any form of pretrial octreotide or lanreotide monotherapy (long- or short-acting [SC, IM, or oral]) should be washed out and will determine the duration of the Screening Period.

Main exclusion criteria: History of ineffectiveness or intolerance of octreotide or lanreotide treatment. History of pituitary radiation therapy within 3 years of Screening. Adrenal insufficiency, diabetes insipidus, or central hypogonadism not treated. High-risk pituitary tumour pattern. Several other medical conditions, particularly uncontrolled. Use of certain medications (acromegaly medication use, Group 1 only; Lanreotide depot or octreotide LAR within 16 weeks before Screening, Group 2 only; Pasireotide LAR, within 24 weeks prior to Screening; Pegvisomant within 16 weeks before Screening; Dopamine agonists within 16 weeks before Screening; Any combination of acromegaly medications at Screening; Proton pump inhibitors throughout the study).

2) Study CRN00808-09

Main inclusion criteria
Adults >=18 years of age with medically stable, confirmed-active acromegaly and on an approved, stable monotherapy dose of long-acting octreotide or lanreotide, for at least 12 weeks prior to Screening. Previous diagnosis of acromegaly confirmed. For subjects who have had pituitary surgery, there must be documentation of IGF-1 concentration >=1.3×ULN at least 12 weeks after last pituitary surgery. Screening average IGF-1 levels of <=1.0×ULN.

Main exclusion criteria
Treatment-naïve or treatment-withdrawn acromegaly subjects. History of pituitary radiation therapy. Use of the following medications (Pasireotide LAR, within 24 weeks prior to Screening; Pegvisomant, within 12 weeks before Screening; Dopamine agonists, within 12 weeks before Screening; Short acting somatostatin analogues, SA-SSAs, within last 12 weeks before the first dose of study drug. Other conditions (similar to those for study 08).

The main inclusion/exclusion criteria of both phase 3 studies were considered acceptable and were adequate to select a population apt to isolate the effect of paltusotine in acromegaly in both new patients and already controlled patients.

Dose titration

Study CRN00808-08

The starting dose of paltusotine in the RC phase was **20 mg QD** (1×20 mg tablet of active paltusotine or matching placebo) for oral self-administration. A dose of 20 mg was selected to minimize potential gastrointestinal side effects in participants washed out from medical therapy or naïve to medical therapy. After confirming tolerability with the participant, **the dose was increased to 40 mg QD** (2×20 mg tablets of active paltusotine or matching placebo) **at the Week 2 visit**.

Dose down-titration was allowed at any time during the RC phase of the study if the dose was not tolerated in the judgement of the investigator.

At Week 6, the dose could be increased to 60 mg QD (3×20 mg tablets of active paltusotine or matching placebo) if the 40 mg dose was acceptably tolerated and based on biochemical control and the Week 4 IGF-1 was >0.9×ULN.

In the OLE phase, the starting dose regimen for participants in the OLE phase is paltusotine 20 mg QD at the week 24/EOR visit, and if tolerated, can be increased to 40 mg QD at the Week 26 visit. The dose could be increased to 60 mg QD if the 40 mg dose was acceptably tolerated and based on biochemical control.

The dosing regimen recommended in the RC and in the OLE phase of study **CRN00808-08** was not in line with the regimen recommended in the SmPC of paltusotine as in the SmPC, the starting dose is 40 mg/day and increased up to 60 mg/day after at least one week based on IGF-1 levels or clinical signs and symptoms. The applicant agreed to amend the section 4.2 to recommend a dosing regimen for initiation of paltusotine in the medically naïve and uncontrolled patients in line with the dosing regimen investigated in the pivotal study **CRN00808-08.**

Study CRN00808-09, the starting dose was paltusotine 40 mg QD (or matching placebo), and titrated (down to 20 mg or up to 60 mg QD) based on biochemical status and tolerability.

In the RC phase, participants were switched from a stable long-acting regimen of octreotide or lanreotide to paltusotine (or placebo). The dose titration design of this study was aimed at maintaining participants in their baseline biochemical status of IGF-1 (≤1×ULN) and optimizing their dose while minimizing the period in which their IGF-1 levels were above baseline.

The starting dose (paltusotine or placebo) was **40 mg** QD for oral self-administration. The dose could be increased from **40 mg to 60 mg** QD through Week 24 based on IGF-1 response and tolerability. Participants who required dose up-titration after Week 24 were considered non-responders. Dose levels could be decreased based on tolerability at any time during the study.

Prior to enrolling in this study, participants had controlled disease on stable doses of existing SRLs for an extended period and would have been acclimated to the safety profile of these treatments. Therefore, a 20 mg starting dose was deemed not necessary in this study, and this is acceptable.

Rescue criteria were provided for participants who required resumption of standard acromegaly treatment during the RC phase.

In the OLE phase, the starting paltusotine dose during the OLE phase was **40 mg** QD for oral self-administration. The paltusotine dose could be increased from 40 mg to 60 mg QD based on IGF-1 response, generally once the first IGF-1 result was available.

Rescue therapy: IGF-1 levels and acromegaly-related symptoms were monitored throughout the studies. Criteria for rescue therapy were provided to ensure that participants who experienced worsening of symptoms associated with acromegaly **and** had increased IGF-1 levels (≥1.5×ULN for study 08 and ≥1.3×ULN for study 09) at the highest dose (paltusotine 60 mg QD or placebo) received rescue injections of standard acromegaly therapy and could safely complete the study.
The patients with rescue therapy in the RC were also included in the OLE phase.

Primary and secondary endpoints

Primary endpoint
In the 2 phase 3 studies, the primary endpoint was the proportion of participants with IGF-1 levels ≤ ULN at EOR. IGF-1 has been reported to be the most reliable biomarker to monitor the efficacy of SRL-treatments in acromegaly. Although serum IGF-1 and GH are known biomarkers of acromegaly disease, given that the secretion of GH is pulsatile, random serum GH concentrations is uncertain. Most symptoms of acromegaly are non-specific, so a normal IGF-1 level in the presence of persistent symptoms has been considered controlled disease.

Key secondary endpoint in study CRN00808**-**08: the change from Baseline in IGF-1, in units of ULN, to EOR.

Main secondary endpoints:
In study CRN00808-08: proportion of participants who achieved IGF-1 <1.3×ULN at EOR; proportion of participants with GH <1 ng/mL at Week 22; change from Baseline in Total Acromegaly Symptoms Diary (ASD) score to EOR.
In study CRN00808-09: change from Baseline in IGF-1, in units of ULN, to EOR; proportion of participants with GH<1.0 ng/mL at Week 34, out of those who had GH <1.0 ng/mL at Baseline; change from Baseline in total ASD*(acromegaly symptoms diary) score to EOR.

The main secondary endpoints are acceptable: the IFG-1 levels are used in clinical practice to assess the effectiveness of acromegaly treatment and to adjust therapy dosage, together with GH levels and clinical symptoms.

The other secondary endpoints are similar in phase 2 and phase 3 studies, "changes from baseline in serum GH levels at EOT (end of trial)", "change from baseline in IGF-1 levels at EOT" and "change from baseline in ASD (Acromegaly symptom diary) at EOT" (only in the phase 2 study CRN00808-02). Of note, in the pivotal phase 3 **CRN00808-08**, the key secondary endpoint is "Change from Baseline in IGF-1".

The ASD is a brief disease-specific symptoms diary developed and validated by the Sponsor in accordance with the *FDA Patient-Focused Drug Development Guidance and Patient-Reported Outcome Measures Guidance*. Of note, the dossier of validation of ASD is still under review by the European Medicines Agency (EMA).

The ASD was developed to fill a recognized need in the availability of a patient-reported measure of acromegaly. The ASD was developed as a novel, daily diary **to assess important symptoms of acromegaly from the patient perspective**. The ASD consists of 7 symptoms (headache pain, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling). Two additional items, difficulty sleeping and difficulty with short-term memory, are also included in the diary. The ASD weekly total score ranges from 0 to 70; for all ASD items, **a higher score indicates greater severity.** The proposed preliminary threshold range to characterize a meaningful change from the patients' perspective for the ASD total is a **4- to 6-point change** for improvement or worsening out of a total score of 70 (Martin et al 2023).

The other PROs in the phase 3 studies are exploratory efficacy endpoints such as "Change from baseline in AcroQoL total score", "Change from baseline in EuroQoL-5 dimensions-5 levels (EQ-5D-5L)", "Change from baseline in acromegaly QoL questionnaire (AcroQoL)", "Patient Global Impression of Improvement (PGI-I) scores" or "Change from Baseline to EOR in Patient Global Impression of Severity (PGI-S)" and also "treatment preference questionnaire".

Other exploratory endpoints are assessed in the phase 3 studies such as "Change from Baseline in residual pituitary tumour volume", "Time to initial response of IGF-1 ≤1.0×ULN".

Statistical considerations

In both pivotal studies **CRN00808-08** and **CRN00808-09**, the estimand framework was formally applied for the primary endpoint, and the primary estimands are considered acceptable. In both cases, a composite strategy was used to handle intercurrent events such as treatment discontinuation, rescue therapy, prohibited medication, and dose titration. These intercurrent events were incorporated into the definition of response, reflecting treatment failure. The primary analysis method (exact logistic regression with fallback to Firth regression) is appropriate given the binary nature of the endpoint and the sample size. The prespecified covariates (including baseline IGF-1 strata and prior treatment strata) are consistently included in both trials.

The statistical methods were well reported in the protocols and the SAPs and can be considered, overall, appropriate to support the testing of the hypotheses for both studies. For the key secondary endpoint, the primary analysis used an ANCOVA model adjusted for treatment, prior treatment strata, and baseline IGF-1. Intercurrent events were handled using a LOCF approach, reflecting a while-on-treatment strategy. A sensitivity analysis based on multiple imputation using placebo on-treatment data was performed to assess robustness.

For secondary endpoints, the Applicant provided detailed estimand definitions, including population, variable, intercurrent event handling, summary measure, and analysis model, which are now considered aligned with the intended clinical questions. The approach applied for continuous and categorical endpoints was consistent with the SAP and was found to be acceptable.

The randomization scheme and blinding/unblinding procedures were well explained and considered adequate. The sample size calculations were comprehensible and reproducible. For study CRN00808-08, the calculation was based on the assumption of equal number of subjects in each stratum and 10% dropout, while in study CRN00808-09 these assumptions were not applied as estimates for the two stratification criteria were not available.

In study **CRN00808-09**, an interim futility analysis was planned but was never conducted due to accelerated recruitment.

For both studies, the strategy adopted to control the type I error at a two-sided alpha level of 0.05 through the primary, key secondary and secondary endpoints was based on a fixed sequential method with pre-specified ordering by clinical relevance. Among secondary endpoints, the Applicant gave particular importance to the change in Total ASD Score, whose validation involved pooled phase II and phase III trials.
Power justifications for the key secondary endpoints were provided and are considered adequate to detect clinically meaningful differences (Question 167).

The conduct of both **CRN00808-08** and **CRN00808-09** is considered adequate. Both studies were randomised, double-blind, and placebo-controlled, with appropriate measures in place to ensure blinding of participants and investigators. No concerns were identified regarding unblinding or bias in treatment administration. The stratification and randomisation processes were prespecified and appropriately implemented.

The Full Analysis Set (FAS), consisting of all randomized participants (excluding screen failures), analysed according to randomization, was used for efficacy analyses in line with the ITT principle. The Per Protocol Set (PPS), including all participants who completed the RC phase without major deviations and with ≥75% treatment compliance, was used for sensitivity analyses. No major protocol deviations affecting safety, confidentiality, or data integrity were reported, and no subjects were excluded from the FAS. Subgroup analyses were well defined in the protocol and are endorsed.

Changes made during the studies were prespecified in SAP amendments. They are not expected to compromise the integrity of the blind or the internal validity of the studies. Overall, the conduct of both studies was adequate, and no major deviations were identified that would impact the reliability of the results. The methodological framework is generally acceptable, with all major statistical issues resolved.

Results of all the pivotal phase 3 studies

Baseline and disposition

In **study CRN00808-08** a total of **209 participants** were screened, of which 111 participants were randomized (54 participants in the total paltusotine group and 57 participants in the placebo) to the RC phase and included in the FAS.

In **study CRN00808-09** a total of **115 participants** were screened, of which 58 participants were randomized (30 participants in the total paltusotine group and 28 participants in the placebo) and included in the FAS.

OLE Phase disposition.

In study CRN00808-08, of the **114 total participants** in the OLE phase, 51 participants were from the paltusotine group, and 52 participants were from the placebo group in the RC phase of the study. Eleven participants previously entered the OLE phase directly. These participants were in the washout group at completion of study target enrolment for the RC phase and had entered screening and met eligibility criteria.

. **44 participants** from the medically naïve group in the RC phase continued in the OLE phase (21 in the prior paltusotine group and 23 in the prior placebo group).

. **34 participants** from the previously treated group in the RC phase continued in the OLE phase (16 in the prior paltusotine group and 18 in the prior placebo group).

. **36 participants** comprised the washout group in the OLE phase, which consists of 14 participants from the prior paltusotine group, 11 participants from the prior placebo group, and 11 participants who enrolled directly into the OLE phase.

13 participants from the medically naïve group discontinued the study (8 in the prior paltusotine group and 5 in the prior placebo group), **5 participants** from the previously treated group discontinued the study (3 in the prior paltusotine group and 2 in the prior placebo group), **2 participants** from the washout group discontinued the study (2 in the prior paltusotine group).

In study CRN00808-09, of the **58 participants**, 53 (91.4%) entered the OLE phase: 27 participants were from the paltusotine group and 26 were from the placebo group in the previous RC phase of the study. Two participants (both in the prior placebo group) had dose reductions due to a TEAE.

Results of the RC phase of study CRN00808-08 (cut-off date: 20 January 2024)

The primary endpoint was met based on the proportion of participants in the paltusotine group (30 of 54 [**55.6%**]) who achieved biochemical response (IGF-1 level ≤ 1.0×ULN) at EOR compared to those in the placebo group (3 of 57 [**5.3%**]) (**p<0.0001**).

However, the proportion of responders is mainly driven by the response of group 3 "washout patients". This was expected as the controlled sub-population of group 3 "washout patients" in study **CRN00808-08** enriches the study with the potential responders and the efficacy of paltusotine must be overestimated. Indeed, the patients of the group 3 "washout patients" were already well-controlled by other SRLs and are more susceptible to respond to paltusotine.

Indeed, the sensitivity analysis of the primary endpoint by stratum showed a higher proportion of responders among the washout patients compared to the proportions of responders in the other groups: **92.3%** (13/14) of patients treated with paltusotine versus **13.3%** (2/15) in the placebo group (**p<0.001)**. In the previously treated patients **66.7%** (12/18) in the paltusotine group versus **0%** in the placebo group (**p<0.001)**. In the medically naïve patients, **22.7%** (5/12) in the placebo group versus **4.2%** (1/24) (**p = 0.1509).**

The sensitivity results within the stratum 1, the effect of paltusotine on the primary endpoint in "medically naïve" patients, **22.7%** (5/22)) versus **4.2%** (1/24) in the group of placebo (p = 0.1509) highlights the lower IGF-1 response observed in this subgroup compared to previously treated patients **66.7%** (12/18) (group 2 "already treated patients") versus 0% in the group of placebo and **92.9%** (13/14) (group 3 in stratum 2 "washout patients") versus **13.3%** (2/15) in the group of placebo. This finding is considered credible given the biological and mechanistic plausibility of a reduced treatment effect in this population. Since this important subgroup is included in the proposed indication and given that it was the only subgroup with very low effect (and not statistically significant), the Applicant was

asked to substantiate the benefit/risk balance of paltusotine in medically naïve patients, and, thus, the inclusion of this subgroup in the indication.

In the RC phase, the proportion of medically naïve patients who normalized their IGF-1 levels was consistent with the literature with approximately **17% to 35%** (*Katznelson 2014*) in both drug-naïve and post-operative patients and with **23.6%** of medically naïve patients treated with depot injectable octreotide (*Colao et al 2014*).

The applicant provided arguments to justify the lower efficacy of paltusotine in medically naïve patients, and this was agreed.

In Study **CRN00808-08**, participants in the medically naïve group had younger age, higher baseline IGF-1 and GH levels, and larger pituitary tumour size/volume compared to participants in the previously treated and washout groups. However, these clinical features in the medically naïve group are consistent with an unfavourable prognosis based on literature (*Marques-Pamies 2024*) suggesting that the medically naïve group would be much more challenging to treat than the previously treated and washout groups in this study. Additionally, in the medically naïve group, the mean time since surgery was 34.2 months at baseline, which is much longer than the 3-month recommendation to start medical treatment following pituitary surgery depending on IGF-1 levels according to acromegaly consensus guidelines (*Melmed 2025*).

Moreover, in the 13th consensus on the multidisciplinary management of acromegaly (*Giustina 2020*), although the absolute cut-off for defining biochemical control is the upper limit of normal, values slightly higher than this cut-off (e.g. within 1.2 to 1.3×ULN) could be considered as a target of treatment depending on the clinical scenario. In study CRN00808-08, the proportion of participants with IGF-1 <1.3×ULN at EOR was a secondary efficacy endpoint. The proportion of participants in the medically naïve group who achieved IGF-1 level <1.3×ULN at EOR was 36.4% (8 of 22) in the paltusotine group compared with 8.3% (2 of 24) in the placebo group (**p=0.0495**).

Other arguments of the applicant to justify the benefit risk of paltusotine in the medically naïve patients are provided in the OLE part.

At EOR, **54 patients** were treated with paltusotine: **3 patients** (**5.6%**) were treated with paltusotine 20 mg (1 medically-naïve patient, 1 previously treated with other SRLs and 1 washout patient), **15 patients** (**27.7%**) (3 naïve, 8 uncontrolled and 4 washout) were treated with paltusotine 40 mg and **36 patient**s (**66.7%**) (18 naïve, 9 uncontrolled and 9 washout) were treated with paltusotine 60 mg.
Among the medically naive patients, **81.8%** are treated with paltusotine 60 mg at the end of the RC phase.
Among responders (30 patients), 1/30 (**33.33%**) were treated with paltusotine 20 mg (1 washout), 13/30 (**43.3%**) (3 naïve, 6 uncontrolled and 4 washout) were treated with paltusotine 40 mg and 16/30 (**53.3%**) (2 naïve, 6 uncontrolled and 8 washout) were treated with paltusotine 60 mg.

It is highlighted that it is unlikely that this issue could be addressed by an increased maintenance dose. Indeed, the long-term efficacy results of the OLE phase of study CRN00808-08 and E-R analyses support paltusotine 60 mg QD as the maximum therapeutic dose. Indeed, in the E-R analysis, based on a population maximum IGF-1 level reductions of 57%, paltusotine doses of 20 mg, 40 mg, and 60 mg corresponded to IGF-1 level reductions of approximately 37%, 43%, and 47%, respectively, while 80 mg would result in 49% reduction in IGF-1. These analyses also showed that additional dose increases beyond 60 mg QD would provide only marginal decreases in IGF-1 levels. However, an issue remains for patients with a high level of IGF-1 at baseline (≥2.5xULN).

To support the effect at the maintenance dose of 60mg QD, the Applicant has provided an Exposure-Response Analyses conducted in stratum 1 (medically naïve patients, and previously treated patients).

Indeed, it was questioned (as part of OC efficacy) whether maintaining a paltusotine dose of 60 mg in patients with high levels of IGF-1 at baseline (1.7xULN) would be beneficial given the predicted effects of a 60 mg dose of paltusotine on IGF-1 dynamics (reduction by 47.5%). Based on the provided plot showing simulations of post-treatment IGF-1 level, for QD 60 mg dosing, by varying levels of baseline IGF-, the Applicant concluded that the maximal dose of paltusotine 60 mg is expected to provide IGF-1 levels ≤1.0xULN across a broad range of baseline IGF-1 levels (>1.7xULN to 4.0xULN). However, such conclusion can only be agreed for IGF-1 levels at baseline < 2.5x ULN and by considering an IMAX effect of 57%. Therefore, the applicant was asked to compute for each Baseline IGF-1(xULN) of 2.0, 2.5, …, 5.0, the proportion of subjects who are expected to achieve Post-treatment IGF-1(xULN) of 0.5-<1, 1-<1.5, 1.5-<2, 2-above, and to thoroughly discuss the results.

The results of the simulation provided by the applicant clearly demonstrated that the probability of achieving IGF-1 normalisation (≤ 1xULN) or near-normalisation (≤ 1.3xULN) markedly decreases with elevated baseline IGF-1 levels.

For baseline IGF-1 of 2.5xULN, **12.8%** are predicted to achieve normalisation and less than **40.1%** near-normalisation. For baseline IGF-1 of 3xULN, **~6%** are predicted to achieve normalisation and less than **23.2%** near-normalisation.

Based on observed (vs predicted) values from the 40 medically naïve patients enrolled in study CRN00808-08 with a mean IGF-1 of 2.2xULN at baseline, **42.5%** (vs 45%) achieved a normalisation, less than **25%** (vs 22.5%) a near-normalisation (IGF-1 levels between 1xULN and 1.5xULN). **32.5%** of the medically naïve participants (vs 32.5%) had an IGF-1 over > 1.5 xULN.

These results highlighted that the achievement of IGF-1 normalisation or near normalisation is dependent of IGF-1 baseline and that a 60 mg QD dose cannot achieve IGF-1 normalisation (or near-normalisation) across a broad range of baseline IGF-1 values.

This was consistent with the E-R analysis which showed that paltusotine doses of 20 mg, 40 mg, and 60 mg corresponded to IGF-1 level reductions of approximately 37%, 43%, and **47%**, respectively.

In study CRN00808-08, the baseline IGF-1 decreased from 0.8 to 1xULN up to 24 weeks. However, in medically naïve patients with a baseline IGF-1 >2.5xULN, a normalisation or a near normalisation of IGF-1 cannot be achieved (suggesting additional measures) and this has been reflected in the SmPC (4.2).

The benefit-risk of paltusotine was considered positive in medically naïve patients in study CRN00808-08 at the dose regimen proposed in this study but given that some uncertainties remained as regards the efficacy of paltusotine in patients with high IGF-1 (e.g ≥ 2.5) at baseline, section 4.2 of the SmPC was amended accordingly.

Statistically significant differences in favour of paltusotine were observed for the key secondary endpoint and other secondary efficacy endpoints. Results of sensitivity analyses to assess the robustness of the key secondary and secondary efficacy analysis were consistent with the results of secondary efficacy endpoints.

Regarding the key secondary endpoint, the LS means (±SE) change from Baseline to EOT in IGF-1×ULN were **-0.819** (±0.0789) for the paltusotine group and **0.087** (±0.0751) for the placebo group, with a treatment difference of **-0.906** (95% CI: -1.106, -0.706) (**p<0.0001**). This result was also confirmed in the different stratum.

Of note, in the medically-naïve patients, the mean IGF-1 levels were about 2.5x ULN at baseline and decrease over time but stayed between 1xULN and 1.5xULN but never decreased under 1xULN while the mean of IGF-1 levels in previously treated patients with other SRLs decreased from 2xULN to ≤ 1xULN (from W2 to W24) and for the washout patients, the IGF-1 levels decrease from 1.5x ULN to under

1xULN (from W2 to W24). The applicant was asked to discuss this difference between the subgroups of patients.
The applicant assessed the impact of baseline IGF-1 levels and duration of treatment and response with paltusotine, participants were evaluated based on mean baseline IGF 1 levels of >2.5 ×ULN and ≤2.5 ×ULN in the medically naïve group, >2.0 and ≤2.0 ×ULN in the previously treated group, and >1.5 ×ULN and ≤1.5 ×ULN in the washout group, with a data snapshot date of 21 May 2025.
Among the medically naïve patients with IGF-1 levels > 2.5x ULN, although there was a substantial reduction of IGF-1 levels during the first two weeks of treatment, mean IGF-1 levels continued to decrease with paltusotine treatment during the RC Phase and the OLE phase after the dose titration reaching near normal mean IGF-1 levels at Week 72 **but stayed above 1xULN**. This supports the recommendation of a warning in section 4.2 for patients with high IGF-1 levels at baseline (e.g > 2.5x ULN).

At EOR, the proportion of participants who achieved biochemical response IGF-1 level <1.3×ULN was **66.7%** (36 of 54) in the paltusotine group compared with **14.0%** (8 of 57) in the placebo group (**p<0.0001**).
This result was also confirmed in the different stratum. Of note, based on the 13th consensus on the multidisciplinary management of acromegaly (*Giustina 2020*), values slightly higher than this cut-off (e.g. within 1.2 to 1.3×ULN) could be considered as a target of treatment.

At EOR, the proportion of participants who achieved GH level <1.0 ng/mL was **57.4%** (31 of 54) in the paltusotine group compared with **17.5%** (10 of 57) in the placebo group (**p<0.0001**). This result was confirmed by sensitivity analyses.

The LS means (±SE) change from Baseline to EOT in total ASD score were **-2.669** (±1.4221) for the paltusotine group and **2.754** (±1.3641) for the placebo group with a treatment difference of **-5.423** (95% CI: -9.070, -1.776), indicating an improvement and stabilization of symptoms for the paltusotine group, and worsening of symptoms for the placebo group. This difference was statistically significant (**p=0.0039**).

There was a better improvement of acromegaly symptoms in the group of washout patients compared to medically naïve patients and compared to the group of previously treated patients. However, the LS means (±SE) change from Baseline to EOT in most bothersome symptoms were **-0.553** (±0.4219) in the paltusotine group and **0.357** (±0.3770) in the placebo group, with a treatment difference of **-0.910** (95% CI: -1.976, 0.157) in favour of paltusotine but not significant (nominal **p=0.0935**).

Results of multiple exploratory endpoint analyses also favoured paltusotine "change from baseline to W22 in GH level", "proportion of participants who achieved GH level <2.5 ng/mL" were statistically significant for the group paltusotine compared to placebo, the Kaplan-Meier median time to initial response (IGF-1≤1.0×ULN for 2 consecutive visits) was **44 days** (15.0 days, not estimable [NE]) for the paltusotine group and was **not reached** (NE, NE) for the placebo group. Paltusotine was associated with stable or reduced pituitary tumour size as measured by MRI.

Regarding the exploratory PROs endpoints, results from the Treatment Preference Questionnaire at Week 24 indicated that **77.8%** (42 of 54) of participants in the paltusotine group and **63.2%** (36 of 57) of participants in the placebo group preferred oral medication over previous injections for acromegaly. The differences of change from baseline to EOR (EOT at W24) in the **EQ-5D-5L** health index score and in the **PGI-I** were significant in favour of paltusotine vs placebo.
However, the difference of the LS means (±SE) change from Baseline to EOT in **PGI-S** and in **AcroQoL** composites and standardized scores were not significant between paltusotine and placebo.

Clinically significant tumour volume reduction (i.e. >20% reduction in tumour volume) was observed in 4 (11.8%) participants in the paltusotine group and in 0 participants in the placebo group. Four (4) placebo participants had ≥20% increase in tumour volume compared to zero (0) paltusotine participants.

Of note, a minority (**3.7%**, 2 of 54) of acromegaly participants who received paltusotine required rescue medication during 24-week treatment period to maintain disease control as opposed to **22.8%** (13 of 57) of those participants who received placebo (nominal **p=0.0059**). This showed that paltusotine is effective in acromegaly.

Results of the OLE phase of study CRN00808-08 (data snapshot dates: 21 May 2025 and 31 August 2025)

A total of **114 participants** enrolled in the OLE phase of study CRN00808-08. Fifty-one participants were from the prior paltusotine group, 52 participants were from the prior placebo group, and 11 participants were previously screened but not randomized and entered the OLE phase directly.

At the data snapshot date of 21 May 2025:

- 31 participants from the medically naïve group were continuing in the study. Indeed, a total of **13 participants** from the medically naïve group discontinued the study during the OLE phase. IGF-1 levels were elevated in all these 13 participants.

- 29 participants from the previously treated group were continuing in the study (data on file). A total of **5 participants** from the previously treated group discontinued the study during the OLE phase. IGF-1 levels were elevated in all these 5 participants.

- 38 participants in the washout group are continuing in the study (data on file). Durning the OLE phase, **2 participants** discontinued the study with elevated IGF-1 levels. 11 additional washout participants were directly included in the OLE phase.

Overall, there were **10 participants** in the medically naïve group, 4 participants in the previously treated group and 1 in the washout group who were withdrawn following physician decision. All had high levels of IGF-1 and most of them on 60 mg/day of paltusotine and none had received adjunctive therapy during the OLE phase. The applicant was asked to clarify the withdrawal of 10 medically naïve participants. 7 participants were in the prior paltusotine group and 3 were in the prior placebo group.

None of these participants achieved normal IGF-1 levels at any time during the study. The applicant justified that the withdrawal of 10 participants in the OLE phase was consistent with the protocol. The reasons for not achieving a normalization of the IGF-1 levels were that they were younger in age, with higher baseline IGF-1 and GH levels, and larger pituitary tumor size/volume compared with the previously treated and washout groups. These parameters are known to be associated with an unfavorable prognosis.

Although the withdrawal was higher among the medically naïve participants, there was a majority of participants in the OLE phase of study CRN00808-08, with approximately **80%** of participants overall and **68%** of medically naïve participants with durable and sustained clinical benefits of paltusotine.

This was consistent with the results of other SRL treatments of acromegaly indicated in medically naïve patients. Indeed, the rates of discontinuation due to treatment failure in the literature were **17.9%** for oral octreotide (*Samson 2020*).

After being treated with placebo for 24 weeks in the RC phase, the time to normalization (IGF-1 <1×ULN) with paltusotine in the OLE is similar as for participants who were originally randomized to paltusotine in the RC phase.

IGF-1 levels for the prior placebo group, and the directly enrolled group showed a rapid decrease over the first two weeks in the OLE phase and continued maintenance and durability of mean IGF-1 levels ≤1.0×ULN were observed in participants in the prior paltusotine group **for up to 120 weeks**, while a decrease in mean IGF-1 level was observed over the initial 2 weeks in the prior placebo group.

The starting paltusotine dose for the OLE was 20 mg resulting in a temporary down titration for prior paltusotine participants from final dose in the RC phase for most participants and a subsequent increase in IGF-1 levels at Week 26. The starting dose of paltusotine in the OLE phase was 20 mg QD, and most participants who were receiving 40 mg QD or 60 mg QD at the end of the RC phase were anticipated to up-titrate to 40 mg QD or 60 mg QD during the OLE phase.

Most participants who were responders in the RC phase continued to be responders in the OLE phase.

No reduced effectiveness of paltusotine overtime was observed in the OLE phase of study **CRN00808-08**.

At the data snapshot date of 31 August 2025, the proportion of participants who achieved IGF-1 level ≤1.0×ULN ranged from **51.3% to 100%** from Week 36 to Week 144 for the overall population (51.0% to 100% for the prior paltusotine group and **37.0% to 100%** for the prior placebo group) and ranged from **50.0% to 80.0%** for the directly enrolled group from Week 36 to Week 120.

The proportion of participants who achieved IGF-1 level <1.3×ULN ranged from **69.9% to 100%** from Week 36 to Week 144 for the overall population (**68.6% to 100%** for the prior paltusotine group and **65.4% to 100%** for the prior placebo group) and was 100% from Week 36 to Week 120 for the directly enrolled group.

These proportions of participants with IGF-1 level ≤1.0×ULN with paltusotine monotherapy was consistent and even better than the acromegaly consensus guidelines which stated that the long-term IGF-1 normalization rate with existing SRLs is approximately **30% to 55**% based on results of multiple studies (*Giustina 2020*).

These proportions were also consistent or improved when compared with the **56% response** rate observed for participants in the paltusotine group at the end of the RC Phase of the study.

Overall, the results of the OLE phase of study CRN00808-08 suggest that all the participants experience over time a durable and/or additional reduction in IGF-1 level and stable/reduced tumour volume for an extended period of time in the OLE phase. The proportion of responders among the medically naïve patients increased overtime in the OLE phase showing that these patients may need a longer duration of treatment to normalize their IGF-1 levels especially if their IGF-1 levels were elevated at baseline (≥2.5 xULN) and this was also consistent with the literature (*Marques-Pamies 2024*). This has been reflected in the SmPC for the prescribers of this new medicine (section 4.2).

The results of the OLE are difficult to interpret as this phase is open and there is no control arm and due to smaller groups of patients especially after W84.

Another point is the need of adjunctive therapies in the OLE phase of study CRN00808-08 for some patients. In case of evidence of efficacy of paltusotine at the maximal dose of 60 mg/day after 6 months but patients have not achieved the normalization of IGF-1 levels after 6 months, in the OLE phase of study CRN00808-08, there was a possibility to use adjunctive therapies such as cabergoline or pegvisomant as proposed from W48.

At the data snapshot date of 21 May 2025, in study **CRN00808-08**, most of the participants were still on monotherapy of paltusotine. Indeed, **15.8 %** (18/114) participants (12 medically naïve and 6 previously treated) used adjunctive therapies from W48. The use of adjunctive therapies was observed more frequently in participants receiving prior placebo (23.1%; 12 of 52 participants) than in

participants receiving prior paltusotine (11.8%; 6 of 51 participants). Thus, it is difficult to interpret the long-term results, and in which extent the increase of the proportion of medically naïve patients with IGF-1 levels ⩽ULN over the OLE phase is only related to the effect of paltusotine as monotherapy.

Thus, the use of adjunctive therapies did not lead to a significant increase of the proportion of patients with IGF-1 levels ⩽ULN nor a significant increase of the proportion of patients with IGF-1 levels < 1.3x ULN. Only one participant who used adjunctive therapy achieved IGF-1 levels ⩽ULN and 2 participants who used adjunctive therapies achieved IGF-1 levels < 1.3xULN.

This demonstrates that the addition of adjunctive therapy did not have at this stage an impact on the long-term efficacy results of paltusotine.

At the data snapshot date of 21 May 2025, the applicant provided a *post-hoc* analysis in excluding the 18 participants who received adjunctive therapies in study CRN00808-08.

When these participants were excluded from the response analyses, the proportion of participants without adjunctive therapy who had IGF-1 ⩽ 1.0 x ULN were quite similar to the proportion of participants with IGF-1 ⩽ 1.0 x ULN in the overall group **(62.0% without adjunctive vs 54.7% overall** at Week 60**; 74.3% without adjunctive vs 63.6% overall** at Week 72**; 73.8% without adjunctive vs 65.4% overall at Week 84**). Similar trends continued up through Week 120. The proportion of participants with IGF-1 ⩽ 1.3 x ULN were also similar between the 2 groups at these visits.

The use of adjunctive therapies is usually proposed in the therapeutically strategy of treatment of the acromegaly patients but there are currently no clinical data with a high level of evidence that can support the use of these therapies in association to paltusotine. The clinical data were collected in the OLE phase of the study 08 which has an open, non-comparative design and enrolled a low number of patients. Thus, it was not possible to recommend adjunctive therapies in the SmPC.

Subgroup analysis

In study CRN00808-08, dividing subject based upon IGF1 values at baseline, the group with IGF1 > 1.78xULN had lower responder rate than IGF1 < 1.78xULN in the paltusotine group (32% vs 76%); this can be expected based on the assumption that more severe disease can be more difficult to treat. Analyses for subgroups based on other common baseline characteristics (e.g. sex, weight) did not highlight differences.

Post-hoc analysis

A *post-hoc* analysis requested by FDA was performed to determine the efficacy of paltusotine among a group of medically naïve patients and not responders to other acromegaly treatments or unknown status and among a group of patient responders to other acromegaly treatments (remotely or recently).

The response is higher in the group of patients already controlled with any previous treatment versus group of patients not controlled with any treatment (**75% vs 57%).** The response to paltusotine is lower in the group of medically naïve patients, uncontrolled patients with other SRLs and status unknown: **34.4%.** The difference between treatment and placebo are all significant whatever the group or subgroup of patients.

This *post-hoc* analysis also shows that the response is lower in the group of uncontrolled patients mainly driven by the medically naïve patients (22.7%) who have a lower response to paltusotine than the uncontrolled patients and patients with unknown status

Results of the RC phase of study CRN00808-09 (cut-off date: 5 December 2023)

The study met statistical significance (**p<0.0001**) on the primary endpoint, based on the proportion of participants in the paltusotine group (25 of 30 [**83.3%]**) who maintained biochemical response (IGF-1 level ≤ 1.0×ULN) **at EOR** compared to those in the placebo group (1 of 28 [**3.6%]).**

At EOR, there were **14 patients** in the paltusotine 40 mg group and **16 patients** in the paltusotine 60 mg group. Among the **25/30 patients** who maintained IGF-1 levels ≤ ULN, 14/25 (**56%**) in the paltusotine 40 mg group and 11/16 (**44%**) in the paltusotine 60 mg group.

Thus, the dose of 40 mg/day with a maximal dose of 60 mg/day is more optimal for maintenance of treatment in well-controlled patients than initiation of treatment in medically naïve patients and uncontrolled patients. However, at the end of the RC phase, **53%** of patients are treated with paltusotine 60 mg. Therefore, the maintenance of the efficacy of paltusotine was also questionable in the long-term in well-controlled patients with other SRLs at baseline.
The sensibility analysis to assess the robustness of the primary endpoints showed similar significant results (**p < 0.0001**) in the completers, PP analysis and in the group of dose titration during the fixed dose period (no patient).

Significant differences in favour of paltusotine were observed for all secondary efficacy endpoints. Results of pre-specified sensitivity analyses to assess the robustness of the secondary efficacy analyses were consistent with the secondary efficacy endpoint results.

- The LS means (±SE) for the change from Baseline **to EOT** in IGF-1×ULN were **0.042** (±0.093) for the paltusotine group and **0.833** (±0.096) for the placebo group, with a treatment difference of **-0.791** (95% CI: -1.057 to -0.525) (**p<0.0001**).
- The proportion of participants who maintained **GH level <1.0 ng/mL**, out of those who had GH level <1.0 ng/mL at Baseline at Week 34, was **87.0%** (20 of 23) in the paltusotine group compared with **27.8%** (5 of 18) in the placebo group (p=0.0003).
- The LS means (±SE) for the change from Baseline to EOT in total ASD score were **-0.606 (±1.504)** for the paltusotine group and **4.588 (±1.593)** for the placebo group, indicating stabilization of symptoms for the paltusotine group and worsening of symptoms for the placebo group, with a treatment difference of -5.164 (95% CI: -9.536 to -0.792) (p=0.0216).
- The proportion of participants who maintained IGF-1 level <1.3×ULN: 93.3% (28 of 30) in the paltusotine group compared **with 28.6% (8 of 28) in the placebo group (nominal p<0.0001).**

Results of multiple exploratory endpoint analyses also favoured paltusotine.
- The LS means (±SE) for the **change from Baseline to Week 34 in GH level** (ng/mL) were **-0.239** (±0.300) for the paltusotine group and **1.721** (±0.309) for the placebo group, with a treatment difference of **-1.960** (95% CI: -2.817 to -1.103) (nominal **p<0.0001**).
- The proportion of participants who maintained **IGF-1 level ≤1.0×ULN and GH level <1.0 ng/mL** from Baseline to EOR was **73.9%** (17 of 23) in the paltusotine group compared with **5.6%** (1 of 18) in the placebo group (nominal **p<0.0001**).
- The Kaplan-Meier median time to loss of biochemical control (first IGF-1>1.0×ULN for 2 consecutive visits), where participants who discontinued treatment prior to reaching IGF-1>1.0×ULN were censored at the time of the last assessment prior to treatment discontinuation, **was not reached** (IQR: 141.0 days, NE) for the paltusotine group and was **84.0 days** (IQR: 58.0, 85.0) for the placebo group. Similar results were observed for the median time to loss of biochemical control using IGF-1>1.3×ULN for 2 consecutive visits.

- The proportion of participants who received rescue therapy was **6.7%** (2 of 30) in the paltusotine group and **60.7%** (17 of 28) in the placebo group (nominal **p<0.0001**), affirming the treatment effect of paltusotine versus placebo.
- Results from the "treatment Preference questionnaire" (TPQ) at Week 36 indicated that the majority of participants (approximately 60% in each treatment group) preferred oral medication over previous injections for acromegaly.
- The treatment difference for **Acro-QoL, EQ-5D-5L health index and PGI-I at EOR** between paltusotine and placebo were all not significant.

OLE Phase of study CRN00808-09 (data snapshot dates: 21 May 2025 and 31 October 2025)

At the data snapshot date of 31 October 2025), a total 53 total participants (27 from the prior paltusotine group and 26 from the prior placebo group) were enrolled in the OLE Phase of Study CRN00808-09.

Eight participants (**15.1%)** overall discontinued the OLE Phase of the study (3 from the prior paltusotine group and 5 from the prior placebo group).
Only 1 participant received adjunctive therapy in the OLE Phase from W60.

The starting dose of paltusotine in the OLE Phase was 40 mg QD day, and most participants who were receiving 60 mg/day at the end of the RC Phase were anticipated to up-titrate to 60 mg/day during the OLE Phase.

The proportion of participants who achieved IGF-1 level ≤1.0×ULN ranged from **74.5% to 93.3%** from Week 48 to Week 180 for the overall population (**50.0% to 96.0%** for the prior paltusotine group and **77.3% to 100%** for the prior placebo group).
The proportion of participants who achieved IGF-1 level <1.3×ULN ranged from **95.7% to 100%** from Week 48 to Week 180 for the overall population (**92.0% to 100%** for the prior paltusotine group and **92.9% to 100%** for the prior placebo group).

Continued maintenance and durability of mean IGF-1 levels ≤1.0×ULN were observed in participants in the prior paltusotine group up to Week 180, while a decrease in mean IGF-1 level was observed over the initial 2 weeks in the prior placebo group that was maintained to Week 180.

Mean GH levels in the OLE Phase showed long-term maintenance and durability from OLE Baseline through Week 180.

Mean ASD Total Scores (symptom burden) generally remained stable throughout the OLE Phase.

The effects of paltusotine are maintained over time as regards to the maintenance of the normalization of IGF-1 levels and GH levels but the acromegaly symptoms slightly increased over time and no clinically significant changes in the tumour volume was highlighted from OLE baseline until W84. At the end of the RC phase, most patients were treated with paltusotine 60 mg/day. The use of adjunctive therapies was permitted from W60 in case of lower efficacy and only one participant used adjunctive therapies at the data snapshot date of 31 August 2025. The results of the OLE phase of study **CRN00808-09** are still on-going and the applicant provided the interim results at the data snapshot date of 31 August 2025 (up to W192)**.**

Updated efficacy results of the OLE phase of study CRN00808-09 (as of the data snapshot date of 31 August 2025) show that paltusotine continues to provide long-term biochemical disease control of acromegaly, with **75% to 93%** of participants overall maintaining IGF-1 normalization (IGF 1 level ≤1.0×ULN) up to Week 180, which represents up to 3.5 years of treatment for participants treated with

paltusotine in the RC phase and continuing with paltusotine in the OLE phase and up to approximately 2.75 years of paltusotine treatment for participants previously treated with placebo who received paltusotine in the OLE phase. These results showing the long-term efficacy of paltusotine are consistent with and potentially better than the long-term IGF-1 normalization rates reported with existing SRL therapies, which are approximately **30% to 55%** based on results of multiple studies (*Giustina 2020*). Paltusotine also provided long-term stabilization in GH level and symptom burden as measured by the ASD Total Score. The overall efficacy profile of paltusotine remains unchanged based on evaluation of the additional data and demonstrates sustained clinical treatment benefits with paltusotine.

Subgroup analysis

No notable difference was observed for any subgroup, and the paltusotine effect was consistent across subgroups.

***Post-Hoc* analysis**

Overall, a *post-hoc* analysis was performed to evaluate the data for participants without prior surgery in the paltusotine clinical studies. The majority of participants enrolled had undergone prior surgical intervention for their pituitary tumours. However, a small subset of participants (N=20) across the acromegaly studies were surgically naïve but had received pharmacological intervention prior to study enrolment. Of note, all the medically naïve patients have undergone pituitary surgery. The effects of paltusotine in terms of lowering IGF1 levels or maintaining normal IGF1 levels were confirmed also in this subgroup of patients but no definitive conclusion can be drawn given the low number of patients. Therefore, this *post-hoc* analysis cannot have an impact on the wording of the indication as regards the place of paltusotine before or after surgery or if surgery is not an option.

5.3.7.2. Conclusions on the clinical efficacy

An advantage of paltusotine is its oral administration, that could improve patient's compliance to treatment and reduce discomfort due to long-term treatment with injections.

Based on the results of the pivotal studies and their OLE phases as well as supportive studies, on literature and based on PK clinical data, the benefit-risk of paltusotine was considered positive in medically naïve patients in study CRN00808-08 at the dose regimen proposed in this study. But uncertainties remain on the possibility of patients with high IGF-1 levels at baseline (i.e ≥ 2.5xULN) including the medically naïve patients to normalize their IGF-1 levels, even at the 60 mg QD dose in monotherapy. Some of them will need longer duration of treatment and/or will need adjunctive therapies to achieve the normalization of their IGF-1 levels and some of them will never normalize their IGF-1 levels. This has been appropriately reflected for the prescribers in section 4.2 of the SmPC.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in

death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The applicant pooled safety data of paltusotine from 5 acromegaly studies into 2 analysis populations: Primary group and Supportive group.

The primary group included data from **84 patients** included in the two RC trials: CRN00808-08 (treatment of acromegaly) and CRN00808-09 (maintenance therapy of acromegaly). In these 2 studies the to-be marketed formulation (15% drug load SDD tablet) was used, at doses ranging **from 20 mg to 60 mg QD** in study CRN00808-08 and **40 mg to 60 mg QD** in study CRN00808-09.
The supportive group included data from 233 patients included 5 acromegaly studies (completed studies CRN00808-02 and CRN00808-03, on-going study CRN00808-05, completed RC phases of studies CRN00808-08 and CRN00808-09, and on-going OLE phases of studies CRN00808-08 and CRN00808-09), exposed for a maximum duration of 4 years. The doses ranged from **10 mg QD to 60 mg QD** and included both the capsule and to-be marketed tablet formulation.

5.4.2. Patient exposure

The safety profile of paltusotine was based primarily on pooled data from the RC phases of the pivotal phase 3 studies (CRN00808-08 and CRN00808-09), which included 84 participants exposed to paltusotine for up to 36 weeks at doses ranging from 20 mg to 60 mg QD. A pooled analysis of safety data from the 2 phase 3 studies (including data from RC and OLE phases) and 3 phase 2 studies (CRN00808-03, CRN00808-02, and CRN00808-05) was also performed and included 233 participants exposed to paltusotine with a maximum duration of 4 years. Additional support for safety is provided by safety data from 297 participants exposed to paltusotine in non-acromegaly studies (9 phase 1 studies in healthy participants, excluding the Japan studies, and 1 phase 1 study in participants with hepatic impairment [at single or repeat doses of paltusotine ranging from 1.25 mg to 240 mg]. A total of 36 participants with carcinoid syndrome were treated with paltusotine at repeat doses of up to 120 mg QD in a phase 2 study. Overall, 583 participants have been exposed to paltusotine across the clinical program. This approach was acceptable.

Overall Extent of Exposure in Participants with Acromegaly in the Primary Group

In study CRN00808-08, during the RC phase, all randomized participants (111 participants, including **54 in the paltusotine group** and 57 in the placebo group) received at least 1 dose of study treatment. Of the 54 participants randomized in the total paltusotine group, 3 participants received paltusotine 20 mg QD, 15 participants received paltusotine 40 mg QD and 36 participants received paltusotine 60 mg QD as their final dose. The median duration (range) of exposure was 24.0 weeks in both paltusotine (range: 7.6 to 24.7 weeks) and placebo (range: 1.1 to 25.0 weeks) groups. A total of 52 participants (96.3%) in the paltusotine group and 50 participants (87.7%) in the placebo group received ≥3 months of study treatment. Three of 54 participants in the paltusotine group and 15 of 57 participants in the

placebo group discontinued study treatment due to TEAEs; of these, 2 and 13 received rescue therapy. Treatment compliance was 97.6% in the paltusotine group and 99.6% in the placebo group.

In study CRN00808-09, during the RC phase, all 58 randomized participants received at least 1 dose of study treatment and were included in the Safety Analysis Set. Of the **30 participants in the paltusotine group**, 14 participants received paltusotine 40 mg QD and 16 participants received paltusotine 60 mg QD as their final dose. The median duration (range) of exposure was 36.0 weeks (16.1 to 36.3 weeks) in the paltusotine group and 22.1 weeks (8.0 to 36.9 weeks) in the placebo group. A total of 28 participants (93.3%) in the paltusotine group and 14 participants (50.0%) in the placebo group received ≥6 to ≤9 months of study treatment. Two of 30 participants (6.7%) in the paltusotine group and 17 of 28 participants in the placebo group discontinued study treatment due to TEAEs and received rescue therapy. Treatment compliance was 97.9% in the paltusotine group and 99.6% in the placebo group.

Overall Extent of Exposure in the Participants with Acromegaly in Supportive Group

In study CRN00808-03, a total of **47 participants** were exposed to paltusotine (25 in Group 1, 10 in Group 2, 5 in Group 3, 4 in Group 4, and 3 in Group 5) and were included in the Safety Analysis Set. Of these, 41 (87.2%) completed 13 weeks of treatment. Median treatment compliance was 100% based on study drug dosing diaries and study drug accountability. Treatment compliance ranged from 67 to 114% based on study drug accountability and 44 to 100% based on study drug dosing diaries.

In study CRN00808-02, a total of **13 participants** were exposed to paltusotine and comprised the Safety Analysis Set. Due to the early discontinuation of the study, most participants did not reach the highest possible dose based on the titration algorithm. Overall, during the study (including during the randomized withdrawal period), 3 participants up-titrated to the highest allowable dose of 30 mg, 9 participants up-titrated to 20 mg, and 4 remained at the initial dose of 10 mg. Twelve of 13 (92.3%) participants completed 9 weeks of dosing with paltusotine. Seven of 11 participants entered the Randomized Withdrawal Period; of these, 3 (23.1%) participants received paltusotine for 4 additional weeks, and 4 (30.8%) received placebo. Only 1 participant discontinued study treatment early, at Week 3. All but 1 participant (who was incorrectly up-titrated from 10 mg to 20 mg and had a compliance of 80.9%) had a compliance of at least 90% regardless of calculation methods.

In Study CRN00808-05, a total of **43 participants** were exposed to at least 1 dose of paltusotine in this study and comprised the Safety Population (ie, the Safety Analysis Set). Overall, the median time from the end of parent study to the start of study CRN00808-05 was 103 days (range: 1 to 889 days).

Of the 43 participants who received paltusotine, the majority received either 60 mg (24 participants, 55.8%) or 40 mg (15 participants, 37.2%) as their final dose; 1 participant each (2.3%) received 10 mg, 20 mg, and 30 mg paltusotine as their final dose.

In the OLE phase of study CRN00808-08, a total of 114 participants were exposed to at least 1 dose of paltusotine and were included in the Safety Analysis Set. Of the 113 participants in the total population, 50 participants received paltusotine and 52 participants received placebo in the RC phase, and 11 participants enrolled directly into the OLE.

In the OLE phase of study CRN00808-09, a total of 53 participants were exposed to at least 1 dose of paltusotine in this study and were included in the Safety Analysis Set. Of the 53 participants in the total population, 27 participants received paltusotine and 26 participants received placebo in the RC phase.

Table 58 Participant exposure in the primary and supportive groups (safety population)

	Primary Group		Supportive Group
	Paltusotine (N=84)	**Placebo (N=85)**	**Total Paltusotine (N=233)**
Duration of Exposure (days)[a]			
N	84	85	233
Mean	191.0	149.8	584.6
SD, SE	47.88, 5.22	59.44, 6.45	436.75, 28.61
Median	169.5	168.0	458.0
Min, Max	53, 254	8, 258	5, 1710
Duration of Exposure (weeks)			
N	84	85	233
Mean	27.28	21.39	83.52
SD, SE	6.841, 0.746	8.491, 0.921	62.392, 4.087
Median	24.21	24.00	65.43
Min, Max	7.6, 36.3	1.1, 36.9	0.7, 244.3
Duration of Exposure (monthly interval)			
> 0 - ≤ 3 Months - n (%)	2 (2.4)	16 (18.8)	28 (12.0)[b]
> 3 - ≤ 6 Months - n (%)	4 (4.8)	15 (17.6)	
> 6 - ≤ 9 Months - n (%)	78 (92.9)	54 (63.5)	
> 6 - ≤ 12 Months - n (%)			44 (18.9)
>12 - ≤ 24 Months - n (%)			94 (40.3)
>24 - ≤ 36 Months - n (%)			31 (13.3)
> 36 Months - n (%)			36 (15.5)

Notes: Percentages are calculated based on the number of participants in the Safety Population. 1 month = 28 days.
[a] Duration of study drug exposure calculated as date of last dose - date of first dose + 1.
[b] Exposure duration calculated as 0 to ≤6 months for the Supportive Group.

The patient exposure in the clinical trials with the indication of treatment of acromegaly was considered of sufficient size to enable the safety assessment. The length of the follow-up (approximately 4 years) was considered sufficient.

5.4.3. Adverse events

Overview of Adverse Events in the Primary Group

Table 59 provides an overview of TEAEs for the RC phases of the individual phase 3 studies and in the Primary Group overall. Paltusotine was well tolerated in the pivotal randomized controlled phase 3 studies and there were no new, unexpected safety findings. The overall safety profile was largely comparable between the 2 phase 3 studies during the RC phases.

Table 59 Overview of TEAEs in the Randomized Controlled Phases of Studies CRN00808-09 and CRN00808-08 and in the Primary Group Overall (Safety Population)

	CRN00808-08 RC		CRN00808-09 RC		Primary Group		
	Paltusotine (N=54) n (%)	**Placebo (N=57) n (%)**	**Paltusotine (N=30) n (%)**	**Placebo (N=28) n (%)**	**Paltusotine (N=84) n (%)**	**Placebo (N=85) n (%)**	**Total (N=169) n (%)**
TEAEs	49 (90.7)	49 (86.0)	24 (80.0)	28 (100)	**73 (86.9)**	**77 (90.6)**	150 (88.8)
Mild TEAE	47 (87.0)	45 (78.9)	23 (76.7)	27 (96.4)	70 (83.3)	72 (84.7)	142 (84.0)
Moderate TEAE	15 (27.8)	26 (45.6)	10 (33.3)	18 (64.3)	25 (29.8)	44 (51.8)	69 (40.8)
Severe TEAE	2 (3.7)	5 (8.8)	0	3 (10.7)	2 (2.4)	8 (9.4)	10 (5.9)
Treatment-Related TEAE	26 (48.1)	15 (26.3)	12 (40.0)	4 (14.3)	**38 (45.2)**	**19 (22.4)**	57 (33.7)
Serious TEAE	0	1 (1.8)	0	1 (3.6)	0	2 (2.4)	2 (1.2)
Treatment-Related Serious TEAE	0	0	0	0	0	0	0
TEAE Leading to Treatment Interruption	2 (3.7)	0	0	1 (3.6)	2 (2.4)	1 (1.2)	3 (1.8)
TEAE Leading to Dose Reduction	3 (5.6)	1 (1.8)	1 (3.3)	0	4 (4.8)	1 (1.2)	5 (3.0)
TEAE Leading to Treatment Discontinuation	3 (5.6)	15 (26.3)	2 (6.7)	17 (60.7)	5 (6.0)	32 (37.6)	37 (21.9)
TEAE Leading to Study Discontinuation	1 (1.9)	1 (1.8)	0	0	1 (1.2)	1 (1.2)	2 (1.2)
TEAE Leading to Death	0	0	0	0	0	0	0
TEAE of Special Interest	22 (40.7)	32 (56.1)	9 (30.0)	24 (85.7)	31 (36.9)	56 (65.9)	87 (51.5)

RC=Randomized Controlled, SAE=serious adverse event, TEAE=treatment-emergent adverse event
Percentages are calculated based on the number of participants in the Safety Population. TEAEs of special interest are defined as symptoms related to acromegaly (acromegaly-related TEAEs).

In the primary group, TEAEs were reported at similar rates in the paltusotine and placebo groups (86.9% vs. 90.6%, respectively). Most were mild or moderate. Severe TEAEs were more common in placebo (9.4%) than in paltusotine group (2.4%) and only 2 severe not related TEAEs occurred in placebo group, both in study CRN00808-08 (headache and pain in extremity).

No SAEs were reported in the paltusotine group. In contrast, two SAEs occurred in the placebo group (benign parathyroid tumour and cholecystitis).

TEAEs leading to treatment discontinuation occurred more frequently in the placebo group than in the paltusotine group.

Table 60 Summary of TEAEs by PT Reported in ≥5% of Participants in Either Treatment Group of the RC Phases of Studies CRN00808-09, CRN00808-08, or in the Primary Group (Safety Population)

	CRN00808-08 RC		CRN00808-09 RC		Primary Group		
System Organ Class Preferred Term	Paltusotine (N=54) n (%)	Placebo (N=57) n (%)	Paltusotine (N=30) n (%)	Placebo (N=28) n (%)	Paltusotine (N=84) n (%)	Placebo (N=85) n (%)	Total (N=169) n (%)
Participants with at Least One Treatment-Emergent Adverse Event	49 (90.7)	49 (86.0)	24 (80.0)	28 (100.0)	73 (86.9)	77 (90.6)	150 (88.8)
Gastrointestinal disorders	29 (53.7)	19 (33.3)	14 (46.7)	12 (42.9)	43 (51.2)	31 (36.5)	74 (43.8)
Diarrhoea	18 (33.3)	10 (17.5)	7 (23.3)	4 (14.3)	25 (29.8)	14 (16.5)	39 (23.1)
Abdominal pain	6 (11.1)	2 (3.5)	5 (16.7)	3 (10.7)	11 (13.1)	5 (5.9)	16 (9.5)
Nausea	5 (9.3)	2 (3.5)	4 (13.3)	2 (7.1)	9 (10.7)	4 (4.7)	13 (7.7)
Constipation	3 (5.6)	1 (1.8)	2 (6.7)	4 (14.3)	5 (6.0)	5 (5.9)	10 (5.9)
Dyspepsia	3 (5.6)	6 (10.5)	1 (3.3)	0	4 (4.8)	6 (7.1)	10 (5.9)
Abdominal distension	2 (3.7)	3 (5.3)	2 (6.7)	1 (3.6)	4 (4.8)	4 (4.7)	8 (4.7)
Abdominal discomfort	5 (9.3)	1 (1.8)	0	0	5 (6.0)	1 (1.2)	6 (3.6)
Abdominal pain upper	1 (1.9)	2 (3.5)	0	2 (7.1)	1 (1.2)	4 (4.7)	5 (3.0)
Flatulence	0	0	2 (6.7)	1 (3.6)	2 (2.4)	1 (1.2)	3 (1.8)
Musculoskeletal and connective tissue disorders	15 (27.8)	19 (33.3)	14 (46.7)	19 (67.9)	29 (34.5)	38 (44.7)	67 (39.6)
Arthralgia	6 (11.1)	13 (22.8)	9 (30.0)	16 (57.1)	15 (17.9)	29 (34.1)	44 (26.0)
Back pain	3 (5.6)	4 (7.0)	1 (3.3)	2 (7.1)	4 (4.8)	6 (7.1)	10 (5.9)
Pain in extremity	3 (5.6)	2 (3.5)	0	3 (10.7)	3 (3.6)	5 (5.9)	8 (4.7)
Muscular weakness	0	2 (3.5)	1 (3.3)	3 (10.7)	1 (1.2)	5 (5.9)	6 (3.6)
Nervous system disorders	16 (29.6)	22 (38.6)	8 (26.7)	14 (50.0)	24 (28.6)	36 (42.4)	60 (35.5)
Headache	11 (20.4)	19 (33.3)	6 (20.0)	10 (35.7)	17 (20.2)	29 (34.1)	46 (27.2)
Paraesthesia	5 (9.3)	3 (5.3)	0	7 (25.0)	5 (6.0)	10 (11.8)	15 (8.9)
Dizziness	1 (1.9)	0	1 (3.3)	2 (7.1)	2 (2.4)	2 (2.4)	4 (2.4)
Infections and infestations	18 (33.3)	21 (36.8)	10 (33.3)	9 (32.1)	28 (33.3)	30 (35.3)	58 (34.3)
Upper respiratory tract infection	4 (7.4)	10 (17.5)	1 (3.3)	0	5 (6.0)	10 (11.8)	15 (8.9)
Urinary tract infection	3 (5.6)	4 (7.0)	2 (6.7)	2 (7.1)	5 (6.0)	6 (7.1)	11 (6.5)
COVID-19	1 (1.9)	0	0	6 (21.4)	1 (1.2)	6 (7.1)	7 (4.1)
Nasopharyngitis	1 (1.9)	2 (3.5)	2 (6.7)	1 (3.6)	3 (3.6)	3 (3.5)	6 (3.6)
Sinusitis	1 (1.9)	4 (7.0)	0	0	1 (1.2)	4 (4.7)	5 (3.0)
Furuncle	3 (5.6)	0	0	0	3 (3.6)	0	3 (1.8)
Gastroenteritis	1 (1.9)	0	2 (6.7)	0	3 (3.6)	0	3 (1.8)
General disorders and administration site conditions	13 (24.1)	21 (36.8)	5 (16.7)	18 (64.3)	18 (21.4)	39 (45.9)	57 (33.7)
Peripheral swelling	2 (3.7)	6 (10.5)	2 (6.7)	10 (35.7)	4 (4.8)	16 (18.8)	20 (11.8)
Fatigue	3 (5.6)	8 (14.0)	2 (6.7)	5 (17.9)	5 (6.0)	13 (15.3)	18 (10.7)
Asthenia	3 (5.6)	3 (5.3)	1 (3.3)	4 (14.3)	4 (4.8)	7 (8.2)	11 (6.5)
Hyperhidrosis	1 (1.9)	5 (8.8)	0	4 (14.3)	1 (1.2)	9 (10.6)	10 (5.9)
Pyrexia	1 (1.9)	3 (5.3)	0	0	1 (1.2)	3 (3.5)	4 (2.4)
Metabolism and nutrition disorders	15 (27.8)	6 (10.5)	5 (16.7)	4 (14.3)	20 (23.8)	10 (11.8)	30 (17.8)
Hyperglycaemia	3 (5.6)	0	1 (3.3)	2 (7.1)	4 (4.8)	2 (2.4)	6 (3.6)
Decreased appetite	2 (3.7)	0	2 (6.7)	0	4 (4.8)	0	4 (2.4)
Hypertriglyceridaemia	3 (5.6)	1 (1.8)	0	0	3 (3.6)	1 (1.2)	4 (2.4)
Investigations	9 (16.7)	9 (15.8)	3 (10.0)	4 (14.3)	12 (14.3)	13 (15.3)	25 (14.8)
Lipase increased	2 (3.7)	3 (5.3)	0	1 (3.6)	2 (2.4)	4 (4.7)	6 (3.6)
Psychiatric disorders	4 (7.4)	6 (10.5)	4 (13.3)	3 (10.7)	8 (9.5)	9 (10.6)	17 (10.1)
Insomnia	0	4 (7.0)	0	1 (3.6)	0	5 (5.9)	5 (3.0)
Blood and lymphatic system disorders	3 (5.6)	7 (12.3)	3 (10.0)	3 (10.7)	6 (7.1)	10 (11.8)	16 (9.5)
Anaemia	3 (5.6)	5 (8.8)	0	1 (3.6)	3 (3.6)	6 (7.1)	9 (5.3)

System Organ Class Preferred Term	CRN00808-08 RC Paltusotine (N=54) n (%)	 Placebo (N=57) n (%)	CRN00808-09 RC Paltusotine (N=30) n (%)	 Placebo (N=28) n (%)	Primary Group Paltusotine (N=84) n (%)	 Placebo (N=85) n (%)	 Total (N=169) n (%)
Iron deficiency anaemia	0	1 (1.8)	2 (6.7)	0	2 (2.4)	1 (1.2)	3 (1.8)
Respiratory, thoracic and mediastinal disorders	4 (7.4)	4 (7.0)	4 (13.3)	3 (10.7)	8 (9.5)	7 (8.2)	15 (8.9)
Cough	2 (3.7)	3 (5.3)	0	0	2 (2.4)	3 (3.5)	5 (3.0)
Dyspnoea	0	0	1 (3.3)	2 (7.1)	1 (1.2)	2 (2.4)	3 (1.8)
Cardiac disorders	4 (7.4)	2 (3.5)	4 (13.3)	1 (3.6)	8 (9.5)	3 (3.5)	11 (6.5)
Sinus bradycardia	4 (7.4)	0	0	0	4 (4.8)	0	4 (2.4)
Palpitations	0	1 (1.8)	2 (6.7)	0	2 (2.4)	1 (1.2)	3 (1.8)
Skin and subcutaneous tissue disorders	5 (9.3)	2 (3.5)	2 (6.7)	2 (7.1)	7 (8.3)	4 (4.7)	11 (6.5)
Alopecia	3 (5.6)	1 (1.8)	0	0	3 (3.6)	1 (1.2)	4 (2.4)
Vascular disorders	1 (1.9)	3 (5.3)	2 (6.7)	0	3 (3.6)	3 (3.5)	6 (3.6)
Hypertension	1 (1.9)	3 (5.3)	1 (3.3)	0	2 (2.4)	3 (3.5)	5 (3.0)

RC = randomized controlled
MedDRA version 24.1. Percentages are calculated based on the number of participants in the Safety Population.
The Primary Group comprises the RC Phases of Studies CRN00808-08 and CRN00808-09.

The most commonly reported adverse events in the primary group were gastrointestinal disorders, including diarrhoea, abdominal pain, and nausea. These events were more frequent in the paltusotine group, particularly among patients who were non-pharmacologically treated (CRN00808-08) compared to those previously treated with SRLs (CRN00808-09). This may reflect a period of physiological adaptation in SRL-naïve patients, where initial GI and pancreatic effects of octreotide analogues are known and expected. GI [especially diarrhoea (50% vs. 33.3%)] and hepatobiliary AEs (18.2% vs. 0) occurred more frequently in treatment-naïve patients.

In clinical trial CRN00808-08, treatment-naïve patients initiated paltusotine at 20 mg, allowing progressive pharmacodynamic adaptation and minimising early GI and hepatobiliary intolerance.

To ensure tolerability and consistency with clinical trial conditions, the recommended starting dose in medically naïve patients was set to be 20 mg once daily and titrate up to 40 mg after tolerance was established (two weeks). This approach is standard for other SRLs and aligns with the principle of using the lowest effective dose to minimise dose-dependent ADRs. The SmPC section 4.2 was aligned accordingly.

Post-initiation of treatment, GI events or recurrence of similar adverse reactions may occur during long-term treatment, particularly after dose increases. To ensure adequate management of adverse events throughout therapy, the SmPC wording was revised to allow for a temporary dose reduction until adverse reactions would be resolved.

Musculoskeletal disorders were more frequently reported in the previously SRL-treated patients (CRN00808-09) compared to non-pharmacologically treated patients (CRN00808-08) [46.7% vs. 27.8%]. The observed imbalance between studies likely reflects differences in baseline disease characteristics (e.g., longer disease duration, older age, higher prevalence of pre-existing musculoskeletal conditions in study CRN00808-09) rather than a treatment or exposure-related safety signal.

AEs within the SCOs *"Nervous system disorders"* and *"Infections and infestations »* were reported at similar overall frequencies but were slightly more common in the placebo groups than in the paltusotine treated participants.

Cardiac disorders were observed only in paltusotine group with sinus bradycardia occurring in 3 (3.6%) patients (all in study CRN00808-08) versus 0 in placebo group**.**

Among TEAEs occurring in ≥10% of patients in the paltusotine group, the most frequent were diarrhoea, headache, arthralgia, abdominal pain, and nausea. In the placebo group, commonly reported events included headache, arthralgia, peripheral swelling, diarrhoea, fatigue, upper respiratory tract infection, paraesthesia, and hyperhidrosis. Diarrheal, nausea, abdominal pain and fatigue are listed as ADRs in the product information.

Overview of Adverse Events in the supportive Group

Table 61 Adverse events in the supportive group

	Paltusotine (N=233) n (%)
Participants With	
Treatment-Emergent Adverse Events (TEAE)	214 (91.8)
Treatment-Related TEAE	112 (48.1)
Serious TEAE	29 (12.4)
Treatment-Related Serious TEAE	6 (2.6)
Mild TEAE	203 (87.1)
Moderate TEAE	111 (47.6)
Severe TEAE	31 (13.3)
TEAE Leading to Treatment Interruption	15 (6.4)
TEAE Leading to Dose Reduction	12 (5.2)
TEAE Leading to Treatment Discontinuation	9 (3.9)
TEAE Leading to Study Discontinuation	6 (2.6)
TEAE Leading to Death	1 (0.4)
TEAE of Special Interest[a]	101 (43.3)

4MSU=4-Month Safety Update, TEAE=treatment-emergent adverse event
Percentages are calculated based on the number of participants in the Safety Population.
[a] TEAE of special interest is defined as symptoms related to acromegaly (acromegaly-related TEAEs).

In the Supportive Group overall, 214 of 233 participants (91.8%) receiving paltusotine reported at least 1 TEAE. Twenty-nine (12.4%) participants experienced at least 1 SAE, including 6 participants (2.6%) with a treatment-related SAE. A single TEAE leading to death was reported (toxicity to various agents, study CRN00808-09, as noted in the previous paragraph). Thirty-one (13.3%) participants experienced at least 1 severe TEAE. Approximately half (48.1%) of participants had at least 1 TEAE that was related to study treatment. Nine (3.9%) participants reported TEAEs that resulted in treatment discontinuation, and 6 (2.6%) participants reported TEAEs that resulted in study discontinuation.

5.4.3.1. Adverse drug reactions

ADRs in the Primary Group

Table 62 Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Primary Group Safety Population

System Organ Class Preferred Term	Paltusotine (N=84) n (%)	Placebo (N=85) n (%)	Total (N=169) n (%)
Participants with at Least One Related Treatment-Emergent Adverse Event	38 (45.2)	19 (22.4)	57 (33.7)
Gastrointestinal disorders	28 (33.3)	15 (17.6)	43 (25.4)
Diarrhoea	20 (23.8)	5 (5.9)	25 (14.8)
Abdominal pain	9 (10.7)	0	9 (5.3)
Nausea	7 (8.3)	2 (2.4)	9 (5.3)
Dyspepsia	2 (2.4)	4 (4.7)	6 (3.6)
Faeces soft	3 (3.6)	2 (2.4)	5 (3.0)
Abdominal distension	3 (3.6)	1 (1.2)	4 (2.4)
Abdominal discomfort	2 (2.4)	1 (1.2)	3 (1.8)
Abdominal pain upper	1 (1.2)	2 (2.4)	3 (1.8)
Constipation	1 (1.2)	2 (2.4)	3 (1.8)
Vomiting	2 (2.4)	0	2 (1.2)
Flatulence	1 (1.2)	1 (1.2)	2 (1.2)
Frequent bowel movements	1 (1.2)	1 (1.2)	2 (1.2)
Faeces pale	1 (1.2)	0	1 (0.6)
Paraesthesia oral	1 (1.2)	0	1 (0.6)
Swollen tongue	0	1 (1.2)	1 (0.6)
Metabolism and nutrition disorders	6 (7.1)	0	6 (3.6)
Decreased appetite	3 (3.6)	0	3 (1.8)
Hyperamylasaemia	1 (1.2)	0	1 (0.6)
Hyperglycaemia	1 (1.2)	0	1 (0.6)
Hyponatraemia	1 (1.2)	0	1 (0.6)
Investigations	3 (3.6)	3 (3.5)	6 (3.6)
Lipase increased	1 (1.2)	2 (2.4)	3 (1.8)
Hepatic enzyme increased	1 (1.2)	1 (1.2)	2 (1.2)
Ejection fraction decreased	1 (1.2)	0	1 (0.6)
Pancreatic enzymes increased	1 (1.2)	0	1 (0.6)
Cardiac disorders	5 (6.0)	0	5 (3.0)
Sinus bradycardia	3 (3.6)	0	3 (1.8)
Bradycardia	1 (1.2)	0	1 (0.6)
Ventricular extrasystoles	1 (1.2)	0	1 (0.6)
Nervous system disorders	3 (3.6)	2 (2.4)	5 (3.0)
Headache	2 (2.4)	1 (1.2)	3 (1.8)
Neuralgia	1 (1.2)	0	1 (0.6)
Paraesthesia	1 (1.2)	0	1 (0.6)
Dizziness	0	1 (1.2)	1 (0.6)
Musculoskeletal and connective tissue disorders	4 (4.8)	0	4 (2.4)
Muscle spasms	2 (2.4)	0	2 (1.2)
Back pain	1 (1.2)	0	1 (0.6)
Muscular weakness	1 (1.2)	0	1 (0.6)
Pain in extremity	1 (1.2)	0	1 (0.6)
Hepatobiliary disorders	3 (3.6)	1 (1.2)	4 (2.4)
Cholelithiasis	2 (2.4)	1 (1.2)	3 (1.8)
Hyperbilirubinaemia	1 (1.2)	0	1 (0.6)
Hyperplastic cholecystopathy	1 (1.2)	0	1 (0.6)
General disorders and administration site conditions	2 (2.4)	2 (2.4)	4 (2.4)
Fatigue	2 (2.4)	0	2 (1.2)
Asthenia	0	1 (1.2)	1 (0.6)

In the primary group, **treatment-related TEAEs** were more frequently observed in the paltusotine group (45.2%) compared to placebo (22.4%).

The applicant submitted grouped data on TEAEs reported in paltusotine and placebo groups. The most frequently reported related TEAEs by SOC were **gastrointestinal disorders, followed by metabolism and nutrition disorders, cardiac disorders, musculoskeletal and connective tissue disorders, nervous system disorders, hepatobiliary disorders, and investigations.**

Within the gastrointestinal SOC, the most common related TEAEs PT were **diarrhoea (n=20, 23.8%), abdominal pain (n=9, 10.7%), and nausea (n=7, 8.3%)**. These events are well-known ADRs to SRLs therapies.

Other frequently reported related TEAEs included **decreased appetite (3.6%), sinus bradycardia (3.6%), headache (2.4%), muscle spasms (2.4%), cholelithiasis (2.4%), and fatigue (2.4 %).**
The applicant has provided a justification for inclusion of the adverse events into the PI, which was focused on all TEAEs, irrespective of causality. However, in the end, the adverse events which have been included in section 4.8 of the paltusotine SmPC were based on them having at least a possible relationship to the treatment received. This also considered that the SRLs class effects remain relevant to paltusotine safety characterisation.

The applicant conducted a dose-based analysis of TEAEs in the primary group. A higher frequency of TEAEs was observed in patients treated with 40 mg compared to 60 mg, for both overall and treatment-related events. In the non-pharmacologically treated population, gastrointestinal disorders were slightly more common at 40 mg (56.3%) than 60 mg (52.6%). Overall, the findings indicate that both doses are similarly tolerated, and the observed variations are not clinically meaningful.

Adverse Events in Medically Naïve, Previously Treated, and Washout Groups of RC Phase of Study CRN00808-08

The applicant also submitted a subgroup analysis of TEAEs reported in medically naïve, previously treated, and washout groups in the RC phase of study CRN00808-08. TEAEs were more frequently reported in medically naïve patients (95.5%) compared to previously treated (88.9%) and washout patients (85.7%).
GI-related AEs such as diarrhoea, abdominal discomfort, and nausea were more frequent in medically naïve patients. This aligns with the known observation that GI AEs are more common during the initial weeks of SRL treatment. Other AEs more common in medically naïve patients included increased lipase, cholelithiasis, eye disorders, metabolism and nutrition disorders, sinus bradycardia, and alopecia.
These differences may reflect a lack of physiological adaptation in SRL-naïve patients. Rapid hormonal suppression (e.g., GH/IGF-1) could lead to systemic effects such as bradycardia or alopecia, while abrupt changes in biliary motility may predispose to cholelithiasis.
TEAEs reported in the first 14 days were consistent with those reported throughout the RC phase. The most frequent SOCs included gastrointestinal, metabolism and nutrition, nervous system, and musculoskeletal disorders.

ADRs in the Supportive Group

Table 63 ADR in the supportive group

System Organ Class Preferred Term		n (%) Exposure-Adjusted Incidence/Year					
	≤3 months	>3 months to ≤6 months	>6 months to ≤9 months	>9 months to ≤12 months	>12 months to ≤18 months	>18 months	Participants with At Least 1 TEAE (Cumulative) (N=233)
Total participants with TEAE within the time period shown	**168 (72.1) 0.45**	**18 (7.7) 0.05**	**12 (5.2) 0.03**	**2 (0.9) 0.01**	**9 (3.9) 0.02**	**5 (2.1) 0.01**	**214 (91.8) 0.57**
Gastrointestinal disorders	**77 (33.0) 0.21**	**6 (2.6) 0.02**	**13 (5.6) 0.03**	**3 (1.3) 0.01**	**8 (3.4) 0.02**	**11 (4.7) 0.03**	**118 (50.6) 0.32**
Diarrhoea	45 (19.3) 0.12	3 (1.3) 0.01	2 (0.9) 0.01	2 (0.9) 0.01	2 (0.9) 0.01	3 (1.3) 0.01	57 (24.5) 0.15
Abdominal pain	18 (7.7) 0.05	1 (0.4) 0.003	3 (1.3) 0.01	0	1 (0.4) 0.003	2 (0.9) 0.01	25 (10.7) 0.07
Nausea	12 (5.2) 0.03	1 (0.4) 0.003	2 (0.9) 0.01	0	1 (0.4) 0.003	3 (1.3) 0.01	19 (8.2) 0.05
Abdominal distension	11 (4.7) 0.03	1 (0.4) 0.003	1 (0.4) 0.003	0	1 (0.4) 0.003	0	14 (6.0) 0.04
Abdominal pain upper	5 (2.1) 0.01	1 (0.4) 0.003	1 (0.4) 0.003	0	2 (0.9) 0.01	3 (1.3) 0.01	12 (5.2) 0.03
Infections and infestations	**41 (17.6) 0.11**	**14 (6.0) 0.04**	**18 (7.7) 0.05**	**13 (5.6) 0.03**	**6 (2.6) 0.02**	**15 (6.4) 0.04**	**107 (45.9) 0.29**
Urinary tract infection	8 (3.4) 0.02	3 (1.3) 0.01	2 (0.9) 0.01	3 (1.3) 0.01	3 (1.3) 0.01	4 (1.7) 0.01	23 (9.9) 0.06
Upper respiratory tract infection	5 (2.1) 0.01	3 (1.3) 0.01	4 (1.7) 0.01	1 (0.4) 0.003	0	4 (1.7) 0.01	17 (7.3) 0.05
COVID-19	3 (1.3) 0.01	0	1 (0.4) 0.003	4 (1.7) 0.01	0	8 (3.4) 0.02	16 (6.9) 0.04
Nasopharyngitis	5 (2.1) 0.01	2 (0.9) 0.01	4 (1.7) 0.01	2 (0.9) 0.01	0	2 (0.9) 0.01	15 (6.4) 0.04
Musculoskeletal and connective tissue disorders	**46 (19.7) 0.12**	**24 (10.3) 0.06**	**4 (1.7) 0.01**	**5 (2.1) 0.01**	**4 (1.7) 0.01**	**7 (3.0) 0.02**	**90 (38.6) 0.24**
Arthralgia	22 (9.4) 0.06	17 (7.3) 0.05	1 (0.4) 0.003	2 (0.9) 0.01	2 (0.9) 0.01	5 (2.1) 0.01	49 (21.0) 0.13
Back pain	7 (3.0) 0.02	2 (0.9) 0.01	1 (0.4) 0.003	0	0	6 (2.6) 0.02	16 (6.9) 0.04
Nervous system disorders	**48 (20.6) 0.13**	**13 (5.6) 0.03**	**7 (3.0) 0.02**	**2 (0.9) 0.01**	**3 (1.3) 0.01**	**6 (2.6) 0.02**	**79 (33.9) 0.21**
Headache	34 (14.6) 0.09	9 (3.9) 0.02	8 (3.4) 0.02	0	3 (1.3) 0.01	1 (0.4) 0.003	55 (23.6) 0.15
Paraesthesia	17 (7.3) 0.05	3 (1.3) 0.01	2 (0.9) 0.01	1 (0.4) 0.003	1 (0.4) 0.003	2 (0.9) 0.01	26 (11.2) 0.07
Metabolism and nutrition disorders	**24 (10.3) 0.06**	**8 (3.4) 0.02**	**12 (5.2) 0.03**	**5 (2.1) 0.01**	**12 (5.2) 0.03**	**9 (3.9) 0.02**	**70 (30.0) 0.19**
Hyperglycaemia	5 (2.1) 0.01	4 (1.7) 0.01	7 (3.0) 0.02	2 (0.9) 0.01	2 (0.9) 0.01	4 (1.7) 0.01	24 (10.3) 0.06

System Organ Class Preferred Term		n (%) Exposure-Adjusted Incidence/Year					
	≤3 months	>3 months to ≤6 months	>6 months to ≤9 months	>9 months to ≤12 months	>12 months to ≤18 months	>18 months	Participants with At Least 1 TEAE (Cumulative) (N=233)
General disorders and administration site conditions	**40 (17.2) 0.11**	**9 (3.9) 0.02**	**6 (2.6) 0.02**	**4 (1.7) 0.01**	**6 (2.6) 0.02**	**2 (0.9) 0.01**	**67 (28.8) 0.18**
Fatigue	18 (7.7) 0.05	5 (2.1) 0.01	0	2 (0.9) 0.01	2 (0.9) 0.01	2 (0.9) 0.01	29 (12.4) 0.08
Peripheral swelling	13 (5.6) 0.03	5 (2.1) 0.01	2 (0.9) 0.01	0	0	1 (0.4) 0.003	21 (9.0) 0.06
Asthenia	7 (3.0) 0.02	1 (0.4) 0.003	1 (0.4) 0.003	0	3 (1.3) 0.01	0	12 (5.2) 0.03
Respiratory, thoracic and mediastinal disorders	**13 (5.6) 0.03**	**8 (3.4) 0.02**	**7 (3.0) 0.02**	**0**	**1 (0.4) 0.003**	**1 (0.4) 0.003**	**30 (12.9) 0.08**
Cough	3 (1.3) 0.01	2 (0.9) 0.01	4 (1.7) 0.01	0	0	3 (1.3) 0.01	12 (5.2) 0.03
Hepatobiliary disorders	**2 (0.9) 0.01**	**6 (2.6) 0.02**	**10 (4.3) 0.03**	**3 (1.3) 0.01**	**1 (0.4) 0.003**	**6 (2.6) 0.02**	**28 (12.0) 0.08**
Cholelithiasis	1 (0.4) 0.003	1 (0.4) 0.003	8 (3.4) 0.02	1 (0.4) 0.003	0	2 (0.9) 0.01	13 (5.6) 0.03

PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event
MedDRA Version 24.1. Percentages are calculated based on the number of participants in the safety population of each respective group.
Note: Total duration of exposure was 373.0 person-years.

In the Supportive Group overall, a total of 112 of 233 (48.1%) participants experienced treatment-related TEAEs. Treatment-related TEAEs reported in ≥5% of participants were diarrhoea (n=42; 18.0%), abdominal pain (n=16; 6.9%), headache (n=13; 5.6%), and cholelithiasis (n=12, 5.2%). None of the frequently reported treatment-related TEAEs increased by >1%. The overall safety profile of paltusotine appears consistent with that of other SRLs.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Deaths

Two SAE of deaths were reported.

One death was reported in paltusotine-treated participants with acromegaly in the OLE phase of study CRN00808-09. The death was due to an SAE (PT term) of "toxicity to various agents" and was not considered treatment-related by the Investigator.

The second case was reported in phase 1 study CRN00808-22 (open-label, randomized crossover study in healthy volunteers).

Serious Adverse Events

Serious Adverse Events in the Primary Group

During the RC phases of either phase 3 study, no treatment-emergent SAEs were reported in the paltusotine group. In the placebo group, a total of 2 participants (one in each study) each experienced 1 treatment-emergent SAE: parathyroid tumour benign in study CRN00808-08 and cholecystitis in study CRN00808-09. Both participants completed the RC Phase and enrolled in the OLE phase of each respective study.

Serious Adverse Events in the Supportive Group

Overall, across all acromegaly studies, a total of 29 of 233 participants (12.4%) treated with paltusotine experienced a total of 36 treatment-emergent SAEs:

- 5 participants in CRN00808-08 (OLE only) experienced a total of 14SAEs.
- 3 participants in CRN00808-09 (OLE only) experienced 8 SAE each.
- 1 participant in CRN00808-03 reported a single SAE.
- 11 participants in CRN00808-05 reported total of 13 SAEs.

No participants reported SAEs in study CRN00808-02.

SAEs reported in 2 or more participants each were cholelithiasis (n=4), deep vein thrombosis (n=2), pneumonia (n=2), and sinus arrest and urinary tract infection (n=2 each). All other SAEs were reported in 1 participant each.

Most participants treated with paltusotine experienced treatment-emergent SAEs that were considered unrelated (not related or unlikely related) to study treatment. Treatment-related and/or severe SAEs are summarized as follows; all these events resolved as of the respective study cut-off dates:

- Six participants experienced treatment-related (possibly or probably related) SAEs. Three participants experienced 1 SAE of cholelithiasis each (two mild and 1 moderate, all with no change in dose), 1 participant experienced sinus arrest (severe) and biliary colic (moderate) which resulted in study treatment interruption; 1 participant for whom study treatment was already interrupted prior to the onset of the SAE experienced bile duct stone (moderate), and 1 participant experienced an SAE of gastritis (severe). All participants subsequently continued paltusotine.
- Eight participants experienced severe SAEs: 1 participant experienced the fatal event of toxicity to various agents, 1 participant experienced urinary tract infection (during a period where study treatment was already interrupted due to a non-serious TEAE) and subsequently umbilical hernia, 2 participants experienced sinus arrest, 1 participant experienced influenza and pneumonia bacterial, and headache, gastritis, and atrioventricular block complete were experienced by 1 participant each, respectively. One severe TEAE (sinus arrest) was considered treatment-related. SAEs of sinus arrest (n=1), atrioventricular block, and gastritis resulted in study interruption. Most participants continued paltusotine; the participant with the SAE of headache discontinued study drug due to a concurrent TEAE of rhinosinusitis that resulted in a need for a prohibited concomitant medication (ciprofloxacin).

Four of 29 SAEs in participants treated with paltusotine were considered acromegaly-related TEAEs by the investigator: pituitary tumour benign and pituitary tumour in study CRN00808-08 (both moderate and considered unlikely related to study treatment), arthralgia in study CRN00808-05 (moderate, considered not related to study treatment), and headache in study CRN00808-03 (severe, considered unlikely related to study treatment).

Most treatment-emergent SAEs in participants receiving paltusotine resolved by each respective study cut-off. In study CRN00808-08, the status of the abovementioned SAEs of pituitary tumour was considered unknown, and the SAE of pituitary tumour benign was considered recovering/resolving. In study CRN00808-05, the SAE of breast cancer was considered recovering/resolving, and renal oncocytoma was not considered recovered/resolved.

5.4.5. Discontinuation due to adverse events

Primary Group

In the Primary Group, TEAEs leading to treatment discontinuation were reported less frequently in the paltusotine group (6.0%) compared with the placebo group (37.6%). TEAEs that led to treatment discontinuation in 2 or more participants in the paltusotine group were arthralgia (3.6%) and paraesthesia (2.4%). TEAEs that led to treatment discontinuation in 2 or more participants in the placebo group were arthralgia (15.3%), headache (14.1%), peripheral swelling (11.8%), fatigue (9.4%), hyperhidrosis (7.1%), paraesthesia (5.9%), muscular weakness (4.7%) and pain in extremity and insomnia (3.5% each).

Supportive Group

In the Supportive Group overall, TEAEs leading to treatment discontinuation were reported for 9 of 233 (3. 9%) participants. TEAEs leading to treatment discontinuation reported for 2 or more participants were arthralgia (1.3%), paraesthesia (0.9%), and lipase increased (0.9%).

Across these cases, there was a consistent potential signal of musculoskeletal and neuropathic AEs leading to discontinuation (neuralgia, paraesthesia, pain in extremity, oral paraesthesia, and muscle spasms, etc.), which may overlap with acromegaly but cannot be definitively dissociated from paltusotine treatment.

Still, it was considered that treatment-related discontinuations (fatigue and decreased appetite) should be included in the SmPC to better describe the safety profile of paltusotine.

5.4.6. Safety in special populations

- **Age (Primary Group)**

A total of 143 participants (67 in the paltusotine group and 76 in the placebo group) were <65 years of age, and 26 participants (17 in the paltusotine group and 9 in the placebo group, respectively) were ≥65 years of age.

In general, while the small number of participants in the ≥65 years of age group, particularly at the study level, precludes a thorough analysis, the TEAE profiles appeared largely similar, and no safety concerns were identified based on these analyses.

Based on population PK analyses of intrinsic factors on the PK of paltusotine, age did not have a meaningful effect on the exposure of paltusotine assessment.

- **Sex (Primary Group)**

In study CRN00808-09, no notable sex-related differences in the incidence of TEAEs were observed. In contrast, study CRN00808-08 showed a higher incidence of TEAEs in women compared to men across both the paltusotine and placebo groups, with moderate TEAEs more frequently reported by women treated with paltusotine (38.5%) than by men (17.9%). Additionally, >20% differences in TEAE incidence between sexes were noted in the SOCs of "gastrointestinal disorders" and "metabolism and nutrition disorders". In the pooled Primary Group, the overall incidence of TEAEs remained higher in women than in men, though no consistent >20% differences were observed by SOC. In study CRN00808-08 gastrointestinal disorders are more common in paltusotine females (69.12%) compared to males (39.3%) subgroup. However, a slightly higher incidence can be observed also in placebo arm (36.4% vs 29.2%, respectively). Conversely, there is no imbalance in study CRN00808-09 (46.7% vs 46.7%, respectively). A similar trend is observed in study 08 in the SOC of Metabolism and nutrition disorders,

where a higher incidence is reported in females compared to males both in paltusotine (42.3% vs 14.3%) and placebo (15.2% vs 4.2%) groups. This type of imbalance is not observed in study 09, where the incidence is slightly higher in males (20.2%) compared to females (13.3%).
Therefore, considering the current data it is not possible to draw firm conclusion about a real sex related differences in paltusotine safety profile and it cannot be excluded that these may be due to a random effect.

- **Participants with Hepatic Impairment**

Hepatic impairment was investigated in the phase 1 study CRN00808-10, in participants with mild (Child Pugh score of 5-6), moderate (score of 7-9), or severe hepatic impairment (score of 10-15), treated with a single dose of 20 mg paltusotine. 36 participants were enrolled in the study (8 each with mild and moderate impairment, and 6 with severe) and 14 matched control participants. Single oral administration of 20 mg paltusotine tablet was generally well tolerated in all groups. One SAE of death (not treatment related) occurred in participant with mild hepatic impairment who died of natural causes on Day 27. Peak and total systemic exposures of paltusotine were similar across all hepatic impairment groups when compared to participants with normal hepatic function. There were no changes in paltusotine plasma exposure that would be considered clinically meaningful or sufficient to warrant dose adjustment for mild, moderate, or severe hepatic impairment.

- **Use in pregnancy and lactation**

Regarding the use of paltusotine in pregnant woman, the effects of the compound remain unknown, which is expected for a newly developed molecule given the lack of data in humans. The available information and knowledge are derived from non-clinical developmental and reproductive studies. Clinically, only two pregnancies were documented during the clinical development of paltusotine. The small number of exposed pregnancies and the limited follow-up restrict the ability to rule out potential risks.
From a non-clinical point of view, no treatment-related malformations or embryofoetal lethality were observed in rats or rabbits in embryofoetal development studies. Moreover, although specific development studies in rats demonstrated decreased pup body weight at the highest dose (500 mg/kg/day, the effects were minimal and inconsistent, and thus not considered adverse at human dose exposure (75 mg/kg/day).
Thus, regarding the pregnancy exposure aspects, non-clinical data suggest that paltusotine does not induce teratogenicity and has no significant adverse impact on foetal development at clinically relevant exposures. Observed effects on embryonic development only occurred at very high doses and were considered as minimal and inconsistent.

In contrast, the data related to fertility seems to be more problematic. Although observed at high doses, the adverse effects at ovarian/uterine examination in females of the fertility study may be related to the pharmacological activity of paltusotine considering the data obtained with somatostatin analogues. Therefore, section 4.6 of the SmPC states that changes in reproductive parameters were reported in female rats.

Regarding breast-feeding, additional specific studies confirmed that paltusotine is secreted in maternal milk. In lactation studies, drug concentrations were higher in milk than in plasma (by 2.4 to 3.8 times), and presence in pup plasma indicated exposure both in utero and via lactation. Foetal and neonatal drug levels were low relative to maternal exposure, and no drug-related toxicological effects were demonstrated at therapeutic dose equivalents.

5.4.7. Immunological events

Not applicable.

5.4.8. Safety related to drug-drug interactions and other interactions

No dedicated PD DDI studies were conducted. The effect of paltusotine on the glucose metabolism remains unclear. Therefore, paltusotine potential PD interactions with glucose metabolism that may lead to DDI with some diabetes treatment was deemed unclear. However, in light of the observed imbalance in glucose dysregulation, cases of drug–drug interaction between paltusotine and concomitant antidiabetic agents were discussed, as reported in clinical trials.

Hyperglycaemia events were reported in both the primary and supportive groups of clinical trials. In the primary group, 6 of 85 participants (7.1%) receiving paltusotine experienced hyperglycaemia, compared with 3.5% in the placebo group. In the supportive group, an additional 12 participants (~7%) reported at least one event, with the cumulative incidence increasing from 7.3% (M2.7.4) to 10.3% (4MSU data cutoff). Events continued to be reported beyond 18 months of exposure. These findings indicate that paltusotine can affect glucose regulation, even in the absence of changes in antidiabetic therapy during the trials.

From a pharmacological perspective, paltusotine inhibits growth hormone, glucagon, and insulin, which may impact glucose homeostasis. Although paltusotine is highly selective for SST2, this mechanism can indirectly affect glycaemic control and may necessitate adjustment of concomitant antidiabetic medications in clinical practice.

In line with other SRL therapies, SmPC section 4.5 mentions that dose adjustments of insulin and antidiabetic medicinal products may be required when paltusotine is administered concomitantly

5.4.9. Vital signs and laboratory findings

- Haematology

No concerns pertaining to haematology were identified from phase 2 and phase 3 analyses in acromegaly participants or in phase 1 studies in healthy volunteers. In the RC phases of study CRN00808-08 and study CRN00808-09, when evaluated by study, changes from baseline in haematology parameters were generally small and comparable between treatment groups.

- Chemistry

In general, no safety signals were apparent from analysis of serum chemistry parameters across acromegaly studies. There were no signals to indicate drug-induced liver injury. In the RC phases of study CRN00808-08 and study CRN00808-09, changes from baseline in serum chemistry parameters were generally small and comparable between treatment groups.

- Liver Function Tests

No toxicologically significant alterations in serum chemistry parameters, including ALT, AST, and ALP, were observed in non-clinical studies in rat and dog. Overall, no participants treated with paltusotine in the Primary Group had liver test abnormalities indicative of drug-induced liver injury. There was 1 case of elevated ALT > 3×ULN in the placebo group.

Five participants treated with paltusotine in the Supportive had 1 abnormal liver function parameter that was >3×ULN. Two of the 5 participants had 1 elevated liver function test (LFT) parameter at baseline. None of the 5 cases were indicative of DILI associated with paltusotine.

However, the occurrence of ALT/AST elevations at higher doses, in study CRN00808-11 [16.7% (n=3) of participants receiving 80 mg paltusotine experienced mild elevations in liver enzymes (ALT and/or

AST)], which may suggest a dose-dependent effect. Moreover, transaminase elevations are a known and relatively frequent class effect of SRL therapies such as octreotide potentially related to the reduced biliary flow. Still, TEAEs of elevated transaminases were infrequent, non-dose-dependent and occurred in equally frequently in participants on placebo. Moreover, no cases of Hy's Law, potential Hy's Law, or drug-induced liver injury (DILI) were observed with paltusotine in the acromegaly programme. Regarding the occurrence of ALT/AST elevations at higher doses in study CRN00808-11 (carcinoid Syndrome Study) the confounding factors related to the background disease makes difficult any definite extrapolation of the effect of paltusotine on the acromegaly populational.
Considering the mild to moderate nature of the reported transaminase elevations, the absence of treatment discontinuations, and the comparison with product information of other SRL therapies, no further modification of section 4.8 of the SmPC was requested.
However, given the occurrence of ALT/AST elevations >3×ULN and the potential class-related hepatic effects, continued monitoring of liver enzyme abnormalities was considered warranted. The applicant will provide a specific and cumulative analysis of hepatic safety (liver enzymes abnormalities) data in future PSURs.

- Amylase and Lipase Levels

In general, no notable differences were observed between paltusotine and placebo groups for amylase and lipase. In the medically naïve group, a small, non-important increase in mean and median lipase was observed at Weeks 8 and 12, trending back to baseline at Week 24; this was not seen in other groups. In general, shifts to worst post-baseline category for both amylase and lipase were similar and infrequent in both paltusotine and placebo groups.
In the paltusotine group, for amylase, 1 of 30 participants with the baseline value of ≤ULN shifted to >1x to ≤2×ULN compared to 2 of 27 participants in the placebo group.
In the medically naïve group of study CRN00808-08, a small increase in lipase with paltusotine was observed at Weeks 8 and 12, trending back to Baseline at Week 24; this was not clinically important and was not observed in the other groups.

- Haemoglobin A1c

In the RC phases of study CRN00808-08 and study CRN00808-09, when evaluated by study, changes from baseline in HbA1c parameters were generally small and comparable between treatment groups.
Changes in worst post-baseline HbA1c values were small in both the paltusotine and placebo groups, with no clinically significant differences observed between the 2 groups (highest postbaseline mean change of 0.28% [SD: 0.370, range: -0.6% to 2.2%] for paltusotine and 0.10% [SD: 0.254, range: -0.5% to 1.0%] for placebo; lowest postbaseline mean change of 0.05% [SD: 0.348, range: -0.8% to 1.5%] for paltusotine and -0.14% [SD: 0.264, range: -1.0% to 0.9%] for placebo).
For study CRN00808-03, there were no clinically significant changes in HbA1c values. In Group 4 (pre-trial therapy with pasireotide monotherapy, n=4), there was a decrease in the HbA1c values from baseline. The mean change from baseline in HbA1c values in Group 4 was -1.40% (SD 0.361, range -1.80 to -1.10%). This was consistent with withdrawal from the known hyperglycaemic effect of pasireotide.
In study CRN00808-02, no participants experienced HbA1c above the ULN.
In the OLE study CRN00808-05, mean and median HbA1c values were consistent from Untreated Baseline to Week 207, and median HbA1c was stable at approximately 6.0% from baseline in parent studies (LA-SRL Baseline) to Week 207. Three participants had clinically significant HbA1c elevation at some point during the study (first participant: Screening and Week 1, second participant: Week 23 only, third participant: Weeks 103, 129, and 155).
In the OLE phases of study CRN00808-08 and study CRN00808-09, mean and median changes in HbA1c from OLE baseline to each visit were small for the total populations of both studies, and by prior treatment groups in each respective RC Phase (and in the Washout Group of CRN00808-08. Changes in

worst postbaseline HbA1c values were small (highest postbaseline mean change of 0.30% [, range: -0.9% to 5.7%]; lowest postbaseline mean of -0.10% [, range: -2.9% to 0.9%]).

- ECG Measurements, QTcF Analysis, Effect on Heart Rate, and Effect on PR Interval

No safety signal of QT prolongation was identified in either the primary or supportive groups. QTcF interval increases >450 msec were observed in similar proportions across paltusotine and placebo groups, with no values >500 msec and no QTcF changes >60 msec. However, the number of patients with a change from baseline > 30 msec was higher in paltusotine group (6% vs 2.4%). In the 4MSU cut-off dates, a cumulative total of 26 of 233 (11.2%) participants had worst post-baseline QTcF intervals of >450 msec.
Therefore, while the thresholds of 60 msec increase and above 500-480-450 shift from baseline were similar between groups, there remained an observation of 30 msec increase from baseline in QT that was more frequent in paltusotine group tan placebo. The Applicant provided results from Study CRN00808-14, which was designed to specifically assess sufficient multiples (>2-fold) of the high clinical exposure scenario, to support a concentration-QTc analysis). It is noted that the exposure reached in the tested experimental condition goes up to 1341 ng/mL, which is >2-fold greater than the high clinical exposure scenario, which is steady state clinical exposure following 60 mg once daily (QD) (the maximum recommended dose) with concomitant medication of a CYP3A4/P-gp/BCRP inhibitor (high clinical exposure; estimated geometric mean Cmax of 583 ng/mL). It was therefore concluded that the provided evidence satisfied the regulatory requirements for a valid exposure-response analysis based on modelling. The concentration-QTc analysis using data from CRN00808-14 predicted a placebo-corrected QTcF change from baseline of 1.4 msec (90% upper CI: 2.76 ms) for 80 mg (Cmax: 500.12 ng/mL); 2.8 msec (90% upper CI: 5.50 msec) for 160 mg (Cmax: 996.28 ng/mL), and 3.8 msec (90% upper CI: 7.41 msec) for 240 mg (Cmax: 1341.28 ng/mL), with all values, including the upper CIs, lying below the 10 msec threshold of regulatory concern. Based on a totality of evidence approach, the waiver for a TQT was confirmed, and no further concerns were raised with respect to the proarrhythmic potential of paltusotine at the intended posology.
A slightly higher incidence of heart rate reduction (from ≥50 bpm to 40–<50 bpm) was observed in the paltusotine group compared to placebo in study CRN00808-08, particularly on triplicate ECGs, but this was not reproduced in study CRN00808-09 and did not lead to bradycardia <40 bpm.

Regarding PR interval, more participants in the paltusotine group showed post-baseline shifts to >200 msec. However, this finding is difficult to interpret due to a higher prevalence of prolonged PR interval at baseline in the placebo group, suggesting a potential regression to the mean rather than a drug-related effect.

5.4.10. Post-marketing experience

Not applicable. The medicinal product was recently approved by the FDA on 25 September 2025, however, no post-marketing experience was gathered yet.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

Safety data collection

The safety data of paltusotine for the treatment and long-term maintenance therapy of acromegaly was pooled into 2 analysis populations: the primary group and the supportive group.
The primary group included data from two RC phase 3 trials: study CRN00808-08 (treatment of acromegaly) and study CRN00808-09 (long-term maintenance therapy of acromegaly). In these two studies the to-be marketed formulation (15% drug load SDD tablet) was used at doses ranging from 20 mg to 60 mg QD in study CRN00808-08 and 40 mg to 60 mg QD in study CRN00808-09. These data were supported by analyses of the RC phases of the individual studies.
The supportive group pooled data from 5 acromegaly studies (completed studies CRN00808-02 and CRN00808-03, on-going study CRN00808-05, completed RC phases of studies CRN00808-08 and CRN00808-09, and ongoing OLE phases of studies CRN00808-08 and CRN00808-09), exposed for a maximum duration of 4 years to support the assessment of long-term safety of paltusotine. The doses ranged from 10 mg QD to 60 mg QD and included both the capsule and to-be marketed tablet formulation.

In addition, a total of 11 clinical studies in healthy volunteers, one phase 1 clinical trial in participants with hepatic impairment (study CRN00808-10) and one phase 2 study for the treatment of carcinoid syndrome (study CRN00808-11) are used to support the safety of paltusotine.

Patient exposure

The patient exposure in the clinical trials with the indication of treatment of acromegaly was considered of sufficient size to enable safety assessment considering the rarity of the disease. The length of the follow-up was considered sufficient for acromegaly indication (approximately 4 years).

In the primary group, 84 patients received at least one dose of paltusotine (54 from study CRN00808-08 and 30 from study CRN00808-09). The mean duration in study CRN00808-08 RC was about 24 weeks in both paltusotine and placebo groups. While, in study CRN00808-09 RC the median duration of exposure was 36 weeks in the paltusotine group and 22.1 weeks in the placebo group.
By dose, the median duration of exposure to 20 mg was 14 days for both the paltusotine and placebo groups, to 40 mg was 62 days and 29 days in the paltusotine and placebo groups, respectively, and to 60 mg was 126 days for both the paltusotine and placebo groups. The major exposure was observed for the 60 mg, although fewer participants in the paltusotine group than in the placebo group (54 versus 79 respectively), received 60 mg of study treatment at any point in the study.
In the supportive group, a total of 233 patients received at least one dose of paltusotine. A total of 12.0%, 18.9%, 40.3%, 13.3%, and 15.5% of participants received >0 to ≤6 months, >6 months to ≤12 months, >12 to ≤24 months, >24 to ≤36 months, and >36 months of paltusotine treatment, respectively.
The patient exposure in the clinical trials with the indication of treatment of acromegaly is considered of sufficient size to enable safety assessment. The length of the follow-up is considered sufficient for acromegaly indication (approximately 4 years).

The majority of patients completed RC phase studies 08 and 09 (97.6% in paltusotine and 95.3% in placebo group). The most common reason of discontinuation is AEs (3.6%) in paltusotine group and use of rescue therapy (35.3%) in placebo group, as expected in this group. Study discontinuation was low and was observed in 6 patients in total. About 92% of patients enrolled in OLE phase.

Demographic characteristics in primary group are overall consistent between groups with the majority being ≤65 years, white and with a prior acromegaly treatment.

Adverse events (AEs)

In the primary group, TEAEs were reported at similar rates in the paltusotine and placebo groups (86.9% vs. 90.6%, respectively). Most were mild or moderate. Severe TEAEs were more common in placebo (9.4%) than in paltusotine group (2.4%) and only 2 severe not related TEAEs occurred in placebo group, both in study CRN00808-08 (headache and pain in extremity). No SAEs were reported in the paltusotine group. In contrast, two SAEs occurred in the placebo group (benign parathyroid tumour and cholecystitis).
The most common TEAEs (≥10% incidence) by PT in paltusotine group were diarrhoea, headache, arthralgia, abdominal pain and nausea. However, among these only AEs belonging to the SOC of gastrointestinal disorders were more common in paltusotine group compared to placebo group. Moreover, also abdominal pain (13.1% versus 5.9%), abdominal discomfort (6.0% versus 1.2%), decreased appetite, sinus bradycardia (4.8% versus 0 for each) and hyperglycaemia (4.8% versus 2.4%) were more common in study drug group compared to placebo group.
For medically naïve patients, progressive pharmacodynamic adaptation is necessary, therefore the recommended starting dose is 20 mg once daily, to be then titrated up to 40 mg after tolerance is established (two weeks). This approach is standard for other SRLs and aligns with the principle of using the lowest effective dose to minimise dose-dependent ADRs.
Cardiac disorders were observed only in paltusotine group with sinus bradycardia occurring in 3 (3.6%) patients (all in study CRN00808-08) versus 0 in placebo group**.**
Musculoskeletal disorders were more frequently reported in the previously SRL-treated patients (CRN00808-09) compared to non-pharmacologically treated patients (CRN00808-08) [46.7% vs. 27.8%]. The observed imbalance between studies likely reflects differences in baseline disease characteristics (e.g., longer disease duration, older age, higher prevalence of pre-existing musculoskeletal conditions in study CRN00808-09) rather than a treatment or exposure-related safety signal.
In the supportive group, 214 of 233 participants (91.8%) receiving paltusotine reported at least 1 TEAE. Twenty-nine (12.4%) participants experienced at least 1 SAE, including 6 participants (2.6%) with a treatment-related SAE. A single TEAE leading to death was reported (toxicity to various agents, Study CRN00808-09, as noted in the previous paragraph). Thirty-one (13.3%) participants experienced at least 1 severe TEAE. Approximately half (48.1%) of participants had at least 1 TEAE that was related to study treatment. Nine (3.9%) participants reported TEAEs that resulted in treatment discontinuation, and 6 (2.6%) participants reported TEAEs that resulted in study discontinuation.

Treatment-related TEAEs
In the primary group, treatment-related TEAEs were more frequently observed in the paltusotine group (45.2%) compared to placebo (22.4%).
The most frequently reported related TEAEs by SOC were gastrointestinal disorders, followed by metabolism and nutrition disorders, cardiac disorders, musculoskeletal and connective tissue disorders, nervous system disorders, hepatobiliary disorders, and investigations.
Within the SOC gastrointestinal disorders, the most common related TEAEs PT were diarrhoea (n=20, 23.8%), abdominal pain (n=9, 10.7%), and nausea (n=7, 8.3%). These events are well-known ADRs to SRLs therapies and were listed as "very common" in the product information.
Other frequently reported related TEAEs included decreased appetite (3.6%), sinus bradycardia (3.6%), headache (2.4%), muscle spasms (2.4%), cholelithiasis (2.4%), and fatigue (2.4%). Section 4.8 of the SmPC reflects the observed treatment-related TEAE accordingly.

Both doses of 40mg and 60mg are similarly tolerated, and the observed variations are not clinically meaningful.

TEAEs were more frequently reported in medically naïve patients (95.5%) compared to previously treated (88.9%) and washout patients (85.7%). GI-related AEs such as diarrhoea, abdominal discomfort, and nausea were more frequent in medically naïve patients. This aligns with the known observation that

GI AEs are more common during the initial weeks of SRL treatment. Other AEs more common in medically naïve patients included increased lipase, cholelithiasis, eye disorders, metabolism and nutrition disorders, sinus bradycardia, and alopecia.
These differences may reflect a lack of physiological adaptation in SRL-naïve patients. Rapid hormonal suppression (e.g., GH/IGF-1) could lead to systemic effects such as bradycardia or alopecia, while abrupt changes in biliary motility may predispose to cholelithiasis.

In the supportive group overall, a total of 112 of 233 (48.1%) participants experienced treatment-related TEAEs. Treatment-related TEAEs reported in ≥5% of participants were diarrhoea (n=42; 18.0%), abdominal pain (n=16; 6.9%), headache (n=13; 5.6%), and cholelithiasis (n=12, 5.2%). None of the frequently reported treatment-related TEAEs increased by >1%. However, the Applicant reports that cholelithiasis was previously below the 5% threshold (3.9%) suggesting an increase of frequency in the long-term.
These ADRs are widely acknowledged in SRL product information. The overall safety profile of paltusotine appears consistent with that of other SRLs.
Although the number of participants at 20 mg (n=4) was limited, a numerically higher proportion of patients experienced related TEAEs (50%) compared to those receiving 40 mg (43%) or 60 mg (32%). Gastrointestinal adverse events appeared more frequent in the 20 mg group. No dose-dependent increase in overall TEAEs or related TEAEs was observed between 40 and 60 mg, which indicates no apparent dose-related safety concerns at higher exposures.

Despite limited number, the trend toward more frequent GI TEAEs at 20 mg, suggests that initial exposure may be associated with transient intolerance. Therefore, initiating treatment at 20 mg, rather than 40 mg, has been considered to improve tolerability and minimize early discontinuations.

Serious adverse events (SAEs) and deaths

No treatment-related deaths were reported with either paltusotine or placebo in any of the 5 acromegaly studies as of each respective study cut-off.
In the RC phase 3 studies (primary group), no SAEs were reported in patients treated with paltusotine.
In the supportive group, 29 of 233 patients (12.4%) experienced a total of 36 SAEs.
Treatment-related SAEs were reported in six participants. Three participants experienced 1 SAE of cholelithiasis each (two mild and 1 moderate, all with no change in dose), 1 participant experienced sinus arrest (severe) and biliary colic (moderate) which resulted in study treatment interruption; 1 participant for whom study treatment was already interrupted prior to the onset of the SAE experienced bile duct stone (moderate), and 1 participant experienced an SAE of gastritis (severe). All participants subsequently continued paltusotine.

AESIs (Adverse events of special interest)

AESIs were reported more frequently in the placebo groups than in the paltusotine groups during the RC studies (65.9% vs 36.9%). The most frequently reported AESIs were similar across both treatment arms and consistent with the overall TEAE profile observed in the primary group. The most frequently reported acromegaly-related TEAEs (≥10% incidence) in the paltusotine group were headache and arthralgia while in the placebo group were arthralgia, peripheral swelling, headache, fatigue, paraesthesia, and hyperhidrosis. In the Supportive Group overall, in general, acromegaly related TEAE profile was consistent with the Primary Group. Of note, several AESIs such as arthralgia, fatigue and headache are listed as ADRs in the product information of other SRL therapies. In addition, the applicant performed an analysis of safety data reported in paltusotine-treated participants for the following categories of safety events known to be associated with approved SRL medications, such as cholelithiasis and complications of cholelithiasis, hyperglycemia and hypoglycemia, thyroid function abnormalities, cardiac function abnormalities, and gastrointestinal events. Hyperglycemia has been added as ADR in section 4.8 of the SmPC and a warning has been added in section 4.4 of the SmPC.

TEAEs of bradycardia were reported for 5 (6.0%) participants in the paltusotine primary group, of which sinus bradycardia was reported in 4 (4.8%) participants. The events were considered asymptomatic; No clear association with dose has been identified. This information was reflected in the 4.4 and 4.8 sections of the SmPC.

There was an additional event of nonserious sinus bradycardia in the supportive group and an additional 3 nonserious events of bradycardia, as well as an additional event of nonserious sinus bradycardia in the participant who had 2 prior events of sinus bradycardia in the RC phase of study CRN00808-08. These events were non-serious, asymptomatic, did not lead to treatment discontinuation and were not associated with adverse cardiovascular outcomes.
No imbalances were observed in the SRL event categories of narrow or broad gallbladder abnormalities. Overall, the majority of TEAEs of cholelithiasis occurred between 6 and 9 months after the start of paltusotine. Section 4.8 of the SmPC reports that events occurred in the first nine months.
In addition, a warning advising on potential occurrence of cholelithiasis and its complications and appropriate evaluation was included in section 4.4 of the SmPC.
A small number of cases of elevated lipase or elevated amylase were reported between paltusotine and placebo groups, in both the primary and the supportive group.

Ocular TEAEs
In non-clinical phototoxicity studies, unilateral corneal dystrophy and retinal degeneration/necrosis were observed in paltusotine-treated rats at the high dose 250 mg/kg/day. It was concluded that the link between paltusotine administration and the adverse effect observed in retina in phototoxicity study after 3-day administration is questionable (please refer to the non-clinical part section).
In phase 3 clinical trials, a review of ocular-related TEAEs revealed a similar incidence between paltusotine and placebo groups (~8%). However, a numerical imbalance in event count was noted: 30 events reported in 22 paltusotine-treated participants vs. 16 events in 9 placebo-treated participants.
Overall, despite the absence of serious adverse events and comparable incidence rates with placebo, the combination of non-clinical findings, an event imbalance, insufficient detail on clinical cases, and on-going adjudication justifies further investigation. Continued ophthalmic monitoring is appropriate, and additional data are needed to better assess the ocular safety profile of paltusotine.
Therefore, this topic will remain under close monitoring in future PSURs, with continued cumulative review of ocular adverse events to confirm the absence of a safety signal over time. In addition, the open-label extension study CRN00808-05 will also collect safety information on ocular adverse events.

Discontinuation due to adverse events
In the primary group, the incidence of TEAEs leading to study treatment discontinuation was lower in the paltusotine group (6.0%) compared with placebo (37.6%), with most placebo discontinuations attributed to acromegaly symptoms. Similar trends were observed for dose reductions or interruptions.
In the Supportive Group overall, TEAEs leading to study discontinuation were reported for 9 of 233 (3.9 %) participants, 5 from the Primary Group, and 3 from the OLE Phase 2/3 studies. TEAEs leading to treatment discontinuation reported for 2 or more participants were arthralgia (1.3%), paresthesia (0.9%), and lipase increased (0/9%)
Across these cases, there is a consistent potential signal of musculoskeletal and neuropathic AEs leading to discontinuation (neuralgia, paraesthesia, pain in extremity, oral paraesthesia, and muscle spasms, etc.), which may overlap with acromegaly but cannot be definitively dissociated from paltusotine treatment.
Treatment-related discontinuations (fatigue and decreased appetite) were included in the SmPC, to better describe the safety profile of paltusotine.

Safety in special populations

Age

Overall, there seem to be no significant differences in TEAEs between participants in the ≥ 65 and < 65 years of **age group**. A slightly higher incidence in musculoskeletal and connective tissue disorders was observed in older patients (41% vs 32.8%), as expected. However, the small number of patients ≥65 years does not allow to draw a firm conclusion.

Sex

A higher incidence of TEAEs was reported in women compared to men. In the Primary Group, a total of 92.7% (38/41) women in the paltusotine group versus 81.4% (35/43) men in the paltusotine group reported at least 1 TEAE. Considering the current data, it is not possible to draw conclusion about a real sex related difference in paltusotine safety profile.

Safety related to drug-drug interactions and other interactions

No dedicated DDI studies was conducted. That was accepted.

Use in pregnancy and lactation

Current knowledge on the effects of paltusotine during pregnancy and lactation is limited.
Non-clinical data suggest that paltusotine does not induce teratogenicity and has no significant adverse impact on foetal development at clinically relevant exposures.
In contrast, the observed adverse effects at ovarian/uterine examination in females of the fertility study may be related to the pharmacological activity of paltusotine considering the data obtained with somatostatin analogues. Section 4.6 of the SmPC 4.6 on fertility mentions that changes in reproductive parameters were reported in female rats.

Additional specific studies confirmed that paltusotine is secreted in maternal milk. In lactation studies, drug concentrations were higher in milk than in plasma (by 2.4 to 3.8 times), and presence in pup plasma indicated exposure both in utero and via lactation. Foetal and neonatal drug levels were low relative to maternal exposure, and no drug-related toxicological effects were demonstrated at therapeutic dose equivalents.

Laboratory and other findings

No toxicologically significant alterations in serum chemistry parameters, including ALT, AST, and ALP, were observed in non-clinical studies in rat and dog. Overall, no participants treated with paltusotine in the Primary Group had liver test abnormalities indicative of drug-induced liver injury. There was 1 case of elevated ALT > 3×ULN in the placebo group.
However, the occurrence of ALT/AST elevations at higher doses, in study CRN00808-11 [16.7% (n=3) of participants receiving 80 mg paltusotine experienced mild elevations in liver enzymes (ALT and/or AST)], which may suggest a dose-dependent effect. Moreover, transaminase elevations are a known and relatively frequent class effect of SRL therapies such as octreotide potentially related to the reduced biliary flow.
The Applicant clarified that in acromegaly program TEAEs of elevated transaminases were infrequent, non-dose-dependent and also occurred in equally frequently in participants on placebo. Moreover, no cases of Hy's Law, potential Hy's Law, or drug-induced liver injury (DILI) were observed with paltusotine in the acromegaly programme. Regarding the occurrence of ALT/AST elevations at higher doses in Study CRN00808-11 (carcinoid Syndrome Study) the confounding factors related to the background disease makes difficult any definite extrapolation of the effect of paltusotine on the acromegaly populational.
However, given the occurrence of ALT/AST elevations >3×ULN and the potential class-related hepatic effects, continued monitoring of liver enzyme abnormalities was considered warranted. The applicant

has agreed to provide a specific and cumulative analysis of hepatic safety (liver enzymes abnormalities) data in future PSURs.

No safety signal of QT prolongation was identified in either the primary or supportive groups. QTcF interval increases >450 msec were observed in similar proportions across paltusotine and placebo groups, with no values >500 msec and no QTcF changes >60 msec. However, the number of patients with a change from baseline > 30 msec was higher in paltusotine group (6% vs 2.4%). In the 4MSU cut-off dates, a cumulative total of 26 of 233 (11.2%) participants had worst post-baseline QTcF intervals of >450 msec.

Therefore, while the thresholds of 60 msec increase and above 500-480-450 shift from baseline were similar between groups, there remains an observation of 30 msec increase from baseline in QT that is more frequent in paltusotine group than placebo.

The Applicant provided results from study CRN00808-14, which was designed to specifically assess sufficient multiples (>2-fold) of the high clinical exposure scenario, to support a concentration-QTc analysis). The provided evidence satisfies the regulatory requirements for a valid exposure-response analysis based on modelling. The concentration-QTc analysis using data from CRN00808-14 predicted a placebo-corrected QTcF change from baseline of 1.4 msec (90% upper CI: 2.76 ms) for 80 mg (Cmax: 500.12 ng/mL); 2.8 msec (90% upper CI: 5.50 msec) for 160 mg (Cmax: 996.28 ng/mL), and 3.8 msec (90% upper CI: 7.41 msec) for 240 mg (Cmax: 1341.28 ng/mL), with all values, including the upper CIs, lying below the 10 msec threshold of regulatory concern. Based on a totality of evidence approach, the waiver for a TQT was confirmed, and no further concerns with respect to the proarrhythmic potential of paltusotine at the intended posology were raised.

Information on cardiac electrophysiology was included in section 5.1 of the SmPC as it is in line with the results of the exposure-QTc analysis and similar to other recently approved products, where QT information is presented as descriptive pharmacodynamic data rather than a warning or precaution.

A slightly higher incidence of heart rate reduction (from ≥50 bpm to 40–<50 bpm) was observed in the paltusotine group compared to placebo in study CRN00808-08, particularly on triplicate ECGs, but this was not reproduced in study CRN00808-09 and did not lead to bradycardia <40 bpm.

In addition, most PR interval shifts were small (≤220 msec) and the absence of higher-grade AV block, temporal relationship, or dose dependency, together with the presence of confounding cardiovascular comorbidities, argue against a direct drug effect. The phase 1 data and the lack of mechanistic plausibility further support this conclusion.

However, as minor PR interval prolongation and isolated cases of AV block were observed in treated patients (including elderly participants with cardiovascular risk factors) this potential adverse event was acknowledged in section 4.4 of the SmPC.

Conclusion

The safety profile of paltusotine was well characterized and in line with other SRL treatments. The most common TEAEs (≥10% incidence) by PT were diarrhea, headache, abdominal pain and nausea. However, bradycardia and gallbladder abnormalities are also reported and addressed in the SmPC.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

Table 64 ADRs proposed for inclusion in the SmPC

System organ class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Hyperglycaemia	Common
	Decreased appetite	Common
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
Cardiac disorders	Sinus bradycardia[a]	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Abdominal pain	Common

System organ class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Hyperglycaemia	Common
	Decreased appetite	Common
	Nausea	Common
	Abdominal discomfort	Common
	Abdominal distension	Common
	Vomiting	Common
Hepatobiliary disorders	Cholelithiasis	Common
	Bile duct stone	Uncommon
Skin and subcutaneous tissue disorders	Alopecia	Common
General disorders and administration site conditions	Fatigue	Common

The applicant presented the section 4.8 of the SmPC based on phase 3 clinical trials data.

5.4.11.2. Conclusions on clinical safety

The safety profile of paltusotine for the treatment of acromegaly, based on pooled data from five clinical studies and supported by both primary and supportive analysis populations, is consistent with other SRL therapies. The safety population size and the median follow-up duration of approximately four years are considered acceptable for a rare disease such as acromegaly. Most TEAEs were mild or moderate in severity, and their frequency was comparable between paltusotine and placebo groups. The most reported ADRs were gastrointestinal disorders (e.g., diarrhoea, abdominal pain, nausea), sinus bradycardia, and cholelithiasis, predominantly occurring during the first three months of treatment and rarely leading to discontinuation.

In addition, other ADRs such as decreased appetite, headache, fatigue, abdominal distension and hyperglycaemia frequently observed during clinical trials and listed in the product information of other SRLs, were also reported with paltusotine and are now reflected in the SmPC. Ocular adverse events have been reported in clinical trials, some of which were assessed as related to paltusotine. All ocular TEAEs were nonserious, mostly mild or moderate, and did not lead to treatment discontinuation. Events were reported infrequently and without consistent temporal or clinical pattern, and potential confounding factors (such as age-related conditions or concomitant medications known to cause ocular symptoms). However, given the biological plausibility based on non-clinical observations and the limited clinical dataset, the possibility of a causal relationship cannot be fully excluded. Therefore, this topic will remain under close monitoring in future PSURs, with continued cumulative review of ocular adverse events to confirm the absence of a safety signal over time. In addition, the long-term safety and tolerability of paltusotine will be evaluated in the OLE of the long-term extension study CRN00808-05 (ACROBAT ADVANCE), which is on-going and a category 3 PASS in the RMP.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 65 Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

6.1.2. Discussion on proposed safety specification

The assessment of safety of paltusotine for the medical treatment and long-term maintenance of therapy of acromegaly is based primarily on pooled data from the RC phases of the pivotal phase 3 studies (CRN00808-08 and CRN00808-09), which included 84 participants exposed to paltusotine for up to 36 weeks at doses ranging from 20 mg to 60 mg QD. A pooled analysis of safety data from the 2 phase 3 studies (including data from RC and OLE phases) and 3 phase 2 studies (CRN00808-03, CRN00808-02, and CRN00808-05) was also performed and included 233 participants exposed to paltusotine with a maximum duration of 6 years.

Results of the safety data from these clinical studies demonstrated that paltusotine was generally well tolerated. There were no unexpected risks identified, and the proposed adverse drug reactions are generally mild to moderate with a low rate of treatment discontinuation and are consistent with those observed with approved SRL therapies. Across the acromegaly studies, the incidence of TEAEs generally did not increase with longer exposure to paltusotine. One notable exception was cholelithiasis, which was reported more frequently with >6 to ≤9 months of paltusotine treatment in the Supportive Group. This is consistent with the mechanism that gallbladder sludge and gallstones build up over time leading to symptoms occurring later in treatment which is in line with the effects of approved SRL therapies. Cholelithiasis is an identified risk that is not considered important. No unexpected safety signals were identified with long-term paltusotine treatment.
However, long-term safety data is recognised to be limited for a treatment that is expected to be used as chronic medication and accordingly long-term safety is proposed as missing information. Population in need of further characterisation: the on-going OLE study CRN00808-05 will further characterise long-term safety of paltusotine. The duration of the OLE study is up to 6 years for CRN00808-05.
The applicant did not propose any important identified or potential risks to be addressed in the RMP. This was accepted.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the safety concerns:

None.

Other forms of routine pharmacovigilance activities for the safety concerns:

None.

The applicant has proposed additional pharmacovigilance activities:

Table 66 Planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CRN00808-05 An Open Label, Long-term Extension Study to Evaluate Safety and Efficacy of CRN00808 in Subjects with Acromegaly (ACROBAT ADVANCE) On-going	To evaluate the long-term safety and tolerability of paltusotine in acromegaly subjects; To evaluate the efficacy of paltusotine in acromegaly subjects.	Long-term safety	FPFV: LPLV: Final study report:	26 Feb 2020 Jun 2026 Jan 2027

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The proposed routine pharmacovigilance activities are acceptable.

6.2.2.2. Additional pharmacovigilance activities

The applicant has proposed adding one on-going open label extension study (CRN00808-05) as category 3 PASS in the RMP, which was accepted.

This is an open label, long-term extension study to evaluate the safety and efficacy of CRN00808 in subjects with acromegaly. In studies CRN00808-02 (patients with normal IGF-1 on injectable SRL monotherapy at baseline and responders to octreotide LAR or lanreotide depot) and CRN00808-03 (patients with suboptimal control with injectable SRL octreotide or lanreotide and with or without cabergoline), participants were switched from SRL-based regimens to once-daily paltusotine for the duration of the study, with the option of continuing in OLE study CRN00808-05. Participant enrolment has been completed, and the study is on-going.

During the follow up, the incidence of treatment-emergent AEs (TEAEs) throughout the study will be monitored as a primary endpoint, and the additional safety endpoints are: "Clinical laboratory tests (hematology, serum chemistry, and urinalysis) at each post-baseline study visit", "Vital signs at each post-baseline study visit", "12-lead electrocardiogram (ECG) at each post-baseline study visit", and "Ophthalmic assessments".

The safety data from the Phase 2 studies (2+3+5) show that Paltusotine was generally well tolerated, with no unexpected safety signals from these studies.

The applicant commits to discuss the long-term safety data from the three studies in the PSUR or other relevant procedures studies if relevant safety data is identified, which was agreed.

6.3. Plans for post-authorisation efficacy studies

There are no planned or on-going post-authorisation efficacy studies. This was found to be acceptable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 67 Planned routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Long term safety (missing information)	Routine risk communication: • Information on duration of paltusotine exposure in SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None

The applicant did not propose any additional risk minimisation measures. This was found to be acceptable.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The safety specification and routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation measures are deemed necessary at this stage.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 0.3 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The active substance is not included in the EURD list, and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 25 September 2025. The applicant will use a data lock point (DLP) of 31 August for administrative convenience, to satisfy annual aggregate safety reporting requirements in the United States, EU and other regions.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical trials.

8.1.2. SmPC section 5.1 justification

Information on the pivotal studies supporting the indication is included in the SmPC section 5.1. Besides key findings, some additional secondary endpoints have been included which are considered of clinical relevance to the prescriber.

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.2.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group.

The QRD group agreed on granting the requested translation exemption for the carton and bottle labels of Palsonify, use of two monolingual packaging materials: German only and English only.

However, the QRD group refused the request of the translation exemption for the package leaflet. Therefore, a printed package leaflet should be provided with the medicinal product in every national language. In the case of Norway, Denmark and Poland, a digital version of the package leaflet in their national languages available for patients is acceptable (no need of a printed version for these three countries).

The labelling subject to translation exemption as per the QRD Group decision above will, however, be translated in all languages in the Annexes published with the EPAR on the EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Palsonify (paltusotine) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, therapeutic indication

Acromegaly is a rare, chronic, progressive growth disorder characterised by excessive secretion of growth hormone (GH) and its effector hormone, insulin-like growth factor (IGF)-1. The disorder is usually the result of a GH-producing pituitary adenoma.

Acromegaly most commonly affects middle-aged adults and if left untreated can result in serious illness and premature death. Patients have disproportionate skeletal, tissue, and organ growth. Once recognised, acromegaly is treatable in most patients. If left uncontrolled, acromegaly is associated with multisystem morbidities and increased mortality, predominantly from cardiovascular, cerebrovascular, and respiratory disease.
The pathophysiology starts with hyper-production of GH by the pituitary adenoma. GH (also known as somatotropin) is a peptide hormone synthesised, stored and secreted by the somatotroph cells of the pituitary gland in a pulsatile manner throughout the day. GH exerts its effects by binding to the Growth Hormone Receptor (GHR) on target cells. The GHR is a transmembrane glycoprotein that binds GH in its extracellular domain and induces downstream signalling leading to receptor dimerisation and activation of intra- and intercellular signal transduction pathways, which trigger production and subsequent release of its effector insulin-like growth factor-1 (IGF-1) (either paracellularly or into the bloodstream).

GHR is expressed in many tissues, the most abundant being the liver (primarily hepatocytes) and adipose tissue. The liver is the major site of IGF-1 production. IGF-1, also known as somatomedin C, has growth-stimulating effects on a wide variety of tissues including activity on osteoblasts and chondrocytes to promote bone growth.
The diagnosis of acromegaly is confirmed on the basis of elevated serum insulin-like growth factor 1 (IGF-1) and lack of growth hormone suppression after glucose administration.

According to the last consensus conference (*Giustina et al 2024*), the diagnosis is based on IGF-1 levels >1.3 times the upper limit of normal for age and characteristic clinical signs of disease. The therapeutic efficacy target is IGF-1 normalized for age.

Of note, in the 13th consensus on the multidisciplinary management of acromegaly (*Giustina et al 2020*), although the absolute cut-off for defining biochemical control is the upper limit of normal (ULN) (SR), values slightly higher than this cut-off (e.g., within 1.2– 1.3 × ULN) could be considered as a target of treatment depending on the clinical scenario.

The initially claimed indication was "medical treatment and long-term maintenance therapy of adult patients with acromegaly".

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1 of this document.

According to the Endocrine Society Clinical Practice Guideline (co-sponsored by the Endocrine Society and the European Society of Endocrinology), the clinical aims in the management of acromegaly include the following: (1) to control biochemical indices of activity (principally GH and IGF-I), (2) to control tumour size and prevent local mass effects, (3) to reduce the signs and symptoms of disease, (4) to prevent or improve comorbidities, and (5) to prevent early mortality.

The optimal treatment should provide robust efficacy in controlling IGF-1 levels and minimising acromegaly symptoms from treatment initiation throughout treatment with an acceptable safety profile, with the ultimate objective to improve patient QoL and satisfaction. Unmet needs include optimizing biochemical and symptom control, reducing treatment burden and enhancing QoL. Of note, recurring symptoms and compromised QoL can be also seen in patients that are biochemically controlled.

The existing therapeutic strategy includes transphenoidal surgery (first-line therapy) and/or medical treatment and/or radiotherapy.

Long-acting somatostatin analogues are used as first line pharmacological treatments in patients not cured by surgery/radiotherapy or requiring additional treatment pre- or postoperatively. For patients not cured by surgery or for whom surgery is contra-indicated, somatostatin receptor ligands (SRLs) are established as first–line medical treatment with potential for further improvements and lead to limited disease control with partial response rate of **30-55%** and continued symptoms.

Five injectable SRLs are currently approved for medical treatment of acromegaly in the EU and are administered by daily (up to three times daily [t.i.d.]): octreotide (S.C Sandostatin and monthly IM Sandostatin LAR), monthly lanreotide (Somatuline Autogel), monthly IM pasireotide (Signifor LAR) and monthly SC octreotide hydrochloride (Oczyesa).

Treatment guidelines mention that in case of partial response, adjunctive therapies can be considered in association to SRLs such as dopamine agonists (cabergoline, bromocriptine) which are used off-label. In case of no response, pegvisomant can be considered in monotherapy.

Despite currently available pharmacological therapies, each of the available acromegaly treatments have safety and/or efficacy limitations that directly impact potential use based on route of administration, treatment-limiting AEs, potential off-target effects due to lack of selective somatostatin receptor binding, an inability to titrate quickly for efficacy or safety, delayed treatment effect, return of breakthrough symptoms at the end of the injection cycle, and/or inadequate biochemical and clinical symptom control.

There remains an unmet need for a targeted therapy that reduces the overall treatment burden and combines rapid, consistent, and durable disease control to treat a wide range of the acromegaly patient population that requires medical treatment.

Paltusotine is an orally administered, reversible-covalent, small molecule agonist of human somatostatin receptor 2 (SST2). Paltusotine tablets are available as immediate-release dosage form containing an amorphous spray-dried dispersion (SDD) of paltusotine in a water-soluble polymer, copovidone. The tablets are supplied in 2 strengths, 20 mg and 30 mg and are coated with a water-soluble film.

Acromegaly is caused by excessive growth hormone (GH) secretion and secondary elevation of insulin-like growth factor-1 (IGF-1). Because GH secretion is pulsatile, elevated serum IGF-1 levels are a useful screening tool for acromegaly. IGF-1 levels are an accepted measure of treatment efficacy in acromegaly as well through its activation of the SST2, paltusotine achieves a reduction of GH and IGF-1 levels, which are both elevated in subjects with acromegaly. It also exhibits bias for G-protein activation and subsequent lowering of intracellular cAMP levels compared to β-arrestin activation and subsequent receptor internalization and desensitization.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to the respective section of this document.

The efficacy of paltusotine has been evaluated based on 2 phase 2 dose studies "**CRN00808-03** and **CRN00808-02", a long-term extension of these studies "CRN00808-05**" and 2 phase 3 studies **"CRN00808-08** and **CRN08008-09".**

The pivotal studies are the 2 phase 3 studies **CRN00808-08** and **CRN00808-09.** The 2 phase 2 studies **CRN00808-02** and **CRN00808-03** are only supportive and only provided limited clinical data as regards the choice of dose for the phase 3 studies. The OLE phases of all these studies are still on-going and will provide clinical data on the long-term use of paltusotine.
The phase 3 study **CRN00808-08 "PATHFNDR-2: Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen"** was a multicentre, randomized, double-blind, placebo-controlled study where participants with non-pharmacologically treated acromegaly including participants with no prior medical therapy, participants who last received medical therapy at least 4 months prior to screening, and participants who were controlled on medical therapy for at least 3 months but agreed to wash out prior to beginning study treatment, were randomly allocated to receive either paltusotine or placebo.

Disease characteristics were generally consistent between the paltusotine and placebo groups. Most participants had a screening IGF-1 >1.3×ULN (**83.8%**).

Baseline mean (SD) IGF-1×ULN levels were **1.985** [0.8086] and **2.207** [1.1049] in the Paltusotine and placebo groups respectively.

Study participants overall had a long-standing disease history, with a median of **72.2 months.**

The majority of participants (**89.2%**) had documented prior pituitary surgery; **all participants** in the medically naïve group had documented prior pituitary surgery.

The starting dose of paltusotine in the RC phase was **20 mg QD** (1×20 mg tablet of active paltusotine or matching placebo) for oral self-administration. A dose of 20 mg was selected to minimize potential gastrointestinal side effects in participants washed out from medical therapy or naïve to medical therapy. After confirming tolerability with the participant, **the dose was increased to 40 mg QD** (2×20 mg tablets of active paltusotine or matching placebo) **at the Week 2 visit**.

Dose down-titration was allowed at any time during the RC phase of the study if the dose was not tolerated in the judgement of the investigator.

Overall, **114 participants** enrolled in the OLE phase of study CRN00808-08. At the data snapshot date of 31 August 2025, twenty-two participants overall (19.3%) discontinued the OLE phase of the study.

The phase 3 **study CRN00808-09 (PATHFNDR-1)** was a randomized, placebo-controlled, multicentre study designed to evaluate the efficacy and safety of paltusotine in participants with acromegaly who were switched from monotherapy with injected long-acting octreotide or lanreotide. In the Randomized Controlled (RC) Phase, eligible participants were randomized (1:1 ratio) to daily oral administration of paltusotine or placebo when their next dose of octreotide/lanreotide was due to begin, for a Treatment Period of **up to 36 weeks**.
Participants who completed the RC phase could be eligible to enrol and receive paltusotine in the **Open-label Extension** (OLE) (on-going) Phase **for up to 200 weeks**.
Randomization was stratified by IGF-1 level (<0.86×ULN, ≥0.86×ULN) **and prior treatment** (lanreotide or octreotide).
Study participants overall had long-standing disease prior to enrolment, with a higher mean (SD) duration since acromegaly diagnosis in the paltusotine group compared with the placebo group (**186.6** [88.3] months versus **120.8** [81.9] months). The majority of participants overall (**86.2%**) had prior pituitary surgery.

The starting dose (paltusotine or matching placebo) was **40 mg** QD for oral self-administration. The dose could be increased from **40 mg to 60 mg** QD through Week 24 based on IGF-1 response and tolerability. Participants who required dose up-titration after Week 24 were considered non-responders. Dose levels could be decreased based on tolerability at any time during the study.

Rescue criteria were provided for participants who required resumption of standard acromegaly treatment during the RC Phase.

In the OLE phase of study CRN00808-09, of the 58 participants randomized in this study, 53 participants (91.4%) entered the OLE phase.

9.3. Favourable effects

In the RC phase of study **CRN00808-08**,

1) The study met its primary endpoint "**proportion of participants who achieved biochemical response (IGF-1 level ≤ 1.0×ULN) at EOR**". In the paltusotine group, this proportion is (30 of 54 [**55.6%**]) compared to those in the placebo group (3 of 57 [**5.3%**]) (**p<0.0001**).

Sensitivity analyses were performed in different stratum of the target population. These results were consistent with the results of the primary endpoint and assess the robustness and consistence of the primary with the primary efficacy endpoint results.
2) Regarding the Key secondary endpoint "**LS means (±SE) change from Baseline to EOT in IGF-1×ULN"** were **-0.819** (±0.0789) for the paltusotine group and **0.087** (±0.0751) for the placebo group, with a treatment difference of **-0.906** (95% CI: -1.106, -0.706) (**p<0.0001**).

Sensitivity Analyses of Key Secondary Endpoint were performed by Stratum and confirmed the robustness and consistence of the results of the key secondary endpoint.
3) Other secondary endpoints favoured paltusotine compared to placebo. The sensitivity analyses performed in different stratum of the target population were consistent with the results of the secondary endpoints and assess the robustness and consistence of the efficacy secondary endpoint results.

- The "proportion of participants who achieved biochemical response IGF-1 level <1.3×ULN" was **66.7%** (36 of 54) in the paltusotine group compared with **14.0%** (8 of 57) in the placebo group (**p<0.0001**).
A Sensitivity Analysis "Proportion of Participants with IGF-1 <1.3×ULN at EOR" was performed by IRT Stratification Factor and has confirmed the results.

- The proportion of participants who achieved GH level <1.0 ng/mL was **57.4%** (31 of 54) in the paltusotine group compared with **17.5%** (10 of 57) in the placebo group (**p<0.0001**).

A Sensitivity Analysis "Proportion of Participants with GH<1.0 ng/mL at Week 22" was performed by Stratification Factor and has confirmed the results.
- The LS means (±SE) change from Baseline to EOT in total ASD score were **-2.669** (±1.4221) for the paltusotine group and **2.754** (±1.3641) for the placebo group, indicating an improvement and stabilization of symptoms for the paltusotine group, and worsening of symptoms for the placebo group. This difference of **-5.423** (95% CI: -9.070, -1.776) was statistically significant (**p=0.0039**).
A Sensitivity Analysis "Change from Baseline to EOR in Total ASD Score" was performed by IRT Stratification Factor and has confirmed the findings.

4) Regarding the main exploratory endpoints, they all favoured paltusotine compared to placebo.

. The proportion of participants who received rescue therapy was **3.7%** (2 of 54) in the paltusotine group and **22.8%** (13 of 57) in the placebo group affirming the treatment effect of paltusotine versus placebo.
. Regarding the exploratory PROs endpoints, results from the Treatment Preference Questionnaire at Week 24 indicated that **77.8%** (42 of 54) of participants in the paltusotine group and **63.2%** (36 of 57) of participants in the placebo group preferred oral medication over previous injections for acromegaly.

The **OLE phase** of study **CRN00808-08 (data snapshot date: 31 August 2025)** has provided reassuring results, in line with the findings of the RC part. For example, the proportion of participants who achieved IGF-1 level ⩽1.0×ULN ranged from 51.3% to 100% from Week 36 to Week 144 for the overall population (51.0% to 100% for the prior paltusotine group and 37.0% to 100% for the prior placebo group) and ranged from 50.0% to 80.0% for the directly enrolled group from Week 36 to Week 120. For a full description of the OLE results, please check the clinical efficacy section of this report.

In the RC phase of study **CRN00808-09**,

1) Primary endpoint: "**proportion of patients with IGF-1 level ≤ 1.0×ULN at EOR"**
The study met statistical significance (**p<0.0001**) based on the proportion of participants in the paltusotine group (25 of 30 [**83.3%])** who maintained biochemical response (IGF-1 level ⩽ 1.0×ULN) **at EOR** compared to those in the placebo group (1 of 28 [**3.6%]).**

2) Significant differences in favour of paltusotine were observed for all secondary efficacy endpoints:
- The LS means (±SE) for the change from Baseline **to EOT** in IGF-1×ULN were **0.042** (±0.093) for the paltusotine group and **0.833** (±0.096) for the placebo group, with a treatment difference of **-0.791** (95% CI: -1.057 to -0.525) (**p<0.0001**).

- The proportion of participants who maintained **GH level <1.0 ng/mL**, out of those who had GH level <1.0 ng/mL at Baseline at Week 34, was **87.0%** (20 of 23) in the paltusotine group compared with **27.8%** (5 of 18) in the placebo group (**p=0.0003**).

- The LS means (±SE) for the **change from Baseline to EOT in total ASD score** were **-0.606** (±1.504) for the paltusotine group and **4.588** (±1.593) for the placebo group, indicating stabilization of symptoms for the paltusotine group and worsening of symptoms for the placebo group, with a treatment difference of **-5.164** (95% CI: -9.536 to -0.792) (**p=0.0216**).
No single ASD item predominantly affected the overall total ASD score, indicating that there was improvement and stabilization across all acromegaly symptoms evaluated in the paltusotine group compared with the placebo group.

3) Results of pre-specified sensitivity analyses to assess the robustness of the primary and secondary efficacy analyses were consistent with the primary and secondary efficacy endpoint results.

As regards the secondary endpoints,

- A sensitivity analysis was performed using a multiple imputation approach for missing data for the secondary efficacy endpoint of change from Baseline to EOR in IGF-1×ULN. In this analysis, IGF-1 results for all assessments following the first occurrence of intercurrent events, such as dropouts, taking rescue therapy or prohibited medications, or up titration in dose after Week 36, were evaluated as missing data.

For this analysis, the LS means (±SE) for the change from Baseline to Week 36 in IGF-1×ULN were **0.045** (±0.108) for the paltusotine group and **0.767** (±0.316) for the placebo group, with a treatment difference of **-0.722** (95% CI: -1.373 to -0.071; nominal **p=0.0301**).

- In addition, missing data on IGF-1×ULN were imputed using a multiple imputation procedure that utilized all observed data from both treatment groups to overcome the convergence issue.

For this analysis, the LS means (±SE) for the change from Baseline to Week 36 in IGF-1×ULN were **0.041** (±0.089) for the paltusotine group and **0.783** (±0.120) for the placebo group, with a treatment difference of **-0.742** (95% CI: -1.032 to -0.453; nominal **p<0.0001**).

4) Results of multiple exploratory endpoint analyses also favoured paltusotine.

- The proportion of participants who received rescue therapy at EOR was **6.7%** (2 of 30) in the paltusotine group and **60.7%** (17 of 28) in the placebo group (nominal **p<0.0001**), affirming the treatment effect of paltusotine versus placebo.
The **OLE phase** of study **CRN00808-09** (**data snapshot date of 31 August 2025**) has provided reassuring results, in line with the findings of the RC part. For example, the proportion of participants

who achieved IGF-1 level ≤1.0×ULN ranged from 74.5% to 93.3% from Week 48 to Week 180 for the overall population (50.0% to 96.0% for the prior paltusotine group and 77.3% to 100% for the prior placebo group). (Note: Only 1 participant reached the timepoints for Week 192 and Week 204 at the time of the data snapshot.). For a full description of the OLE results, please check the clinical efficacy section of this report.

9.3.1. Uncertainties and limitations about favourable effects

In the pivotal study **CRN00808-08**, the efficacy of paltusotine at the maximal dose of 60 mg/day seems limited especially in medically naïve patients. In patients with high IGF-1 levels (>1.7 xULN) (medically naïve, uncontrolled, more severe disease) at baseline, the normalisation of IGF-1 is questionable as the efficacy of paltusotine in these patients was lower (about 32%) compared to the whole population Therefore, the efficacy of paltusotine in these patients is lower. This is consistent with the fact that based on an ER analysis, at doses of paltusotine up to 60 mg, the maximal reduction of the IGF-1 levels is 47%.
The applicant provided a plot showing the simulations of post-treatment IGF-1 based on varying levels of baseline IGF-1 for a QD dose of 60 mg and concluded that a dose of 60 mg is expected to provide IGF-1 levels ⩽1.0xULN across a broad range of baseline IGF-1 levels (>1.7xULN to 4.0xULN). However, such conclusion can only be agreed for IGF-1 levels at baseline < 2.5x ULN and by considering an IMAX effect of 57%. Therefore, the applicant was asked to compute for each Baseline IGF-1(xULN) of 2.0, 2.5, …, 5.0, the proportion of subjects who are expected to achieve Post-treatment IGF-1(xULN) of 0.5-<1, 1-<1.5, 1.5-<2, 2-above, and to thoroughly discuss the results.

The results of the simulation clearly demonstrate that the probability of achieving IGF-1 normalisation (≤ 1xULN) or near-normalisation (≤ 1.3xULN) markedly decreases with elevated baseline IGF-1 levels.

For baseline IGF-1 of 2.5xULN, **12.8%** are predicted to achieve normalisation and less than **40.1%** near-normalisation. For baseline IGF-1 of 3xULN, **~6%** are predicted to achieve normalisation and less than **23.2%** near-normalisation.

Based on observed (vs predicted) values from the 40 medically naïve patients enrolled in study CRN00808-08 with a mean IGF-1 of 2.2xULN at baseline, **42.5%** (vs 45%) achieved a normalisation, less than **25%** (vs 22.5%) achieved near-normalisation and **32.5%** (vs 32.5%) had IGF-1 levels over > 1.5 xULN. More precisely, a near normalisation of IGF-1 <1.3xULN is achieved in **55%** of the 40 naïve patients. These results highlight that the achievement of IGF-1 normalisation or near normalisation is dependent on the IGF-1 levels at baseline and that a 60 mg QD dose cannot achieve IGF-1 normalisation (or near-normalisation) across a broad range of baseline IGF-1 values.

This was consistent with the E-R analysis which showed that paltusotine doses of 20 mg, 40 mg, and 60 mg corresponded to IGF-1 level reductions of approximately 37%, 43%, and **47%**, respectively.

In study CRN00808-08, the baseline IGF-1 decreased from 0.8 to 1xULN up to 24 weeks. However, in the medically naïve patients with a baseline IGF-1 >2.5xULN, a normalisation or a near normalisation of IGF-1 cannot be achieved.

Thus, uncertainties related to the efficacy of paltusotine in patients with high IGF-1 levels (i.e≥ 2.5 ULN) still remain especially for the medically naïve patients given that IGF-1 levels reduction is 47% at the maximal dose of paltusotine 60 mg/day. Some of these patients will need a longer duration of treatment and/or will need adjunctive therapies to achieve the normalization of their IGF-1 levels and some of them will never normalize their IGF-1 levels. This has been reflected in section 4.2 of the SmPC.

Although the withdrawal of patients was higher among the medically naïve participants, there was a majority of participants in the OLE Phase of Study CRN00808-08, with approximately 80% of participants overall and 68% of medically naïve participants with durable and sustained clinical benefits of paltusotine.

This was consistent with the results of other SRL treatments of acromegaly indicated in medically naïve patients. Indeed, the rates of discontinuation due to treatment failure in the literature were 17.9% for oral octreotide (*Samson 2020*).

Another point is the need of adjunctive therapies in the OLE phase of study CRN00808-08 and in study CRN00808-09. Concomitant administration of adjunctive therapies was only possible in the OLE phase of study CRN00808-08 from W48 and from W60 in study CRN00808-09. Thus, it is difficult to interpret the long-term results, and to determine to what extent the observed increase of the proportion of medically naïve patients with IGF-1 levels ≤ULN during the OLE phase can be attributed solely to the effect of paltusotine as monotherapy.

At the data snapshot date of 21 May 2025, the use of adjunctive therapies was limited and did not lead to a significant increase of the proportion of patients with IGF-1 levels ⩽ULN nor a significant increase of the proportion of patients with IGF-1 levels < 1.3x ULN. This can show that the addition of adjunctive therapies did not have at this stage an impact on the long-term efficacy results of paltusotine.

9.4. Unfavourable effects

The patient exposure in the clinical trials with the indication of treatment of acromegaly is considered of sufficient size to enable safety assessment. The length of the follow-up was considered sufficient for acromegaly indication (approximately 4 years).

In the primary group, 84 patients received at least one dose of paltusotine (54 from study CRN00808-08 and 30 from study CRN00808-09). Among them, 3 patients received a dose of 20 mg QD, 29 received a dose of 40 mg QD and 52 received a dose of 60 mg QD which is the final dose. The mean duration in study CRN00808-08 RC was 24 weeks in both paltusotine and placebo groups. While, in study CRN00808-09 RC the median duration of exposure was 36 weeks in the paltusotine group and 22.1 weeks in the placebo group.

By dose, the median duration of exposure to 20 mg was 14 days for both the paltusotine and placebo groups, to 40 mg was 62 days and 29 days in the paltusotine and placebo groups, respectively, and to 60 mg was 126 days for both the paltusotine and placebo groups.

In the supportive group, a total of 233 patients received at least one dose of paltusotine. A total of 12.0%, 18.9%, 40.3%, 13.3%, and 15.5% of participants received >0 to ≤6 months, >6 months to ≤12 months, >12 to ≤24 months, >24 to ≤36 months, and >36 months of paltusotine treatment, respectively.- In the primary analysis group, TEAEs were reported at similar rates in the paltusotine and placebo groups (86.9% vs. 90.6%, respectively). The majority of TEAEs were mild or moderate. Severe TEAEs were reported in 2 out of 84 participants (2.4%) in the paltusotine group, both occurring in study CRN00808-08 (headache and pain in extremity), compared to 8 out of 85 participants (9.4%) in the placebo group.

- Treatment-related TEAEs were more frequently observed in the paltusotine group (45.2%) compared to placebo (22.4%).

- No SAEs were reported in the paltusotine group. In contrast, two SAEs occurred in the placebo group (benign parathyroid tumour and cholecystitis).

- In the Primary Group, treatment-related TEAEs were reported more frequently in the paltusotine group (38 of 84 participants, 45.2%) compared with the placebo group (19 of 85 participants, 22.4%).

- The most frequently reported TEAEs and related-TEAEs by were:

Gastrointestinal disorders: ADRs of diarrhoea (n=20, 23.8%), abdominal pain (n=9, 10.7%), and nausea (n=7, 8.3%). The GI events were predominately mild in severity, the majority of events of diarrhoea and nausea occurred in the first 14 days. In the Primary Group, there was 1 study drug discontinuation due to nausea in Study CRN00808-08, in the paltusotine group. Furthermore, 1 participant in study CRN00808-08 (previously treated group) had mild TEAEs of diarrhoea and abdominal pain on the 60 mg dose, requiring dose reduction to 40 mg and then to 20 mg. These events are well-known ADRs to SRLs therapies and are listed in the product information.

Bradycardia: Paltusotine is associated with a reduction in heart rate consistent with other SRL treatments. There was an increased rate of sinus bradycardia/bradycardia TEAEs in the paltusotine group (4 participants with at least 1 TEAE of sinus bradycardia and 1 participant with a TEAE of bradycardia) vs 0 in the placebo group. Related sinus bradycardia/bradycardia were reported at 3.6% (3 cases) and 1.2% (1 case) respectively in the paltusotine group. The TEAEs were all non-serious, and the participants were asymptomatic. Of the 5 events, 4 were of mild severity and 1 was moderate. There were no severe events of bradycardia. In all 5 participants, the first events of bradycardia occurred in the first 3 months of treatment. No participants discontinued paltusotine because of bradycardia. This event is listed as "common" ADR in the product information.

Cholelithiasis: in acromegaly studies, cholelithiasis appears to be causally related to paltusotine treatment, consistent with known effects of other SRLs. This is supported by ultrasound findings, delayed onset of events, no imbalance in risk factors, and a higher incidence of biliary TEAEs in treatment-naïve patients compared to those previously treated in the Primary Group. Overall, there was a similar incidence of TEAEs of cholelithiasis between paltusotine (n=2, 2.4%) and placebo (n=3, 3.5%) treatment groups. The two cases in the paltusotine group were related (2.4%). The 2 events on paltusotine both occurred in participants who had received a maximum dose of 60 mg, and who were in the medically naïve group. In the OLE of Phase 3 studies, there were a total of 7 participants with biliary-related TEAEs. Cholelithiasis is listed as "common" ADR in the product information.

Hyperglycaemia: the incidence of hyperglycaemia was higher in the paltusotine group compared to the placebo group 4.8% (n=4) vs. 2.4% (n=2) respectively. From a pharmacological perspective, paltusotine inhibits growth hormone, glucagon, and insulin, which may impact glucose homeostasis. Therefore, this adverse effect was listed in the product information.

9.4.1. Uncertainties and limitations about unfavourable effects

Ocular AEs will be closely monitored in future PSURs, with continued cumulative review of ocular adverse events to confirm the absence of a safety signal over time.

Given the occurrence of ALT/AST elevations >3×ULN and the potential class-related hepatic effects, continued monitoring of liver enzyme abnormalities is considered warranted. The applicant has agreed to provide a specific and cumulative analysis of hepatic safety (liver enzymes abnormalities) data in future PSURs.

9.5. Effects table

Table 68 Effects Table for Palsonify in the medical treatment and long-term maintenance therapy of adults with acromegaly compared to placebo data cut-off: 20/01/2024 (CRN00808-08), 5/12/2023 (CRN00808-09)

Effect (short description)	*paltusotine*	*Placebo*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects				
RC phase **Primary endpoint**: Proportion of participants who achieved biochemical response (IGF-1 level ≤ 1.0×ULN) at EOR (%)	**30/54 (55.6)** 20 mg: 1/3= 33.3 40 mg : 13/15= 86.7 60 mg: 16/36 = 44.4	**3/57 (5.3)**	Odds ratio (Paltusotine/placebo) 42.806 Inc: IC 95% (8.444; 455.621) ***p<0.0001*** **SOE: sensitivity analyses** ***. Sensitivity analysis* #1:** 30/50 (60) vs 3/41 (7.3) **p< 0.0001** . **Sensitivity Analysis #2** 30/52 (57.7) vs 3/53 (5.7) **p< 0.0001** . **Sensitivity Analysis #3 :** 30/54 (55.6) vs 3/57 (5.3) **p< 0.0001** . **Sensitivity Analysis #4:** **- stratum 1**: . Medically naïve or previously treated: 17/40 (42.5) vs 1/42 (2.4) **p< 0.0001** . Medically-naïve: 5/22 (22.7) vs 1/24 (4.2) **p= 0.1509** . Previously treated: 12/18 (66.7) vs 0/18 (0) **p< 0.0001** **- Stratum 2 :** Washout: 13/14 (92.9) vs 2/15 (13.3) **p< 0.0001**	**CRN00808-08**
RC phase **Key secondary endpoint** "LS means (±SE) change from Baseline to EOT in IGF-1×ULN"	**-0.819** (±0.0789)	**0.087** (±0.0751)	***≠ -0.906*** **Inc:** *(95% CI: -1.106, -0.706) (**p<0.0001**).* **SOE: Sensitivity Analyses by stratum** - **Stratum 1**: -0.887 (±0.0903) vs 0.070 (± 0.0881): ≠ -0.957 (95% CI: -1.210, -0.705) (**p<0.0001**). - **Stratum 2** : -0.600 (±0.1044) vs 0.152 (±0.1008) : ≠-0.752 (95% CI: -1.052, -0.453) **(p<0.0001**). - **Within stratum 1** : . Medically naive: -0.829 vs 0.046 ≠-0.875 (95% CI: -1.254, -0.495): (**p<0.0001**). . Previously treated: -0.964 vs 0.108 ≠-1.072 (95% CI: -1.408, -0.736) (**p<0.0001**)	**CRN00808-08**

Effect (short description)	*paltusotine*	*Placebo*	*Uncertainties/ Strength of evidence*	*Ref*
RC **Secondary endpoint** "Proportion of participants who achieved biochemical response IGF-1 level <1.3×ULN" (%)	**36/54 (66.7)** 20 mg: 2/3 (66.7) 40 mg: 14/15 (93.3) 60 mg: 15/36 (58.3)	**8/57 (14)**	Odds ratio (paltusotine/placebo): 18.319 **Inc:** CI 95% (5.637, 79.156) **p< 0.0001** **SOE:** Sensitivity Analyses by IRT stratification factor: **- stratum 1**: 22/40 (55) vs 4/52(9.5) **p<0.0001** **- stratum 2**: 14/14 (100) vs 4/15 (26.7) **p<0.0001** **- within stratum 1:** . Medically naive: 5/22 (36.4) vs 2/24 (8.3) **p = 0.495** **.** Previously treated: 14/18 (77.8) vs 2/18 (11.1), **p<0.0001**	**CRN00808-08**
RC **Secondary endpoint** "Participants who achieved GH level <1.0 ng/mL at W22" (%)	**31/54 (52.5)**	**10/57 (17.5)**	Odds ratio (Paltusotine/placebo): 7.588 **Inc**: CI 95% (2.776, 23.483) **p< 0.0001** **SOE:** Sensitivity Analyses by IRT stratification factor: **- stratum 1**: 21/40 (52.5) vs 3/42 (7.1) **p<0.0001** **- stratum 2**: 10/14 (71.4) vs 7/15 (46.7) **p = 0.3297** **- within stratum 1:** . Medically naive: 8/22 (36.4) vs 1/24 (4.2) **p= 0.0148** **.** Previously treated: 13/18 (72.2) vs 2/18 (11.1) **p= 0.0005**	**CRN00808-08**
RC **Secondary endpoint** "LS mean Change from Baseline to EOR in Total ASD Score"	**-2.669** (±1.4221)	**2.754** (±1.3641)	≠ **-5.423** **Inc:** (95% CI: -9.070, -1.776) (**p=0.0039**) **SOE:** Sensitivity Analyses by IRT stratification factor: **- stratum 1**: -4.187 (±1.6047) vs 0.163 (±1.5647): ≠-4.349 (95% CI: -8.831, -0.132) **p=0.0570**). - **stratum 2**: -1.610 (±2.2087) vs 5.777 (±2.0544): ≠-7.387 (95% CI: -13.638, -1.137) (**p=0.0224**). **- within stratum 1:** . Medically naive:≠ -5.858 (95% CI: -11.336, -0.380) **p =0.0367** **.** Previously treated:≠ -1.963(95% CI: -9.444, 5.518) **p=0.5967**	**CRN00808-08**
RC **Primary endpoint**: "Proportion of patients with IGF-1 IGF-1 level ⩽ 1.0×ULN at EOR" (%)	**25/30** (**83.3**)	**1/28** (**3.6**)	**Odds ratio (Paltusotine/placebo):** 126.526 **Inc:** CI 95% (13.733, > 999.999) **p<0.0001** **SOE:** Sensitivity analyses **.** ***Sensitivity analysis* #1:** 25/28 (89.3) vs 1/11 (9.1), **p< 0.0001** **.** ***Sensitivity analysis* #2:** 25/30 (83.3) vs 1/27 (3.7), **p< 0.0001** **.** ***Sensitivity analysis* #3:** 25/30 (83.3) vs 1/28 (3.6), **p< 0.0001**	**CRN00808-09**

Effect (short description)	*paltusotine*	*Placebo*	*Uncertainties/ Strength of evidence*	*Ref*
RC **Secondary endpoint** "LS mean Change from Baseline to EOR in IGF-1×ULN"	**0.042** (±0.093)	**0.833** (±0.096)	**≠ -0.791** **Inc**: (95% CI: -1.057 to -0.525), **p<0.0001** **SOE: Sensitivity analysis** **-** Multiple imputation for missing data: 0.045 vs 0.767 : ≠ -0.722 (-1.373, -0.071), **p = 0.0301** **-** Multiple imputation using all observed values: 0.041 vs 0.783: ≠ -0.742 (-1.032, -0.453), **p < 0.0001**	**CRN00808-09**
RC **Secondary endpoint** "Proportion of participants who maintained GH level <1.0 ng/mL at W34" (%)	**20/23** (**87**)	**5/18** (**27.8**)	**Odds ratio (Paltusotine/placebo):** 16.609 **Inc:** CI 95% (2.864, 181.355), **p = 0.0003**	**CRN00808-09**
RC **Secondary endpoint** "LS means (±SE) for the change from Baseline to EOT in total ASD score"	**-0.606** (±1.504)	**4.588** (±1.593)	**≠-5.164** **Inc:** (95% CI: -9.536 to -0.792) (**p=0.0216**)	**CRN00808-09**
Unfavourable effects				
Diarrhoea	23.8%	5.9%	Consistent with the known safety of SRLs, listed as very common ADR in the PI	(1)
Abdominal pain	10.7%	0	Consistent with the known safety of SRLs, listed as very common ADR in the PI	(1)
Nausea	8.3%	2.4%	Consistent with the known safety of SRLs, listed as very common ADR in the PI	(1)
Sinus bradycardia	3.6%	0	Consistent with the known safety of SRLs, listed as common ADR in the PI	(1)
Cholelithiasis	2.4%	1.2%	Consistent with the known safety of SRLs, listed as common ADR in the PI	(1)

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; <sBA: serum bile acids>; <PELD: paediatric end-stage liver disease>; <MELD: model for end-stage liver disease score>; <SBD: surgical biliary diversion>; <OLT: orthotopic liver transplantation>; <PE: primary endpoint>; <SE: secondary endpoint>; <OR: odds ratio>.

(1): Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Primary Group Safety Population

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The efficacy of paltusotine was demonstrated in the 2 pivotal phase 3 studies **CRN00808-08** and **CRN00808-09**. The results of the primary endpoints, secondary and exploratory endpoints are in favour of paltusotine compared to placebo. Results of pre-specified sensitivity analyses to assess the robustness of the primary and secondary efficacy analyses were consistent with the primary and secondary efficacy endpoint results.

However, in study **CRN00808-08**, the efficacy of paltusotine was mainly driven by the high effect size of paltusotine in the washout subgroup of patients. Indeed, the proportion of patients with IGF-1 level ≤1.0×ULN was **92.9%** (13 of 14) in the paltusotine group versus 13.3% in the placebo group. However, the efficacy of paltusotine in the whole population may be overestimated as these patients were already controlled by other SRLs and thus more susceptible to respond to paltusotine.

Although the effect of paltusotine was overall demonstrated in this study as regards to the primary, secondary and exploratory endpoints, there were some uncertainties related to the efficacy of paltusotine especially in medically naïve patients.

In the 2 phase 2 studies **CRN00808-02** and **CRN00808-03**, used for phase 3 dose selection, there were no medically naïve patients. The choice of dose for these patients for the phase 3 program is not based on the clinical data of these phase 2 studies.

As regards of the primary endpoint "proportion of patients with IGF-1 IGF-1 level ≤ 1.0×ULN at EOR" in study **CRN00808-08**, looking at the sensitivity results within the stratum 1, the effect of paltusotine on the primary endpoint in "medically naïve" patients was **22.7%** (5/22) of responder versus **4.2%** (1/24) in the placebo group (p = 0.1509). This highlights a lower IGF-1 response observed in this subgroup compared to previously treated patients (% of responders in the Palsonify group and in the Placebo group respectively: **66.7%** (12/18) versus 0% in group 2 "already treated patients", and **92.9%** (13/14) versus **13.3%** (2/15) in group 3 stratum 2 "washout patients".
The sensitivity analysis of the primary endpoint did not show a clear difference between paltusotine and placebo within Stratum 1 in medically naïve patients. This finding was considered credible given the biological and mechanistic plausibility of a reduced treatment effect in this population. Since this important subgroup (medically naïve patients) is included in the proposed indication and given that it was the only subgroup with limited effect (and not statistically significant) the Applicant was asked to substantiate the benefit/risk balance in medically naïve patients to be included in the indication.

The applicant adequately justified the lower efficacy of paltusotine in the medically naïve patients. Indeed, the proportion of medically naïve participants with IGF-1 ⩽ULN at the end of RC phase was consistent with the literature (*Katznelson 2014, Colao 2016*). This proportion increased overtime based on the non-controlled longer-term results of the OLE Phase. This suggests that these patients may need a longer duration of treatment to normalize their IGF-1 levels especially participants with high IGF-1 levels at baseline also in line with the literature (*Marques-Pamies 2024*).

As regards the efficacy of paltusotine for the maintenance of treatment in already well controlled patients with other SRLs investigated in study **CRN00808-09**, the efficacy was well demonstrated as regards primary, secondary and exploratory endpoints. Thus, the broad indication proposed by the applicant has been approved for medical treatment of adult patients with acromegaly which includes initiation and maintenance of treatment in adult patients with acromegaly.

The applicant initially recommended a posology of 40 mg/day for initiation for all the patients (medically naïve and non-medically naïve) with an increase to 60 mg/ day after 2 to 4 weeks on Palsonify 40 mg once daily, based on insulin-like growth factor-1 (IGF-1) levels or clinical signs and symptoms. As the starting dose of 40 mg/day has not been investigated in medically naïve patients and given the risk of adverse events especially serious gastro-intestinal adverse events, the posology recommendations were adapted accordingly for the medically naïve patients.

In both phase 3 studies, at the end of the RC phase, most of the patients were treated with paltusotine 60 mg. This proportion was 66.7% in **CRN00808-08** [18 naïve/22, 9 uncontrolled/18 and 9/14 washout]).

Of note, among the medically naive patients, **81.8%** patients were treated with paltusotine 60 mg**.** This is consistent with higher IGF-1 levels at baseline.

In study **CRN00808-09**, this proportion was **53%** at the end of the RC phase.

Overall, the long-term efficacy results of the OLE phase of study CRN00808-08 and E-R analyses support paltusotine 60 mg QD as the maximum therapeutic dose. In the E-R analysis, based on a population maximum IGF-1 level reductions of 57%, paltusotine doses of 20 mg, 40 mg, and 60 mg corresponded to IGF-1 level reductions of approximately 37%, 43%, and 47%, respectively, while 80 mg would result in 49% reduction in IGF-. Thus, dose increases beyond 60 mg QD would have been not relevant, as providing only marginal decreases in IGF-1 levels. These results highlight that the achievement of IGF-1 normalisation or near normalisation is dependent of IGF-1 baseline and a 60 mg QD dose cannot achieve IGF-1 normalisation (or near-normalisation) across a broad range of baseline IGF-1 values. This is consistent with the E-R analysis which showed that paltusotine doses of 20 mg, 40 mg, and 60 mg corresponded to IGF-1 level reductions of approximately 37%, 43%, and **47%**, respectively.

Thus, based on all the updated clinical data of the OLE phase and on literature, the benefit-risk of paltusotine is considered positive in medically naïve patients in study CRN00808-08 at the dose regimen proposed in this study. But given that uncertainties on the possibility of patients with high IGF-1 levels at baseline (i.e $\geqslant$ 2.5xULN) including the medically naïve patients to normalise their IGF-1 levels, even at the 60 mg QD dose in monotherapy still remain, section 4.2 of the SmPC has been amended to mention that monitoring of IGF-1 levels and assessment of symptoms should be made periodically per the clinician's discretion and that normalization of IGF-1 levels may require a longer treatment duration in patients with high IGF-1 levels at baseline.

Although the withdrawal of patients was higher among the medically naïve participants, there was a majority of participants in the OLE phase of study CRN00808-08, with approximately 80% of participants overall and 68% of medically naïve participants with durable and sustained clinical benefits of paltusotine.

This is consistent with the results of other SRL treatments of acromegaly indicated in medically naïve patients. Indeed, the rates of discontinuation due to treatment failure in the literature were 17.9% for oral octreotide (*Samson 2020*).

Another point is the need of adjunctive therapies in the OLE phase of study CRN00808-08 and in study CRN00808-09, which makes it difficult to interpret the long-term results, and in which extent the increase of the proportion of medically naïve patients with IGF-1 levels ≤ULN over the OLE phase is only related to the effect of paltusotine as monotherapy. As the need for adjunctive therapies is currently limited, there is no impact on the proportion of patients who achieved normalization of their IGF-1 levels.

The safety profile of paltusotine for the treatment of acromegaly, based on pooled data from five clinical studies and supported by both primary and supportive analysis populations, appears consistent with other SRL therapies. The safety population size (84 in the primary group and 233 in the supportive group) and the median follow-up duration of approximately four years are considered acceptable for a rare disease such as acromegaly.

Most TEAEs were mild or moderate in severity, and their frequency was comparable between paltusotine and placebo groups. The most frequently reported related TEAEs by SOC were gastrointestinal disorders, followed by metabolism and nutrition disorders, cardiac disorders, musculoskeletal and connective tissue disorders, nervous system disorders, hepatobiliary disorders, and investigations. Section 4.8 of the SmPC was aligned appropriately.

Ocular adverse events have been reported in clinical trials, some of which were assessed as related to paltusotine. All ocular TEAEs were nonserious, mostly mild or moderate, and did not lead to treatment discontinuation. Events were reported infrequently and without consistent temporal or clinical pattern, and potential confounding factors (such as age-related conditions or concomitant medications known to cause ocular symptoms). However, given the biological plausibility based on nonclinical observations and

the limited clinical dataset, the possibility of a causal relationship cannot be fully excluded. Therefore, this topic will remain under close monitoring in future PSURs, with continued cumulative review of ocular adverse events to confirm the absence of a safety signal over time.
In addition, the long-term safety and tolerability of paltusotine will be evaluated in the OLE of the long-term extension study CRN00808-05 (ACROBAT ADVANCE), which is on-going and a category 3 PASS in the RMP.

9.6.2. Balance of benefits and risks

The efficacy of paltusotine was demonstrated in the 2 pivotal phase 3 studies **CRN00808-08** and **CRN00808-09** at the dose regimen investigated in these pivotal studies. Paltusotine was able to achieve and maintain normal IGF-1 levels in most patients. An advantage of paltusotine is its oral administration, that could improve patient's compliance to treatment and reduce discomfort due to long-term treatment with injections.

However, the efficacy of paltusotine is lower in patients with high IGF-1 levels (i.e ≥ 2.5x ULN) at baseline including the medically naïve patients, and the efficacy of paltusotine at doses up to 60 mg/day in monotherapy is still questionable for these patients. This has been reflected in section 4.2 of the SmPC for the prescribers of this new medicine.

The safety profile of paltusotine in acromegaly, based on pooled data from five clinical studies with adequate follow-up and population size for a rare disease, is overall consistent with other SRL therapies. Most TEAEs were mild or moderate, with similar frequency between paltusotine and placebo. Gastrointestinal disorders were the most common ADRs, followed by sinus bradycardia and cholelithiasis, primarily occurring early in treatment.
Based on the results, from a clinical point of view, the benefit/risk balance of paltusotine in the following indication is positive. That is why the final indication reads:

"Palsonify is indicated for the medical treatment of adult patients with acromegaly."

9.6.3. Additional considerations on the benefit-risk balance

Input has been received from a healthcare professionals' organisation, **European Society of Endocrinology (ESE)**. No new insight was provided since the points raised were already well understood in the current scientific literature and guidelines. The following points were mentioned by the ESE in the beginning of the procedure and considered during the assessment:
- medical therapy in patients in acromegaly is needed for patients who cannot undergo surgery or cannot be cured by surgery. The main drug classes used in the clinical practice in Europe nowadays are injectable somatostatin analogues and the growth hormone antagonist pegvisomant. To date, there is no approved oral acromegaly therapy available in the European market.
- treatment duration: in patients who are not cured by surgery or who cannot obtain surgery, acromegaly treatment is needed lifelong. In patients, who receive radiotherapy, and can be cured by radiotherapy, the medical treatment may be only needed till the radiotherapy reaches the maximal effects (up to a few years).
- new drugs are needed for use in patients who cannot tolerate other drugs because of side effects. Some patients remain refractory to the currently available drugs. In addition, an oral drug is expected to improve patients' compliance and satisfaction.
- the lack of oral therapies accounts among the unmet clinical needs in patients with acromegaly. Other unmet clinical needs are: 1) late diagnosis, patients leave for years with the disease prior to being

diagnosed and this has a severe impact on comorbidities lifelong; 2) the limited success of neurosurgical techniques (surgery, radiotherapy) in some cases, especially in big tumours with extrasellar extension; 3) Inability to localise and neurosurgical treat the tumour in some cases with persistent disease, which then need lifelong medical therapy; 4) The reduced quality of life in patients with acromegaly, even when IGF1 gets normal under specific medical therapy.

Feedback was also received from a patient organization, namely **Dutch Pituitary Foundation**, and has been taken into account; the points are summarised below:

- current medication is painful to administer, and it requires a HCP to give the injection. Patients are unable to administer the injection by themselves. Also, patients complain about the hardened injection spot.
- the wear-off effect is considered a big problem; a number of patients struggle to make is to the next injection. A new medicine that mitigates this wear-off effect will be welcomed by most patients. The wear-off phase will be noticed by increased tiredness and increased joint problems and mostly occurs in the last week before the new injection.
- keeping the current medication cooled is inconvenient when travelling. Also, the need to find a HCP for giving the injection during a stay abroad is considered difficult.

The current medication can cause serious side effects, as Diabetes Mellitus II and in some patients de gallbladder needs to be removed.

9.7. Benefit-risk conclusions

9.7.1. CHMP conclusions

The balance benefice-risks of paltusotine in the claimed indication is positive.

10. Appendix

CHMP AR on new active substance claim dated 26 February 2026