EU RISK MANAGEMENT PLAN

Palsonify (paltusotine)

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP:	01 Sep 2024	Version number:	0.3
Date of final sign off:	21 Jan 2026		

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

Other RMP versions under evaluation:

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

QPPV name: Dilyana Karaivanova

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration time curve
AUC_{0-24}	area under the plasma concentration time curve from time 0 to 24 hours
$AUC_{0-\tau}$	area under the plasma concentration time curve over a dosing interval at steady state
AV	atrioventricular
BCRP	breast cancer resistance protein
BMI	body mass index
Bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma drug concentration
CMV	cytomegalovirus
CNS	central nervous system
CSR	clinical study report
CYP	cytochrome P450
di-HCl	dihydrochloride
EC_{50}	effective concentration that results in half-maximal response
ECG	electrocardiogram
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EOR	End of the Randomised Control Phase
EPAR	European Public Assessment Report
EU	European Union

Abbreviation/Term	Definition
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	first patient first visit
F1	first filial
GH	growth hormone
GI	gastrointestinal
GLP	Good Laboratory Practice
GMR	geometric mean ratio
HbA1c	haemoglobin A1c
hERG	human ether-à-go-go-related gene
HMG	hot melt granulation
IC_{50}	concentration inhibiting 50% of the response
IGF-1	Insulin-like growth factor-1
INN	International Nonproprietary Name
ISS	integrated summary of safety
LAR	long-acting release
LD	lactation day
LE	Long-Evans
LPLV	last patient last visit
MATE1	multidrug and toxin extrusion protein 1
MATE2-K	multidrug and toxin extrusion protein 2
MEC	molar extinction coefficient
NOAEL	no-observed-adverse-effect level
NRU-PT	neutral red uptake phototoxicity test
OLE	Open-label Extension
PBPK	physiologically-based pharmacokinetic(s)
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PPI	proton pump inhibitor
PSUR	periodic safety update report
PT	preferred term
QD	once daily

Abbreviation/Term	Definition
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	corrected QT interval
QTcF	absolute QT interval corrected for heart rate by Fridericia's formula
RC	Randomised Controlled
RMP	risk management plan
SAE	serious adverse event
SA-SSA	short acting somatostatin analog
SDD	spray-dried dispersion
SKK	Sanwa Kagaku Kenkyusho Co., Ltd
SmPC	summary of product characteristics
SOC	system organ class
SRL	somatostatin receptor ligand
SST	somatostatin
SST2	somatostatin receptor type 2
TEAE	treatment-emergent adverse event
UGT	uridine 5'-diphospho-glucuronosyltransferase
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase family 1 member A1
ULN	upper limit of normal
US	United States
UVR	ultraviolet radiation

PART I PRODUCT OVERVIEW

Table Part I.1: Product Overview

Active substance (INN or common name)	Paltusotine
Pharmacotherapeutic group (ATC Code)	Pituitary and hypothalamic hormones and analogues (H01CB06)
Marketing Authorisation Applicant	Crinetics Pharmaceuticals Europe GmbH
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Palsonify
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: SST2 agonist
	Summary of mode of action: Similar to the natural hormone SST, paltusotine demonstrates potent suppression of GH and IGF-1 secretion. Paltusotine exerts its pharmacological activity via highly selective binding (>4 000-fold) to SST2 and exhibits little or no affinity for other SST receptor subtypes. Paltusotine inhibits cAMP accumulation via human SST2 activation with an average drug (agonist) concentration that results in half-maximal response (EC_{50}) of 0.25 nM.
	Important information about its composition: Paltusotine tablets are available as an immediate-release dosage form containing an amorphous SDD of paltusotine in a water-soluble polymer, copovidone.
Hyperlink to the Product Information	Paltusotine Product Information (Module 1.3.1)
Indication in the EEA	Current: Palsonify is indicated for the medical treatment of adult patients with acromegaly.
	Proposed: Not applicable

Dosage in the EEA	Current: The recommended initial dose is 40 mg paltusotine by oral route once a day. After 2 to 4 weeks on Palsonify 40 mg once daily, based on IGF-1 levels or clinical signs and symptoms, the dose can be increased to 60 mg once daily. For medically naïve patients, the recommended initial dose is 20 mg Palsonify by oral route once daily for 2 weeks and if well tolerated, the dose should be increased to 40 mg once daily. After 2 to 4 weeks on Palsonify 40 mg once daily, if 40 mg is well tolerated, the dose can be increased to 60 mg based on IGF-1 levels or clinical signs and symptoms. Based on tolerability, the dose may be temporarily reduced by 20 mg. Once adverse reactions have resolved, paltusotine can be resumed at the previous dose. Monitoring of IGF-1 levels and assessment of symptoms should be made periodically as per the clinician's discretion.
	Proposed: Not applicable
Pharmaceutical forms and strengths	Current: <u>Palsonify 20 mg film-coated tablets</u> Each film-coated tablet contains 20 mg of paltusotine (as paltusotine hydrochloride). Pink, biconvex oval film-coated tablets, 16 mm length and 8 mm width, debossed with "PAL" on one side and "20" on the other side. <u>Palsonify 30 mg film-coated tablets</u> Each film-coated tablet contains 30 mg of paltusotine (as paltusotine hydrochloride). Yellow, biconvex oval film-coated tablets, 18 mm length and 9 mm width, debossed with "PAL" on one side and "30" on the other side.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

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

Acromegaly is a serious, chronic, rare disease caused by excess secretion of GH by a benign pituitary adenoma, which leads to increased production of IGF-1 from the liver and other organs. The chronic and persistent excess production of GH and IGF-1 leads to bone and cartilage overgrowth, organ enlargement, changes in glucose and lipid metabolism, multiple comorbidities, and premature death mainly due to cardiovascular complications. Symptoms of acromegaly include abnormal growth of hands and feet, alteration of facial features, thickening of tissue leading to arthritis, diabetes, hypertension, joint pain, fatigue, headache, hyperhidrosis, asthenia, paraesthesia, soft tissue oedema, sleep apnoea, and excessive snoring (Carroll 2022; Melmed 2016; NIDDK 2020; Ramos-Leví 2019).

Incidence and Prevalence

Due to the rarity of acromegaly, the scientific literature reports variable incidence and prevalence estimates from different geographies, health systems, time frames, and data sources. It is estimated that the prevalence of acromegaly in the EU and 3 EEA Member States is approximately 1.1 cases per 10,000, equating to 50,257 cases (Orphan Drug Designation EMA/OD/0000234998).

Demographics of the population in the proposed indication and risk factors for the disease

Most studies report a median age at diagnosis of acromegaly in the fifth decade of life ranging between 40.5 and 47 years (males: 36.5–48.5 and females 38–56) (Agustsson 2015; Daly 2006; Fernandez 2010; Gruppetta 2013; Raappana 2010). Relevant epidemiological data on young-onset acromegaly are sparse, and this is mainly attributed to the rarity of the condition. Furthermore, the scientific literature reports a similar distribution of prevalence between males and females (Lavrentaki 2016).

Since acromegaly is rare and physical changes occur slowly over many years, the condition sometimes takes a long time to recognise. Diagnostic delay remains considerable with median estimated intervals of 4.5–5 years from first symptoms until diagnosis. In addition, diagnosis delays of 15 or even 25 years have been reported resulting in significant challenges to timely disease management (Daly 2006; Fernandez 2010; Hoskuldsdottir 2015; Mestron 2004).

Treatment Goals

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

Current treatment options

Surgical Intervention

Transsphenoidal surgical resection of the pituitary adenoma is the first treatment for acromegaly and leads to an overall remission rate of 54.8% (including 52.7% for macroadenomas and 77.9% for microadenomas) (Starnoni 2016). However, for some patients, surgical removal is not an option, they may choose not to have surgery, or they may experience delays before a surgical appointment becomes available. For many others, surgical intervention does not achieve biochemical control (IGF-1 normalisation) nor does it adequately resolve acromegaly symptoms, necessitating additional adjunctive pharmacotherapy (Fleseriu 2021; Fleseriu 2022; Giustina 2020; Katznelson 2014; Starnoni 2016).

Radiotherapy

Radiotherapy may be considered as a means to control tumour growth and/or for lowering of GH secretion in patients with residual tumour after surgery who do not have access to medical therapy, or if medical therapy is unsuccessful or not tolerated (Carroll 2022; Katznelson 2014; Melmed 2016; NIDDK 2020). However, radiation therapy is used less frequently due to the long duration of onset of action (Giustina 2020).

Medical Therapy

Medical therapy is recommended for patients who do not achieve biochemical control after surgery, for patients for whom surgical intervention is not an option, or for patients who choose not to have surgery. Approved pharmacotherapy for acromegaly includes SRLs, GH receptor antagonists, and dopamine agonists (Giustina 2020).

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.

Natural history of the indicated condition including mortality and morbidity

If left untreated, acromegaly has a mortality rate that is nearly 2-fold higher than the general population; the principal contributors to which are cardiovascular diseases (hypertension, acromegalic cardiomyopathy, atherosclerosis, coronary artery disease, and congestive heart failure), metabolic diseases (diabetes), respiratory disease, and cerebrovascular diseases. All-cause mortality is highest in the first 5 years following diagnosis (Carroll 2022; Melmed 2016; NIDDK 2020; Orme 2024; Ramos-Leví 2019).

Important comorbidities in the target population

Patients with acromegaly have metabolic complications that affect both glycaemic and lipid metabolism and are mostly due to GH excess. Most patients have insulin resistance with impaired insulin sensitivity, and increased liver and kidney gluconeogenesis due to chronic GH excess, which contributes to glycaemic abnormalities (Frara 2016; Møller 2009).

Cardiovascular disease is one of the most prevalent comorbidities in patients with acromegaly, with arterial hypertension being the most common disorder, with prevalence ranging from 18%

to 60% and being present since early stages (Casini 2011; Gadelha 2019). Furthermore, acromegaly patients have a higher occurrence of arterial hypertension, insulin resistance and diabetes predisposing them to cerebrovascular events (Schöfl 2017).

Respiratory disorders are common in acromegaly and occur due to anatomical changes in the craniofacial region and upper respiratory tract such as tongue swelling, changes in respiratory mucosa and cartilage, lung chest volume and geometry, along with changes in muscle structure, reduced lung elasticity, and increased pulmonary distensibility (Pivonello 2017; van Haute 2008).

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Paltusotine is a novel and potent nonpeptide, orally bioavailable SST2 agonist developed by Crinetics Pharmaceuticals, Inc. (Crinetics) that is highly selective for SST2 and exhibits little or no affinity for other somatostatin receptor subtypes or other receptors, transporters, and ion channels that are common drug targets.

Early exploratory nonclinical studies were conducted with the di-HCl salt of paltusotine. Later, a polymorphically stable salt, ie, monohydrochloride salt (paltusotine.HCl) was selected for development. All GLP nonclinical toxicity studies have been conducted with the paltusotine.HCl salt form.

The key safety findings from nonclinical studies and relevance to human usage are summarised in Table Part II: Module SII.1.

Table Part II: Module SII.1: Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Toxicity	
Single dose toxicity studies Single dose non-GLP toxicity studies in rats and dogs were conducted to enable dose selection for repeat-dose toxicity studies. Parameters evaluated included viability, clinical signs, and body weight, which were assessed for 4 to 6 days postdose. Paltusotine was well tolerated up to the highest doses tested, and no mortality or test-article related clinical signs were observed (M2.6.6 Section 2.1, M2.6.6 Section 2.2). **Repeat-dose toxicity studies** Paltusotine was well tolerated in GLP 28-day (rat and dog), 13-week (rat and dog), 26-week (rat only), and 39-week (dog only) oral repeat-dose toxicity studies. In all studies, there was little or no difference in toxicities between male and female animals. The NOAEL was established at the highest dose evaluated in rat (500 mg/kg/day) and dog (75 mg/kg/day). Toxicity studies in rats demonstrated nondose-dependent and nonadverse decreases in body weight and body weight gain at all doses tested (25, 75, and 500 mg/kg/day). This effect was considered an extension of pharmacological effects, which results in a decrease in GH and IGF-1 in animals that are in their growth phase. Upon cessation of dosing, animal body weight gain appeared to be similar to or exceeded the vehicle treated animals (M2.6.6 Section 3.2.1). In dog toxicity studies, clinical observations included emesis, abnormal stool (characterised 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	Gastrointestinal events are discussed as a risk not considered important in Part II: Module SVIISVII.1.1. Diarrhoea, abdominal pain, nausea, abdominal discomfort, abdominal distension, and vomiting are adverse reactions in the paltusotine summary of product characteristics (SmPC). The observed changes in body weight are not considered of relevance to humans. In the Primary Group (RC Phases of the pivotal Phase 3 studies, Study CRN00808-08 and Study CRN00808-09), changes in body weight were not observed in paltusotine treated participants compared with placebo (weight increased 0 vs n=2, 2.4%; weight decreased 0 vs n=1, 1.2%), respectively (ISS Table 14.3.1.3). Four participants (4.8%) treated with paltusotine experienced loss of appetite AEs; loss of appetite was not observed in the placebo group (ISS Table 14.3.1.3). In the Supportive Group (pooled analysis of safety data from the 2 Phase 3 Studies CRN00808-08 and CRN00808-09 including data from RC and OLE Phases and 3 Phase 2 Studies CRN00808-03, CRN00808-02, and CRN00808-05 OLE), 4 participants (1.7%) gained weight, 4 participants (1.7%) lost weight, and 1 participant (0.4%) had poor weight gain (ISS Table 14.3.1.4). Overall, 5 participants (2.1%) treated with paltusotine experienced a loss of appetite (ISS Table 14.3.1.4). No effects on the thymus were observed in the clinical studies in the Primary Group or the Supportive Group (ISS Table 14.3.1.3,

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
and consequential decreased body weight were readily resolved by offering the standard pellet diet mixed with canned food. Emesis was dose-dependent but sporadic (not in all animals and not after each dose), and generally resolved over repeated dosing. Abnormal stool resolved upon cessation of dosing (M2.6.6 Section 3.2.2). Additionally, nonadverse decreases in thymus weights and thymic lymphoid depletion were observed only in dogs in the 3-month study but not in the longer-term 9-month study. These thymus findings are often observed due to secondary (indirect) effects of stress (Everds 2013) and not considered a direct effect of paltusotine. Upon cessation of dosing, animal body weight gain recovered, and thymus effects exhibited partial to complete recovery. In the 26-week rat and 39-week dog studies, the NOAEL doses of 500 mg/kg/day in rats and 75 mg/kg/day in dogs correspond to steady state AUC_{0-24} exposures that were 6.9- and 25-fold higher, respectively, than the anticipated steady state clinical exposures at the recommended therapeutic dose of 60 mg.	ISS Table 14.3.1.4). The observed thymus related changes are not relevant for humans.
Reproductive/developmental toxicity studies Paltusotine was well tolerated in the fertility and early embryonic development study in male and female rats. There were no paltusotine-related mortalities and findings were limited to nonadverse clinical observations of abnormal coloured faeces, and reduced body weight, body weight gain, and food consumption which were expected effects based on the pharmacological activity of paltusotine. As such, the NOAEL for general toxicity was considered 500 mg/kg/day, the highest dose evaluated. There were no paltusotine-related effects on any mating and fertility parameters in males and females and reproductive organ weights or sperm parameters in males at any dose. A decrease in corpora lutea was noted in females at 500 mg/kg/day, which resulted in fewer implantation sites and live embryos/litter. Based on these data, the reproductive NOAEL was 500 mg/kg/day in males and 75 mg/kg/day in females. In the embryo-foetal development studies, the maternal and developmental NOAEL for the rat was determined to be 500 mg/kg/day, the highest dose evaluated. In the rabbit, the maternal and developmental NOAEL was considered 25 mg/kg/day based on 1) decreased body weight, body weight gain, and food consumption, which were expected effects based on the pharmacological activity of paltusotine but considered adverse due to the occurrence of abortions in pregnant females at 75 mg/kg/day and 2) reduced mean foetal weights at 75 mg/kg/day. There was no evidence of teratogenic effects at any dose evaluated in rats or rabbits.	As with the majority of clinical studies, female patients who were pregnant were excluded from study participation for safety reasons (Part II: Module SIVSIV.1). Throughout the clinical development programme, there were two pregnancies (one each in Study CRN00808-07 and Study CRN00808-05). In Phase 1 Study CRN00808-07 a healthy participant received a single 20 mg dose of paltusotine and became pregnant approximately 2 weeks later; no further details on the outcome of pregnancy are available (M2.7.4 Section 6.4). In Study CRN00808-05, a female acromegaly participant had a positive pregnancy test during Week 16 of the study and following a CMV infection during pregnancy and a caesarean section had a neonate with ankyloglossia, interatrial communication (patent foramen ovale), mineralizing vasculopathy and neonatal wet lung syndrome (M2.7.4 Section 6.4). There are other explanations for these conditions rather than a causal association with paltusotine. The paltusotine SmPC advises healthcare professionals that 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 clinically relevant exposure of paltusotine. However, effects on rat female reproductive parameters were observed at 500 mg/kg/day.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
In the pre- and postnatal development study no paltusotine-related mortalities were observed, and findings were limited to nonadverse clinical observations of abnormal coloured faeces, and expected pharmacological effects of reduced body weight, body weight gain, and food consumption. Based on these data, the maternal NOAEL was considered 500 mg/kg/day. Maternal administration at 500 mg/kg/day resulted in decreased pup body weights throughout the preweaning and postweaning periods; thus, the developmental NOAELs during both these periods was considered 75 mg/kg/day. On LD 20 (or Day 20 postpartum), maternal plasma and milk concentrations and pup plasma concentrations of paltusotine were observed to increase with increasing dose. On LD 20, concentrations in plasma for female rats were lower than the values observed in milk (2.3- to 3.8-fold greater in milk) at 4 hours postdose. Paltusotine concentrations in pup plasma and maternal milk demonstrate that pups were likely exposed in utero and/or via lactational transfer. In a separate single dose PK study, oral administration of paltusotine at 25 mg/kg or 500 mg/kg to pregnant rats showed measurable paltusotine concentrations in embryos and foetuses, demonstrating placental transfer (Report 20458479; M2.6.4 Section 4.2.3).	In addition, healthcare professionals are advised that animal studies do not indicate direct or indirect harmful effects at human exposure with respect to reproductive toxicity. As there are limited data from the use of paltusotine in pregnant women, it is preferable to avoid the use of Palsonify during pregnancy as a precautionary measure. Since the therapeutic benefits of a reduction in GH levels and normalisation of IGF-1 concentration in female acromegalic patients could potentially restore fertility, female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with paltusotine. There are no clinical data regarding exposure during lactation. The paltusotine SmPC advises healthcare professionals that available toxicological data in animals have shown excretion of paltusotine/metabolites in milk and that it is unknown whether paltusotine/metabolites are excreted in human milk. As a risk to the suckling newborns/infants cannot be excluded, breast-feeding should be discontinued during treatment with Palsonify.
Genotoxicity Paltusotine was tested in a GLP battery of in vitro and in vivo genotoxicity studies. Paltusotine did not cause gene mutation or chromosomal damage in a bacterial mutagen assay, in vitro micronucleus assay, or an in vivo rat micronucleus test (M2.6.6 Section 4.1, M2.6.6 Section 4.2, M2.6.6 Section 4.3).	These results suggest that paltusotine does not present a genotoxic hazard to humans.
Carcinogenicity No paltusotine-related neoplasms were noted in 6-month rasH2 mouse (up to 300 mg/kg/day) (M2.6.6 Section 5.2) and 2-year rat (up to 500 mg/kg/day) (M2.6.6 Section 5.3) carcinogenicity studies at the highest doses evaluated, which provided AUC_{0-24} exposures that were approximately 2.8-fold (mouse) and 34-fold (rat) higher than the anticipated steady state clinical AUC exposures at the recommended therapeutic dose of 60 mg.	Based on these results, paltusotine does not present a carcinogenic risk to humans.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Safety Pharmacology	
Cardiovascular System Paltusotine inhibited hERG tail currents in vitro, with a IC_{50} value of 4.8 µM (2190 ng/mL) (M2.6.2 Section 4.3.1). Additionally, in an ion channel screening assay, paltusotine caused little or no inhibition (IC_{50} >5 µM or >2280 ng/mL) of ion channels that are known to participate in maintenance of normal cardiac action potential and rhythm (namely, hCav1.2, hHCN1, hHCN2, hHCN4, hKir3.1/hKir3.4, hKvLQT1/hminK, and hNav1.5) (M2.6.2 Section 4.3.2). These IC_{50} values are >700-fold higher than the anticipated unbound steady state C_{max} of paltusotine in humans of 0.0065 µM (2.96 ng/mL) for the highest proposed dose of 60 mg. In the GLP telemetered dog cardiovascular safety pharmacology study (Report 424-0016-SP), administration of a single oral dose of paltusotine up to 10 mg/kg, the highest dose tested, was associated with a transient decrease in heart rate and increase in blood pressure approximately 6 and 19 hours post dose, which were within biological variability for these parameters, not clearly dose dependent, and not accompanied by adverse effect on arrhythmogenesis (M2.4 Section 2.3; M2.6.2 Section 4.3.4). At 10 mg/kg, the unbound plasma C_{max} after a single administration of paltusotine was 16 ng/mL, which is approximately 5.5-fold higher than the anticipated unbound steady state C_{max} in human at a 60 mg dose. There were no noteworthy paltusotine-dependent changes in ECG parameters (ie, time interval between P and R waves [PR], time interval of the QRS complex [QRS], time interval between Q and T wave [QT], QTc intervals or ECG gross morphology and rhythm). Additionally, quantitative and qualitative analysis of ECGs collected in the chronic dog toxicity study (Report 424-0037-TX) did not identify any adverse effect on cardiac rhythm or ECG parameters after once daily, repeated dosing for 39 weeks at doses up to 75 mg/kg/day, the highest dose evaluated (M2.6.6 Section 3.2.2.3). At this dose, the unbound steady state C_{max} in dogs (148 ng/mL; average of sexes) is approximately 50-fold above the anticipated unbound steady state C_{max} in human at a 60 mg dose (M2.6.2 Section 6).	Similar to other SRL treatments (Sandostatin LAR SmPC 2022; Somatuline Autogel SmPC 2024), sinus bradycardia is an adverse reaction of paltusotine and discussed as a risk not considered important in Part II: Module SVIISVII.1.1. The ECG data in the clinical studies do not suggest a signal for PR prolongation or QTc prolongation and a review of SAEs of AV conduction abnormalities did not indicate any additional risk (Part II: Module SIVSIV.1). The paltusotine SmPC informs healthcare professionals that at 4.6 times the exposure of the paltusotine 60 mg therapeutic dose, clinically significant QTc interval prolongation was not observed. The paltusotine SmPC warns healthcare professionals that cardiac conduction abnormalities and other ECG changes such as PR interval prolongation and bradycardia have occurred with paltusotine in clinical studies. These ECG changes may occur in patients with acromegaly. Dose adjustments of concomitantly used medicinal products that have bradycardia effects (eg, beta blockers) may be necessary.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Central nervous system The potential neurobehavioural effects of paltusotine were evaluated using the functional observational battery when administered as a single oral gavage dose to male Sprague Dawley rats (n=8/group) at 0 (vehicle), 25, 75, or 500 mg/kg (Report 424-0017) (M2.6.2 Section 4.2). Paltusotine produced no meaningful effects on the acute central or peripheral nervous system at doses up to 500 mg/kg, which is associated with unbound C_{max} exposures that are approximately 21-fold higher than the anticipated unbound steady state clinical C_{max} at a 60 mg dose for acromegaly.	Paltusotine is not recognised to cause CNS AEs. In the Primary Group, AEs in the Nervous system disorders SOC were observed at a lower rate in the paltusotine group compared with the placebo group (n=24, 28.6% vs 36, n=42.4%), respectively (ISS Table 14.3.1.3). In this SOC, the most frequently reported AEs in the paltusotine group compared with the placebo group were headache (n=17, 20.2% vs n=29, 34.1%), paraesthesia (n=5, 6.0% vs n=10, 11.8%), and dizziness (n=2, 2.4% vs n=2, 2.4%), respectively (ISS Table 14.3.1.3). In the Supportive Group, a similar pattern was observed with slightly higher incidences; 79 participants (33.9%) treated with paltusotine experienced Nervous system disorders AEs and the most frequent were headache (n=55, 23.6%), paraesthesia (n=26, 11.2%), and dizziness (n=10, 4.3%) (ISS Table 14.3.1.4). These AEs are TEAEs of special interest defined as symptoms determined by the Investigator to be related to acromegaly (referred to as acromegaly-related TEAEs) (M2.7.4 Section 2.1.5.3). Headache and dizziness are adverse reactions in the paltusotine SmPC.
Respiratory system The potential respiratory effects of paltusotine were evaluated when administered a single oral gavage dose to male Sprague Dawley rats (n=6/group) at 0 (vehicle), 25, 75 or 500 mg/kg (Report 424-0018-SP) (M2.6.2 Section 4.3). Paltusotine produced no meaningful acute respiratory effects at doses up to 500 mg/kg, which is associated with unbound C_{max} exposures that are approximately 21-fold higher than the anticipated unbound steady state clinical C_{max} at a 60 mg dose for acromegaly.	Paltusotine is not recognised to cause respiratory AEs. In the Primary Group, Respiratory disorders AEs were observed at a similar rate in the paltusotine group compared with the placebo group (n=8, 9.5% vs n=7, 8.2%), respectively (ISS Table 14.3.1.3). In this SOC, the most frequently reported AEs in the paltusotine group compared with the placebo group were cough (n=2, 2.4% vs n=3, 3.5%) and dyspnoea (n=1, 1.2% vs n=2, 2.4%), respectively (ISS Table 14.3.1.3). In the Supportive Group, a similar pattern was observed with slightly higher incidences; 30 participants (12.9%) treated with paltusotine experienced Respiratory disorders AEs and the most frequent AEs were cough (n=12, 5.2%) and dyspnoea and sleep apnoea syndrome (both n=5, 2.1%) (ISS Table 14.3.1.4). Dyspnoea and sleep apnoea syndrome are TEAEs of special interest (acromegaly-related TEAEs) (ISS Table 14.3.1.17; ISS Table 14.3.1.18).

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Mechanisms for Drug Interactions	
Pharmacokinetic drug interactions In vitro CYP enzyme inhibition/induction, protein binding, and transporter studies were conducted (M2.6.4 Section 9). • In vitro, paltusotine did not induce human CYP1A2, CYP2B6, or CYP3A4 at concentrations ≤10 µM. • Paltusotine was not a reversible inhibitor of human CYP enzymes, except CYP2C19 (IC_{50}=6.35 µM). Basic drug interaction calculations (per ICH M12 guidance [ICH M12]) suggested a low inhibition risk with CYP2C19 substrates. • Time-dependent inhibition was only observed for CYP2D6 and CYP3A4/5. • Assessment of a drug interaction risk indicates that paltusotine has a low or weak propensity to alter the PK of substrates of CYP2D6 or CYP3A4/5. • Paltusotine weakly inhibited UGT1A1, UGT1A3, and UGT1A9 at concentrations >10 µM. • Among intestinal, hepatic, and renal transporters, paltusotine was only a substrate for P-gp and BCRP. Thus, an inducer of P-gp could reduce the exposure of paltusotine. • Paltusotine inhibited P-gp (IC_{50}=9.3 µM), MATE1 (IC_{50}=0.18 µM), and MATE2-K (IC_{50}=2.5 µM) transporters. Assessment of a drug interaction risk suggests the possibility of an intestinal interaction with P-gp substrates, while there is a low risk for interaction with MATE1 and MATE2-K substrates. No in vivo nonclinical studies were performed to specifically investigate the potential PK interactions with drugs that are likely to be co-administered with paltusotine.	The potential drug interactions between paltusotine and carbamazepine, metformin, cyclosporine, midazolam, and lansoprazole were evaluated in clinical studies with healthy participants. Additionally, results from PBPK modelling were used along with the dedicated clinical studies to define the clinical implications of paltusotine drug interactions (M2.7.2 Section 3.5). Drug-drug interactions are discussed as a risk not considered important in Part II: Module SVIISVII.1.1 with a summary of the findings presented below. • Concomitant use of paltusotine with strong inducers of CYP450, CYP3A4/5, UGT1A1, and P-gp (eg, carbamazepine) may require increased doses of paltusotine due to approximately 40% and 70% decreases in paltusotine C_{max} and AUC, respectively. • Concomitant use of paltusotine with moderate CYP3A4 inducers (eg, efavirenz) may require increased doses of paltusotine due to approximately 5% and 30% decreases in paltusotine C_{max} and AUC, respectively. • Concomitant use of paltusotine with PPIs (eg, lansoprazole) may require increased doses of paltusotine due to dose dependent decreases in paltusotine AUC (approximately 20% for 20 mg dose and 40% for 60 mg dose). • Cyclosporine doses may need to be adjusted when administered concomitantly with paltusotine due to approximately 50% and 35% decreases in cyclosporine C_{max} and AUC when co-administered with paltusotine. Advice for healthcare professionals on drug-drug interactions is presented in the paltusotine SmPC.
Other Toxicity Related Information or Data	
Phototoxicity and Ophthalmic findings The potential phototoxicity of paltusotine was evaluated in in vitro and in vivo studies. Paltusotine was calculated to have a MEC >1000 mol-1 cm-1 at wavelengths between 203 nm to 350 nm (Report 18-085-00), indicating a potential for phototoxicity (M2.6.6 Section 8.1.1). Based on these results, an in vitro 3T3 NRU-PT was conducted to evaluate the in vitro phototoxic potential of paltusotine as measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to paltusotine and ultraviolet radiation (+UVR), as compared with the viability of fibroblasts exposed to paltusotine in the absence of ultraviolet radiation (-UVR). The	Following a review of the phototoxicity rodent study data, the US FDA requested ophthalmologic monitoring assessments (visual acuity, visual fields, fundus photography, and ocular coherence tomography) to be conducted in all participants in ongoing paltusotine clinical studies of 6 month duration or longer to assess any potential clinical relevance in humans. Therefore, ophthalmic assessments were added to study protocols for ongoing Studies CRN00808-08, CRN00808-09, CRN00808-05, and CRN00808-11. In the Primary Group, ocular-related TEAEs within the Eye Disorders SOC were reported in 7 of 84 (8.3%) participants in the paltusotine group and 7 of

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
photoirritancy factor and mean photo effect were calculated to be >5 and >0.15, respectively, for paltusotine thereby meeting the criteria for positive in vitro phototoxicity. An in vivo phototoxicity study in LE rats was conducted to enable risk assessment of the positive in vitro phototoxicity result obtained with paltusotine (M2.6.6 Section 8.1.2). Administration of paltusotine for 3 consecutive days at doses of 10, 75, and 250 mg/kg/day, followed by a single UVR exposure after the last administration resulted in no adverse skin reactions (for example, erythema or oedema) or ocular observations (by ophthalmology or histopathology as described below), which was considered consistent with no drug effect on phototoxicity. Corneal dystrophy and inferior focal retinopathy were both observed during ophthalmic examination and not considered paltusotine related. Corneal dystrophy was observed bilaterally in 2 rats administered 10 mg/kg/day and one rat administered 75 mg/kg/day. This finding was not observed in the high-dose group. The results were not considered related to paltusotine administration by a board-certified veterinary ophthalmologist and pathologist and were considered incidental (common background finding), related to the study procedure, and/or consistent with observed photic injury related to ultraviolent radiation exposure commonly observed in phototoxicity studies. Overall, there was no evidence of dermal or ocular phototoxicity in LE rats at free plasma concentrations that were 21 times higher than highest expected steady state clinical C_{max} at a 60 mg dose for acromegaly.	85 (8.2%) participants in the placebo group up to 31 May 2024 (M2.7.4 Section 2.1.6.1). Conjunctivitis viral (n=2) was the only TEAE reported in more than 1 participant in the paltusotine group. In the placebo group, TEAEs reported in more than 1 participant included dry eye, eye pain, and vision blurred (n=2 each). None of the TEAEs in either the paltusotine or the placebo groups were considered treatment-related by the Investigator, and all were nonserious. All TEAEs within the paltusotine group were mild. In the placebo group, TEAEs of abnormal sensation in eye, dry eye, dermatochalasis, eyelid ptosis, and eye pain (n=1 each) were considered moderate. A comprehensive review by both the Sponsor and an independent ophthalmology expert of ocular-related TEAEs identified from 17 Sponsor-conducted acromegaly and non-acromegaly studies (including completed Phase 1 studies, the ongoing Phase 1 Study CRN00808-22, and the ongoing carcinoid syndrome Study CRN00808-11) was conducted across the paltusotine clinical programme using the cutoff date 03 Sep 2024 using the ocular-related TEAE search strategy (M2.7.4 Appendix E Section 1.1.3.3). In the Supportive Group, a total of 23 ocular-related TEAEs were reported in 233 participants (M2.7.4 Appendix E Section 5.2.1). The most common TEAEs were cataracts and conjunctivitis viral (n=4 [1.7%] each), as well as blepharitis, conjunctivitis, and hordeolum (n=2 [0.9%] each). None were serious.
	Across the 17 studies, the cumulative blinded search of ocular-related TEAEs identified a total of 55 ocular-related TEAEs in 35 participants across 9 of 17 studies with paltusotine (M2.7.4 Appendix E Section 5.2.2). Based on blinded review, the independent ophthalmology expert reviewer assessment concluded that there were no severe or serious ocular-related events reported (M2.7.4 Appendix E Section 5.2.2.1). The independent reviewer noted the 1 participant in Study CRN00808-08 had 2 ocular-related TEAEs (abnormal sensation in eye [verbatim: swelling sensation in both eyes] and eye pain [verbatim: pain in both eyes]) leading to discontinuation of study treatment due to multiple concomitant events in addition to the ocular events (headache, aggravated insomnia, increased fatigue, shoulder and neck pain, and increased joint pain). The participant was in the placebo group at the time of the events and received acromegaly rescue therapy. The independent reviewer assessed these events as moderate in

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	severity and possibly related to study drug. Per the independent reviewer assessment, 10 participants experienced 17 events that were considered possibly related to study drug. These events were all classified as mild in severity by the independent reviewer. The possible relatedness was based on the temporal relationship to study drug intake but as per the independent reviewer assessment, was most likely explained by the underlying illness or other concomitant medications in each of the cases. Of note, after the independent review was completed, the Sponsor unblinded these 10 participants with 17 events. Six events in 6 participants occurred on paltusotine and 11 events in 5 participants occurred on placebo (including 1 participant who crossed over to paltusotine from placebo in the OLE in Study CRN00808-09 and is therefore represented in both groups). The independent reviewer noted that none of the 55 TEAEs correlate with the ophthalmic and microscopic findings described in the nonclinical phototoxicity study. The conclusion of the independent expert was that there were no clinically significant paltusotine-related ocular safety concerns identified in the studies based on the data available for the studies evaluated in the review. Separately, the Sponsor conducted a review of the same 55 ocular-related TEAEs, using the original study Investigator-reported assessments of severity, causality, and seriousness of the events (M2.7.4 Appendix E Section 5.2.2.2). The Sponsor concluded that there were no events that were suggestive of significant ocular toxicity. Cumulatively, there was no signal of ocular-related toxicities associated with paltusotine based on independent ophthalmology review of data from initial ophthalmology monitoring assessments in ongoing studies, blinded review of ocular-related TEAEs across the paltusotine program by an independent ophthalmology expert, and Sponsor review.

Conclusions from the nonclinical development programme

The nonclinical evaluation of paltusotine in safety pharmacology, general toxicity, genotoxicity, carcinogenicity, development and reproductive toxicity, and phototoxicity studies provided support and guidance for the safe human use of paltusotine in clinical trials for acromegaly.

No safety concerns have been identified from the nonclinical development programme.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The paltusotine clinical development programme includes 2 pivotal, global, randomised, double-blind, placebo-controlled clinical studies (Studies CRN00808-08 and CRN00808-09) and 3 Phase 2 studies (Studies CRN00808-02, CRN00808-03, and CRN00808-05) in participants with acromegaly; 11 Phase 1 clinical studies in healthy volunteers (including 2 studies with paltusotine under license agreement with study Sponsor SKK in Japan); and 1 Phase 1 clinical study in participants with hepatic impairment.

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 randomisation. Eligible participants were enrolled into 3 groups: (1) participants with no prior medical therapy, (2) participants who last received medical therapy at least 4 months prior to Screening, and (3) participants who were controlled on SRL therapy (octreotide or lanreotide) for at least 3 months at Screening but agreed to wash out prior to beginning study treatment. Participants were randomised 1:1 to receive paltusotine or placebo in a blinded manner for up to 24 weeks in the RC Phase followed by an optional OLE Phase to receive paltusotine for up to 200 weeks. The RC Phase is completed, and the OLE Phase is ongoing.

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 biochemically controlled throughout Screening and on long-acting octreotide or lanreotide monotherapy. Participants were randomised to switch to paltusotine or placebo when their next dose of SRL was due to begin and were evaluated for 36 weeks in the RC Phase followed by an optional OLE Phase to receive paltusotine for up to 200 weeks. The RC Phase is completed, and the OLE Phase is ongoing.

Additional supportive safety data in participants with acromegaly are available from 2 completed Phase 2 studies (Studies CRN00808-03 and CRN00808-02) and 1 ongoing Phase 2 OLE study (Study CRN00808-05). In the completed studies (Studies CRN00808-03 and CRN00808-02), participants were switched from injectable SRL-based treatment regimens to QD oral paltusotine for the duration of each study, with the option of continuing in an OLE study (Study CRN00808-05). All 3 studies utilised an older formulation of paltusotine (HMG capsules) at study start; participants in the OLE Study CRN00808-05 were transitioned to the 20 mg and 30 mg 15% drug load SDD tablet formulation as of the study cutoff.

Study CRN00808-03 is a completed Phase 2, open label exploratory study to evaluate the safety, PK, and efficacy of paltusotine in participants with acromegaly who were either sub-optimally controlled on injectable SRL (octreotide or lanreotide) therapy alone or in combination with cabergoline; or required combination therapy or pasireotide to achieve normal IGF-1 at baseline. Doses of 10 to 40 mg QD paltusotine were investigated using 10 mg HMG capsules.

Study CRN00808-02 is a completed Phase 2, double-blind, placebo-controlled, randomised withdrawal study to evaluate the safety, PK, and efficacy of paltusotine in participants with acromegaly who had normal IGF-1 on injectable SRL monotherapy at baseline and were responders to octreotide LAR or lanreotide depot. Doses of 10 mg to 30 mg were investigated using 5 mg and 10 mg HMG capsules. Crinetics halted enrolment in the study early due to business reasons; participants already enrolled in this study at the time of enrolment cessation continued until study completion.

Study CRN00808-05 is an ongoing Phase 2 long-term OLE study to evaluate the safety and efficacy of paltusotine in participants with acromegaly who were previously enrolled in Study CRN00808-02 or Study CRN00808-03. Doses of 10 mg to 60 mg QD were investigated using 10 mg HMG capsules and 20 and 30 mg SDD tablets. Participant enrolment has completed, and the study is ongoing.

To evaluate the overall safety profile of paltusotine for the medical treatment of adult patients with acromegaly, analyses were performed for two safety groupings:

Primary Group

The Primary Group includes pooled data from the RC Phases of the pivotal Phase 3 studies (Studies CRN00808-08 and CRN00808-09). These 2 studies included 84 participants treated with paltusotine for up to 36 weeks at doses ranging from 20 mg to 60 mg QD (Study CRN00808-08) and 40 mg to 60 mg QD (Study CRN00808-09). The studies also included 85 participants treated with placebo.

Supportive Group

The Supportive Group comprises a pooled analysis of safety data from the 2 Phase 3 Studies CRN00808-08 and CRN00808-09 (including data from RC and OLE Phases) and the 3 Phase 2 studies (Studies CRN00808-03, CRN00808-02, and CRN00808-05 OLE) and includes 233 participants exposed to paltusotine with a maximum duration of 4 years.

Overall clinical trial exposure data are presented for each of the Phase 3 and Phase 2 studies followed by exposure data presented for the Primary Group and Supportive Group.

Table Part II: Module SIII.1: Extent of Paltusotine Exposure by Study in Participants with Acromegaly (Safety Population)

Study	Total Number of Participants	Mean Duration (days)	Person-year
CRN00808-02	2	42.00	0.23
CRN00808-03	13	70.23	2.50
CRN00808-05	45	1248.71	153.85
CRN00808-08	117	376.37	120.56
CRN00808-09	56	624.93	95.81
Total	233	584.64	372.95

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1. For participants enrolled in Studies CRN00808-02/CRN00808-03 to CRN00808-05, the participant exposure is counted in Study CRN00808-05.
Source: ISS Table 14.1.3.3
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

Table Part II: Module SIII.2: Duration of Paltusotine Exposure in the Primary Group (Safety Population)

Treatment duration (months)	Paltusotine (N=84) n (%)	Paltusotine Person-years
>0 to ≤3	2 (2.4)	0.34
>3 to ≤6	4 (4.8)	1.20
>6 to ≤9	78 (92.9)	42.38
Total		43.92

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1. 4 weeks are considered as 1 month.
Source: ISS Table 14.1.3.1
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024.

Table Part II: Module SIII.3: Duration of Paltusotine Exposure in the Supportive Group (Safety Population)

Treatment duration (months)	Paltusotine N=233 n (%)	Paltusotine Person-years
>0 to ≤3	12 (5.2)	1.32
>3 to ≤6	16 (6.9)	4.43
>6 to ≤12	44 (18.9)	33.16
>12 to ≤24	94 (40.3)	122.42
>24 to ≤36	31 (13.3)	66.32
>36	36 (15.5)	145.31
Total		372.95

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1. 4 weeks are considered as 1 month.
Source: ISS Table 14.1.3.2
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

Table Part II: Module SIII.4: Paltusotine Exposure by Dose Level in the Primary Group (Safety Population)

Dose Level	Paltusotine	
	N=84 n (%)	Person-year
20 mg	55 (65.5)	3.11
40 mg	84 (100)	22.08
60 mg	54 (64.3)	18.73
Total		43.92

Notes: Person-year is the total exposure calculated in years for that particular group. 1. Different formulation is not differentiated under the same dose level. 2. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1. 3. Records with no dose information are not included in this calculation.
Source: ISS Table 14.1.3.4
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024.

Table Part II: Module SIII.5: Paltusotine Exposure by Dose Level in the Supportive Group (Safety Population)

Dose Level	Paltusotine	
	N=233 n (%)	Person-year
10 mg	60 (25.8)	20.11
20 mg	175 (75.1)	28.66
30 mg	48 (20.6)	7.42
40 mg	222 (95.3)	210.17
60 mg	122 (52.4)	105.87
Total		372.22

Notes: Person-year is the total exposure calculated in years for that particular group. 1. Different formulation is not differentiated under the same dose level. 2. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1. 3. Records with no dose information are not included in this calculation.
Source: ISS Table 14.1.3.5
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

Table Part II: Module SIII.6: Paltusotine Exposure by Age Group and Gender in the Primary Group (Safety Population)

	Paltusotine	
	N=84 n (%)	**Person-year**
Duration of Exposure by Age Group (years)		
<65	67 (79.8)	34.06
≥65	17 (20.2)	9.86
65 to ≤74	14 (16.7)	8.02
>74 to ≤84	3 (3.6)	1.84
>84	0	0
Duration of Exposure by Gender		
Male	43 (51.2)	22.18
Female	41 (48.8)	21.74
Total		43.92

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1.
Source: ISS Table 14.1.3.8, ISS Table 14.1.3.6
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024.

Table Part II: Module SIII.7: Paltusotine Exposure by Age Group and Gender in the Supportive Group (Safety Population)

	Paltusotine	
	N=233 n (%)	**Person-year**
Duration of Exposure by Age Group (years)		
<65	192 (82.4)	301.80
≥65	41 (17.6)	71.15
65 to ≤74	34 (14.6)	59.65
>74 to ≤84	7 (3.0)	11.50
>84	0	0
Duration of Exposure by Gender		
Male	110 (47.2)	175.21
Female	123 (52.8)	197.74
Total		372.95

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1.
Source: ISS Table 14.1.3.9, ISS Table 14.1.3.7
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

Table Part II: Module SIII.8: Paltusotine Exposure by Race in the Primary Group (Safety Population)

Duration of Exposure by Race	Paltusotine	
	N=84 n (%)	Person-year
White	51 (60.7)	27.80
Asian	15 (17.9)	6.63
Multiple/Other	9 (10.7)	4.46
Black or African American	4 (4.8)	2.28
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Unknown	5 (6.0)	2.75
Missing	0	0
Total		43.92

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1.
Source: ISS Table 14.1.3.10
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024.

Table Part II: Module SIII.9: Paltusotine Exposure by Race in the Supportive Group (Safety Population)

Duration of Exposure by Race	Paltusotine	
	N=233 n (%)	Person-year
White	154 (66.1)	269.94
Asian	36 (15.5)	36.23
Multiple/Other	22 (9.4)	36.96
Black or African American	11 (4.7)	17.49
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Unknown	10 (4.3)	12.33
Missing	0	0
Total		372.95

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1.
Source: ISS Table 14.1.3.11
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

Table Part II: Module SIII.10: Paltusotine Exposure by Ethnicity in the Primary Group (Safety Population)

Duration of Exposure by Ethnicity	Paltusotine	
	N=84 n (%)	Person-year
Hispanic or Latino	29 (34.5)	14.79
Not Hispanic or Latino	48 (57.1)	25.45
Not Reported	0	0
Unknown	7 (8.3)	3.68
Total		43.92

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1.
Source: ISS Table 14.1.3.12
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024.

Table Part II: Module SIII.11: Paltusotine Exposure by Ethnicity in the Supportive Group (Safety Population)

Duration of Exposure by Ethnicity	Paltusotine	
	N=233 n (%)	Person-year
Hispanic or Latino	77 (33.0)	135.06
Not Hispanic or Latino	144 (61.8)	222.52
Not Reported	1 (0.4)	0.34
Unknown	11 (4.7)	15.03
Total		372.95

Notes: Person-year is the total exposure calculated in years for that particular group. Duration of paltusotine exposure calculated as date of last dose - date of first dose + 1.
Source: ISS Table 14.1.3.13
Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria from the RC Phases of the 2 pivotal, global, blinded, randomised, placebo-controlled Phase 3 Studies CRN00808-08 and CRN00808-09 are discussed below.

Exclusion criteria to ensure standardisation of the trial population that are common to most clinical trials are not presented, including:

- History of major surgery/surgical therapy for any cause within 4 weeks prior to Screening.
- Known history of hepatitis B or human immunodeficiency virus, or active hepatitis C infection.
- Active malignant disease within the last 5 years with exception of basal and squamous cell carcinoma of the skin with complete local excision and resected carcinoma in situ of cervix.
- Clinically significant concomitant disease including, but not limited to, cardiovascular disease, severe renal insufficiency (eGFR <30 mL/min/1.73 m^2), or significant liver disease (including cirrhosis).
- Concomitant mental condition rendering him/her unable to understand the nature, scope, and possible consequences of the study, and/or evidence of poor compliance with medical instructions.
- Known allergy or hypersensitivity to any of the test materials or related compounds.
- Known history of, or current alcohol or drug abuse, within the last year.
- An employee or immediate family member of an employee of Crinetics or Investigator and clinical site staff.
- Subjects who have received an investigational drug (either approved or not approved) in any prior clinical study within 30 days or 5 half-lives (whichever is longer) prior to Screening.
- Clinically significant abnormal findings during the Screening Period or any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject's safety or ability to complete the study.
- Active COVID-19 confirmed or suspected based on clinical symptoms.
- History of unstable angina or acute myocardial infarction within the 12 weeks preceding the Screening Visit or other clinically significant cardiac disease at the time of Screening as judged by the Investigator.

Exclusion criteria related to ongoing or recent conditions or treatments that may interfere with the study results are likewise not presented, including:

- Participation in any previous clinical study with paltusotine.
- History of ineffectiveness or significant intolerance of octreotide or lanreotide treatment, as determined by the Investigator. (Study CRN00808-08 only)
- Treatment-naïve or treatment-withdrawn acromegaly subjects. (Study CRN00808-09 only)
- Subjects with adrenal insufficiency, diabetes insipidus, or central hypogonadism who are not receiving adequate hormone replacement therapy at the time of Screening, as determined by the Investigator.
- High-risk pituitary tumour pattern as defined by:
  - Compression of the optic chiasm or invasion of adjacent brain structures (other than sphenoid sinus or cavernous sinus)
  - History of tumour growth within 1 year after surgery (if performed) or radiation (unless it occurred during a period of medical therapy interruption)
  - Anticipated requirement for neurosurgical intervention or radiation therapy within the time course of the study.
  - Pituitary carcinoma currently or at any time in the past.
- Use of the following medications as outlined:
  - Any history of acromegaly medication use (Study CRN00808-08 Group 1 only)
  - Lanreotide depot or octreotide LAR (within 16 weeks before Screening in Study CRN00808-08 Group 2 only)
  - Pasireotide LAR (within 24 weeks prior to Screening)
  - Pegvisomant (within 16 weeks before Screening in Study CRN00808-08; within 12 weeks before Screening in Study CRN00808-09)
  - Dopamine agonists (within 16 weeks before Screening in Study CRN00808-08; within 12 weeks before Screening in Study CRN00808-09)
  - Any combination of 2 or more acromegaly medications at Screening (Study CRN00808-08 only)
  - SA-SSAs within last 12 weeks before the first dose of study drug (Study CRN00808-09 only)
- History of pituitary radiation therapy

The remaining exclusion criteria from Studies CRN00808-08 and CRN00808-09 are presented below and may be grouped together.

Symptomatic cholelithiasis

Reason for exclusion:

Based on the mechanism of action, paltusotine may inhibit gallbladder contractility and decrease bile acid secretion, which may lead to gallbladder stones or sludge. This is in line with other SRL medications. Cholelithiasis and complications of cholelithiasis are adverse reactions of Sandostatin® LAR (octreotide acetate) and Somatuline® Autogel (lanreotide) and there are warnings on how to manage cholelithiasis in the SmPCs (Sandostatin LAR SmPC 2022; Somatuline Autogel SmPC 2024).

Patients with symptomatic cholelithiasis were excluded from participation in the studies as their inclusion could have impacted the safety assessment of paltusotine.

Is it considered to be included as missing information? No

Rationale:

Cholelithiasis and complications of cholelithiasis are an identified risk that is not considered to be important (Part II: Module SVIISVII.1.1).

The paltusotine SmPC warns healthcare professionals that paltusotine may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder stones or sludge. Cholelithiasis and its complications have been reported with the use of paltusotine. If complications of cholelithiasis are suspected, healthcare professionals are advised that evaluation and appropriate treatment should be initiated, and benefit-risk should be considered in determining whether or not to continue treatment with paltusotine. Cholelithiasis and bile duct stone are adverse reactions of paltusotine with frequencies of common (≥1/100 to <1/10) and uncommon (≥1/1 000 to <1/100), respectively. In randomised studies, cholelithiasis occurred between 6 and 9 months after the start of paltusotine. No patients discontinued paltusotine due to cholelithiasis.

As it is recognised that paltusotine can cause cholelithiasis, it is unlikely that patients with symptomatic cholelithiasis would be treated with paltusotine in clinical practice.

Use of the following medications as outlined:

PPIs (from start of Screening) until the end of the study

Reason for exclusion:

Patients administered concomitant PPIs were excluded from participation in Study CRN00808-08 because of the potential interaction with paltusotine.

Use of PPIs was permitted in Study CRN00808-09. In this study, 5 participants treated with paltusotine, and 2 participants treated with placebo were using PPIs as concomitant medication. While the number of participants using PPIs as concomitant medication is small, a subgroup analysis found that the paltusotine treatment effect was consistent across subgroups including the PPI subgroup; 4 of the 5 participants treated with paltusotine while using PPIs as concomitant medication were responders (IGF-1 ≤1.0xULN at the EOR) whereas neither of the 2 participants treated with placebo were responders (Study CRN00808-09 CSR Section 11.4.1.1.3).

As paltusotine exhibits pH-dependent solubility, the effect of PPIs on paltusotine PK was evaluated in healthy participants in Phase 1 Study CRN00808-07 with lansoprazole, a commonly

used PPI (M2.7.2 Section 3.5.1.1). Results indicated that administration of a PPI reduces paltusotine exposure in healthy participants in a dose-dependent manner. At the 20 mg dose of paltusotine SDD tablet, paltusotine C_{max} and AUC_{0-24} were modestly decreased by 16% and 21% in presence of a PPI, respectively, compared with the SDD tablets administered alone; at 60 mg dosing, both C_{max} and AUC_{0-24} decreased by approximately 40% in presence of a PPI, compared with the SDD tablets administered alone. To minimise the loss of efficacy due to reduction in exposures, co-administration of paltusotine with PPIs may require increased doses of paltusotine.

Additionally, results from PBPK modelling were used along with the dedicated clinical study to define the clinical implications of paltusotine drug interactions. Based on the "no-effect boundary," co-administration of paltusotine with PPIs (eg, lansoprazole) may require increased doses of paltusotine (M2.5 Section 3.2).

Is it considered to be included as missing information? No

Rationale:

The paltusotine SmPC warns healthcare professionals that PPIs have been shown to cause dose-dependent decreases in paltusotine AUC of approximately 20% and 40% for 20 mg and 60 mg dose levels, respectively. Co-administration of paltusotine with PPIs demonstrated a dose-dependent decrease in paltusotine exposure. In case of co-administration with PPIs (eg, lansoprazole), dose of Palsonify should be increased to two-fold the therapeutic dose or 120 mg daily, whichever is less. It is expected that this guidance will be followed in clinical practice.

Current use of medications that are strong inducers of CYP3A4 within 2 weeks prior to Screening

Reason for exclusion:

Patients administered concomitant strong inducers of CYP3A4 were excluded from participation in the studies because of the potential interaction with paltusotine.

Paltusotine is metabolised primarily hepatically via glucuronidation and oxidation. In vitro, glucuronidation was the major pathway of metabolism and is primarily mediated by UGT1A1 and UGT1A9. Oxidation was a secondary pathway and was primarily catalysed by CYP3A4/5 with a minor contribution from CYP2D6.

Co-administration of carbamazepine (a strong inducer of CYP3A4, UGT1A1, and P-gp) and paltusotine in healthy participants was evaluated in Study CRN00808-15 Cohort 1 and showed 44% and 70% decrease in paltusotine plasma C_{max} and AUC_{0-inf}, respectively (M2.7.2 Section 3.5.1.2). To minimise the loss of efficacy due to reduction in exposure, co-administration of paltusotine with strong CYP3A4 inducers may require the dose of paltusotine to be increased.

Additionally, the reduction in exposures with concomitant dexamethasone (weak CYP3A4 inducer) or efavirenz (moderate CYP3A4 inducer) was evaluated using a PBPK model. There was no clinically meaningful change in paltusotine exposures in the presence of dexamethasone; therefore, dose adjustment is not necessary. The reduction in paltusotine AUC was approximately 30% in the presence of efavirenz (M2.7.2 Section 3.5.1.2). Based on the "no-effect boundary," co-administration of paltusotine with moderate CYP3A4 inducers (eg, efavirenz) may require increased doses of paltusotine (M2.7.2 Section 5.4).

Is it considered to be included as missing information? No

Rationale:

The paltusotine SmPC informs healthcare professionals of how paltusotine is metabolised and warns that strong inducers of multiple enzymes and transporters (CYP3A4/5, UGT1A1, and P-gp) have been shown to decrease paltusotine C_{max} and AUC of approximately 40% and 70%, respectively. Co-administration of paltusotine with strong inducers of multiple enzymes and transporters (CYP3A4/5, UGT1A1, and P-gp) reduced paltusotine exposure and may affect therapeutic response. In case of co-administration with strong inducers of multiple enzymes and transporters (CYP3A4/5, UGT1A1, and P-gp) (eg, carbamazepine), dose of Palsonify should be increased up to three-fold the therapeutic dose or 120 mg daily, whichever is less. Dose adjustments of Palsonify may be necessary when paltusotine is co-administered with a moderate CYP3A4 inducer (eg, efavirenz). It is expected that this guidance will be followed in clinical practice.

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.

Reason for exclusion:

As with the majority of clinical studies, female patients who were pregnant or lactating were excluded from study participation for safety reasons. A negative pregnancy test was required during Screening and prior to the first dose of study drug.

The inclusion criteria specified that females who engage in heterosexual intercourse must be of nonchildbearing 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.

One of the acceptable highly effective methods of contraception included noncyclic, stable dose (monophasic) combined oestrogen-progestin oral hormonal contraception associated with consistent inhibition of ovulation. Oral contraceptives containing oestrogens were to be in stable use for at least 12 weeks prior to Screening. To emphasise this, current use of oral oestrogen replacement therapy for <12 weeks prior to Screening was an exclusion criterion.

Is it considered to be included as missing information? No

Rationale:

Throughout the clinical development programme, there were two pregnancies (one each in Study CRN00808-07 and Study CRN00808-05). In Phase 1 Study CRN00808-07, a healthy participant taking oral contraception (Yasmin [ethinylestradiol and drospirenone]) which had been used continuously for over 5 years received a single 20 mg dose of paltusotine and became pregnant approximately 2 weeks later; no further details on the outcome of pregnancy are available (M2.7.4 Section 6.4). In Study CRN00808-05, a female acromegaly participant had a positive pregnancy test during Week 16 of the study and following a CMV infection during pregnancy and a caesarean section had a neonate with ankyloglossia, interatrial communication (patent foramen ovale), mineralising vasculopathy and neonatal wet lung syndrome (M2.7.4 Section 6.4). The participant had a copper intrauterine device that was removed

approximately 3 weeks prior to the positive pregnancy test. There are other explanations (M2.7.4 Section 6.4) for these conditions rather than a causal association with paltusotine.

The paltusotine SmPC advises healthcare professionals that animal studies do not indicate direct or indirect harmful effects at human exposure with respect to reproductive toxicity.

Embryo-foetal development studies in rats and rabbits with doses up to 500 mg/kg/day (rat) and 75 mg/kg/day (rabbit) showed no evidence of teratogenic effects (up to 11 times and 5.2 times the clinical dose of 60 mg based on AUC in rat and in rabbit, respectively). In rabbits, the highest dose showed an increased incidence of abortions associated with maternal toxicity (decreased food intake and body weight loss) and a decrease in mean foetal body weights. This was not observed at the 25 mg/kg/day dose (2.9 times the clinical dose of 60 mg based on AUC).

As there are limited data from the use of paltusotine in pregnant women, it is preferable to avoid the use of Palsonify during pregnancy as a precautionary measure.

Since the therapeutic benefits of a reduction in GH levels and normalisation of IGF-1 concentration in female acromegalic patients could potentially restore fertility, female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with paltusotine.

There are no clinical data regarding exposure during lactation. The paltusotine SmPC advises healthcare professionals that in a pre- and postnatal development study in rat, decreased body weight was observed during the preweaning and postweaning development periods at 500 mg/kg/day, the highest dose tested. There were no treatment-related effects on sexual maturation, neurobehavioral or reproductive function of the first filial (F1) generation rats at any dose level. Excretion of paltusotine into maternal milk was demonstrated with milk-to-plasma concentration ratios at 4 hours postdosing on lactation day (LD) 20 ranging from 2.4- to 3.8-fold.

It is unknown whether paltusotine/metabolites are excreted in human milk and as a risk to the suckling newborns/infants cannot be excluded, breast-feeding should be discontinued during treatment with Palsonify.

Use in females who are pregnant or lactating is not considered missing information because it is not expected to be further characterised during the postmarketing period. Pregnancy cases will be followed up using routine pharmacovigilance activities.

Systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg during Screening.

Reason for exclusion:

Patients with elevated blood pressure were excluded from participation in the studies as their inclusion could have impacted the safety assessment of paltusotine.

Is it considered to be included as missing information? No

Rationale:

In clinical practice it is expected that some patients treated with paltusotine will have underlying hypertension as hypertension is one of the many symptoms of acromegaly (Part II: Module SI).

In the RC Phase of Study CRN00808-08, participants in both the paltusotine (N=54) and placebo (N=57) groups had a medical history of hypertension at baseline (n=24, 44.4% vs n=25, 43.9%),

respectively (Study CRN00808-08 CSR Table 14.1.2.8). Similarly in the RC Phase of Study CRN00808-09, participants in the paltusotine (N=30) and placebo (N=28) groups had a medical history of hypertension at baseline (n=18, 60.0% vs n=11, 39.3%), respectively (Study CRN00808-09 CSR Table 14.1.2.5).

However, paltusotine is not recognised to cause hypertension. In the Primary Group (RC Phases of Study CRN00808-08 and Study CRN00808-09), changes from baseline for blood pressure were generally small and comparable between groups (M2.7.4 Section 4.1.1).

In the Supportive Group overall, no clinically important changes from baseline in vital signs were observed based on worst postbaseline values (M2.7.4 Section 4.1.2).

As hypertension is a common comorbidity in patients with acromegaly, it is therefore expected that blood pressure will be adequately monitored and treated in clinical practice.

Resting (at least 10 minutes) palpated pulse rate <45 bpm or >105 bpm during Screening.

Reason for exclusion:

Approved SRL treatments are recognised to cause cardiac function abnormalities including bradycardia and conduction abnormalities/arrythmias. Sinus bradycardia is an adverse reaction of lanreotide (Somatuline Autogel SmPC 2024) and bradycardia, tachycardia, and arrhythmias are adverse reactions of octreotide (Sandostatin LAR SmPC 2022).

Cardiovascular safety pharmacology studies with paltusotine in dogs showed a transient nondose-dependent decrease in heart rate and increase in blood pressure, which were considered small in magnitude and within normal biological variation (Table Part II: Module SII.1).

Patients with abnormal heart rates were excluded from participation in the studies as their inclusion could have impacted the safety assessment of paltusotine.

Is it considered to be included as missing information? No

Rationale:

Sinus bradycardia is discussed as a risk not considered important in Part II: Module SVIISVII.1.1.

The paltusotine SmPC warns healthcare professionals that cardiac conduction abnormalities and other ECG changes such as PR interval prolongation and bradycardia have occurred during treatment with paltusotine in clinical studies. These ECG changes may occur in patients with acromegaly. Dose adjustments of concomitantly used medicinal products that have bradycardia effects (eg, beta blockers) may be necessary. Sinus bradycardia (combined term of sinus bradycardia and bradycardia) is an adverse reaction of paltusotine with a frequency of common (≥1/100 to <1/10).

In the clinical studies, the events of bradycardia in patients treated with paltusotine were asymptomatic and did not lead to the discontinuation of the medicinal product. The events occurred in patients with and without a history of bradycardia, occurred in the first three months of treatment and there was no clear dose association. The mean reduction in heart rate was 6 bpm.

QTcF >480 msec (or QTc interval >500 msec in the presence of complete bundle branch block) or PR interval >240 msec during Screening

Reason for exclusion:

Approved SRL treatments are recognised to cause cardiac function abnormalities including bradycardia and conduction abnormalities/arrythmias. Sinus bradycardia is an adverse reaction of lanreotide (Somatuline Autogel SmPC 2024) and bradycardia, tachycardia, and arrhythmias are adverse reactions of octreotide (Sandostatin LAR SmPC 2022).

There were no ECG abnormalities such as QT prolongation or arrhythmias observed in the cardiovascular safety pharmacology study or repeat-dose toxicity studies (up to 9 months) in dogs at the highest doses tested, which provide safety margins of 5.5-fold (at 10 mg/kg) and 50-fold (at 75 mg/kg/day), respectively, for the highest dose used in clinical trials, 60 mg for acromegaly (Table Part II: Module SII.1).

Patients with QTcF >480 msec (or QTc interval >500 msec in the presence of complete bundle branch block) or PR interval >240 msec were excluded from participation in the studies as their inclusion could have impacted the safety assessment of paltusotine.

Is it considered to be included as missing information? No

Rationale:

A dedicated assessment on concentration-QTc relationships to address any potential risk of QTc interval prolongation was performed. Collective review of data demonstrated no clinical or nonclinical signals of concern for drug-induced ventricular arrhythmias and therefore the potential for effects of paltusotine on cardiac repolarisation is very low (M2.5 Section 3.3.3).

In the first-in-human, double-blind, randomised, placebo-controlled, single- and multiple-dose, Phase 1 Study CRN00808-01 in healthy volunteers, ECG, 24-hour telemetry and Holter data were collected, and analysed. Paltusotine did not have clinically significant effects on AV conduction (as measured by the PR interval), or cardiac depolarisation (as measured by the QRS duration). There were no clinically relevant ECG morphological changes. Continuous Holter recordings and telemetry demonstrated no evidence of paltusotine-related AV block, supraventricular or ventricular tachyarrhythmias (M2.7.4 Section 5.5.2).

In the Primary Group (RC Phases of the pivotal Phase 3 Studies CRN00808-08 and CRN00808-09), no participants in either the paltusotine or placebo groups had a QTcF interval of >500 msec or change of >60 msec (M2.7.4 Section 4.4.2.1). In the paltusotine group, 7 of 84 (8.3%) participants had abnormal postbaseline QTcF intervals of >450 msec. One participant with a medical history of hypertension had an interval of >480 msec. Five (6.0%) participants had a change from baseline of >30 msec. None of the participants in paltusotine group had corresponding ECG interpretations that were considered clinically significant. In the placebo group, 6 of 85 (7.1%) participants had abnormal postbaseline QTcF intervals of >450 msec, and 2 (3.4%) participants had a change from baseline of >30 msec. No safety signals were identified in the Primary Group based on QTcF analysis.

In the Supportive Group (pooled analysis of safety data from the 2 Phase 3 Studies CRN00808-08 and CRN00808-09 including data from RC and OLE Phases and 3 Phase 2 Studies CRN00808-03, CRN00808-02, and CRN00808-05 OLE), 23 of 233 (9.9%) participants had abnormal postbaseline QTcF intervals of >450 msec, and 2 (0.9%) participants

had intervals of >480 msec (both in Study CRN00808-05) (M2.7.4 Section 4.4.2.2). No participants had an interval >500 msec. Additionally, 12 (5.2%) participants had a change from baseline of >30 msec; none had a change of >60 msec. The incidence of QTcF changes was comparable to the paltusotine group of the Primary Group. No safety signals were identified in the Supportive Group based on QTcF analysis.

In the Primary Group there were no cardiovascular SAEs. In the Supportive Group, 3 participants (1.3%) experienced a cardiovascular SAE (ISS Table 14.3.1.14). The first participant with a relevant medical history of type 2 diabetes mellitus, hyperlipidaemia, hypertension, and CAD was hospitalised for worsening CAD (M2.7.4 Section 5.5.6.1). Dosing with paltusotine was temporarily interrupted and the participant underwent CABG surgery for three vessel CAD. Three days postoperatively (Day 398), the participant experienced an 18 sec sinus pause/arrest, which resolved spontaneously. A dual-chamber pacemaker was implanted due to the postoperative sinus arrest. Neither the moderate CAD nor severe sinus arrest were considered related to paltusotine treatment.

Sinus arrest occurred in a second participant with a relevant medical history of hypertrophic cardiomyopathy, arterial hypertension, apnoea/hypopnea, sinus bradycardia, impaired glucose tolerance, and glaucoma (M2.7.4 Section 5.5.6.1). The participant underwent pacemaker placement without complications and recovered. Paltusotine was temporarily discontinued while cosuspect medication timolol and ophthalmic dorzolamide and latanoprost were discontinued. The Investigator assessed the event of sinus arrest as possibly related to paltusotine.

The third elderly (>80 years) participant with a history of hypertension, dyslipidaemia, diabetes mellitus, and panhypopituitarism experienced severe total atrioventricular block (confirmed by ECG) and was hospitalised the same day (M2.7.4 Section 5.5.6.1). Paltusotine was permanently withdrawn and the atrioventricular block complete resolved following treatment. The Investigator assessed the event of atrioventricular block complete as unlikely related to paltusotine, and the alternative causality was the pre-existing history of hypertension.

These SAEs are not indicative of additional new safety risks in relation to AV block/sinus arrest or ventricular tachyarrhythmias as the cases were confounded.

Overall, there is no evidence from nonclinical or clinical studies that paltusotine prolongs the QT interval.

The paltusotine SmPC informs healthcare professionals that at 4.6 times the exposure of the paltusotine 60 mg therapeutic dose, clinically significant QTc interval prolongation was not observed. Healthcare professionals are warned that cardiac conduction abnormalities and other ECG changes such as PR interval prolongation and bradycardia have occurred during treatment with paltusotine in clinical studies. These ECG changes may occur in patients with acromegaly. Dose adjustments of concomitantly used medicinal products that have bradycardia effects (eg, beta blockers) may be necessary.

ALT and/or AST >3× ULN, and/or total bilirubin >1.5×ULN during Screening. Subjects with previously diagnosed Gilbert's syndrome not accompanied by other hepatobiliary disorders and associated with total bilirubin <3.5 mg/dL (<51.3 µmol/L) will be permitted.

Reason for exclusion:

Patients with ALT and/or AST >3×ULN, and/or total bilirubin >1.5×ULN were excluded from participation in the studies as their inclusion could have impacted the safety assessment of paltusotine.

Is it considered to be included as missing information? No

Rationale:

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. 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 (M2.7.2 Section 2.1.4.1, M2.7.2 Section 3.3.7).

The paltusotine SmPC informs healthcare professionals that no dose adjustment is required in patients with mild, moderate or severe hepatic impairment.

Poorly controlled diabetes mellitus defined as having a HbA1c ≥8.5% (≥69 mmol/mol), or estimated HbA1c based on fructosamine if HbA1c is not evaluable (eg, due to haemoglobinopathies).

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.

Reason for exclusion:

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and other approved somatostatin analogues, inhibits the secretion of insulin and glucagon (Somatuline Autogel SmPC 2024). Hence, patients treated with lanreotide may experience hypoglycaemia or hyperglycaemia. The lanreotide SmPC advises that blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and any anti-diabetic treatment should be adjusted accordingly. Likewise, octreotide may affect glucose regulation because of its inhibitory action on GH, glucagon, and insulin release (Sandostatin LAR SmPC 2022). The octreotide SmPC recommends monitoring glucose tolerance and antidiabetic treatment in patients with concomitant type 1 diabetes mellitus and also to monitor patients with insulinomas.

Patients with poorly controlled diabetes were excluded from participation in the studies as their inclusion could have impacted the safety assessment of paltusotine.

Is it considered to be included as missing information? No

Rationale:

Paltusotine is highly selective (>4000-fold) for SST2 relative to other human somatostatin receptor subtypes (M2.7.4 Appendix E Section 6). Paltusotine is also very selective (>2000-fold) for SST2 over a large panel of other receptors, channels, and enzymes known to be targets of other drugs (M2.6.2 Section 3.2), thus reducing the risk of unwanted off-target activities or toxicities.

In nonclinical studies, the effect of paltusotine on postprandial glucose excursion was examined in the rat using an oral glucose tolerance test. These data suggest that under the conditions examined, paltusotine does not alter glucose metabolism in the rat (M2.6.2 Section 4.1).

Diabetes is a recognised symptom of acromegaly (Part II: Module SI). Therefore, it was not unexpected that approximately 20-50% participants treated with paltusotine included in Studies CRN00808-08 and CRN00808-09 had a medical history of diabetes at baseline (Table Part II: Module SIV.1).

Hyperglycaemia and hypoglycaemia were identified as AEs known to be associated with approved SRLs. In the Primary Group, there was an imbalance in TEAEs related to hyperglycaemia (as an SRL event category) in the RC Phase (7.1% [n=6] paltusotine vs 3.5% [n=3] placebo) (ISS Table 14.3.1.19), disfavouring paltusotine, but on review of the individual cases, there were significant confounding factors in each case, including the occurrence of isolated, single increases. There was no evidence of an important increase in HbA1c or blood glucose in participants who received paltusotine compared to placebo in Studies CRN00808-08 and CRN00808-09, and the data did not show a difference in the incidence of progression of diabetes status between the paltusotine and placebo groups (M2.7.4 Section 5.3).

A relationship was found between paltusotine exposure and the change from baseline HbA1c in Study CRN00808-08 but not in Study CRN00808-09. For Study CRN00808-08, there was a linear increase in HbA1c with paltusotine exposure. However, the mean change of HbA1c predicted from the linear model at the 60 mg dose of paltusotine was 0.23% and was not considered clinically meaningful (M2.7.2 Section 3.6.2).

The paltusotine SmPC warns healthcare professionals that because of its effect on GH, glucagon, and insulin, paltusotine may affect glucose regulation. Hyperglycaemia was reported in patients treated with Palsonify in clinical studies. Healthcare professionals are advised to monitor blood glucose levels when Palsonify treatment is initiated or the dose is altered, and to adjust antidiabetic treatment accordingly. Hyperglycaemia is an adverse reaction of paltusotine with a frequency of common (≥1/100 to <1/10).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table Part II: Module SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme. Throughout the clinical development programme, there were two pregnancies (one each in Study CRN00808-07 and Study CRN00808-05) (Part II: Module SII; Module SIV.1).
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with clinically significant concomitant liver disease (including cirrhosis) or ALT and/or AST >3×ULN, and/or total bilirubin >1.5×ULN were excluded from participation in Studies CRN00808-08 and CRN00808-09 (Module SIV.1). Study CRN00808-10, a Phase 1, open-label clinical evaluated the safety, tolerability, and PK of a single 20 mg dose of paltusotine in participants with varying degrees of hepatic impairment compared with healthy participants (M2.7.2 Section 2.1.4.1). A total of 36 participants were enrolled in the study including 8 with mild (Child Pugh score of 5-6), 8 with moderate (score of 7-9), and 6 with severe (score of 10-15) hepatic impairment, and 14 matched control participants. Peak and total systemic exposures of paltusotine were similar across all hepatic impairment groups when compared with participants with normal hepatic function. There did not appear to be an imbalance in the distribution of baseline covariates used in participant matching (age and BMI) as the GMRs were similar in both analyses. Furthermore, 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. Mild, moderate, and severe hepatic impairment did not have a meaningful effect on the exposure of paltusotine; therefore, dose adjustment is not necessary in patients with varying degree of hepatic impairment.

Type of Special Population	Exposure
• Patients with renal impairment	Patients with clinically significant concomitant severe renal insufficiency (eGFR <30 mL/min/1.73 m^2) were excluded from participation in Studies CRN00808-08 and CRN00808-09 (Module SIV.1). A clinical study in participants with renal impairment was not conducted because only 3.9% of the total radioactive dose was recovered in urine in ADME Study CRN00808-06 (M2.7.2 Section 2.1.1.3). The effect of eGFR on paltusotine exposure was assessed in the population PK model and the effect of mild, moderate, or severe renal impairment on paltusotine exposure was assessed using PBPK simulations (M2.7.2 Section 3.3.8). Population PK analyses found that eGFR was not a significant covariate on paltusotine clearance. Data from 315 participants showed a median (IQR) eGFR (CKD-EPI) of 109 (97, 119) mL/min/1.73 m^2 with a range from 52 mL/min/1.73 m^2 to 148 mL/min/1.73 m^2, of which a majority of these participants had normal renal function or mild impairment. PBPK simulations of paltusotine 60 mg QD dosing for 2 weeks were used to compare virtual participants with mild, moderate, or severe renal impairment to a virtual healthy control group with matched demographics and baseline characteristics. The results showed that simulated geometric mean $AUC_{0-\tau}$ and C_{max} values increased ≤15% across all renal impairment groups relative to the healthy control group. Collectively, clinical mass balance data, population PK analyses, and PBPK simulations demonstrate that renal impairment has a minimal impact of paltusotine exposure regardless of the severity of renal impairment. No dose adjustments of paltusotine based on renal impairment are required.
• Patients with cardiovascular impairment	Patients with clinically significant concomitant cardiovascular disease were excluded from participation in Studies CRN00808-08 and CRN00808-09 (Module SIV.1). In the RC Phase of Study CRN00808-08, 11 participants (20.4%) treated with paltusotine and 10 participants (17.5%) treated with placebo had a medical history of a cardiac disorder (Study CRN00808-08 CSR Table 14.1.2.8). The most frequently reported medical history PTs in the paltusotine and placebo groups were mitral valve incompetence (n=2, 3.7% vs n=2, 3.5%), sinus bradycardia (n=2, 3.7% vs n=2, 3.5%), cardiomyopathy (n=2, 3.7% vs n=1, 1.8%), left ventricular hypertrophy (n=2, 3.7% vs n=0), and myocardial ischaemia (n=2, 3.7% vs n=0), respectively.

Type of Special Population	Exposure
	For the RC Phase of Study CRN00808-09, the paltusotine group had more participants with a medical history of a cardiac disorder than the placebo group (n=10, 33.3% vs n=4, 14.3%, respectively (Study CRN00808-09 CSR Table 14.1.2.5). The most frequently reported PTs in the paltusotine and placebo groups were left ventricular hypertrophy (n=3, 10.0% vs n=1, 3.6%), left atrial enlargement (n=2, 6.7% vs n=1, 3.6%), and sinus bradycardia (n=2, 6.7% vs 0), respectively.
• Hypertension	Patients with systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg during Screening were excluded from participation in Studies CRN00808-08 and CRN00808-09 (Module SIV.1). In the RC Phase of Study CRN00808-08, participants in both the paltusotine (N=54) and placebo (N=57) groups had a medical history of hypertension at baseline (n=24, 44.4% vs n=25, 43.9%), respectively (Study CRN00808-08 CSR Table 14.1.2.8). Similarly in the RC Phase of Study CRN00808-09, participants in the paltusotine (N=30) and placebo (N=28) groups had a medical history of hypertension at baseline (n=18, 60.0% vs n=11, 39.3%), respectively (Study CRN00808-09 CSR Table 14.1.2.5).
• Diabetes	Patients with poorly controlled diabetes mellitus defined as having a HbA1c ≥8.5% (≥69 mmol/mol), or estimated HbA1c based on fructosamine if HbA1c is not evaluable (eg, due to haemoglobinopathies), 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 or with diabetes insipidus were excluded from participation in Studies CRN00808-08 and CRN00808-09 (Module SIV.1). In the RC Phase of Study CRN00808-08, participants in both the paltusotine (N=54) and placebo (N=57) groups had a medical history of diabetes at baseline; type 2 diabetes mellitus (n= 7, 13.0% vs n=6, 10.5%), glucose tolerance impaired (n=2, 3.7% vs n=9, 15.8%), diabetes mellitus (n=2, 3.7% vs n= 6, 10.5%), hyperglycaemia (n=1, 1.9% vs n=1, 1.8%), respectively (Study CRN00808-08 CSR Table 14.1.2.8). Similarly in the RC Phase of Study CRN00808-09, participants in the paltusotine (N=30) and placebo (N=28) groups had a medical history of diabetes at baseline; diabetes mellitus (n=6, 20.0% vs n=2, 7.1%), glucose tolerance impaired (n=4, 13.3% vs n=2, 7.1%), type 2 diabetes mellitus (n=3, 10.0% vs n=3, 10.7%), impaired fasting glucose (n=2, 6.7% vs 0), and insulin resistance (n=1, 3.3% vs 0), respectively (Study CRN00808-09 CSR Table 14.1.2.5). HbA1c baseline levels in participants in the Primary Group and Supportive Group are presented in the table below.

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td></td><td>HbA1c Baseline Levels in Participants in the Primary Group and Supportive Group (Safety Populations)
<table>
<tr><th rowspan="2">HbAlc Groups - n (%)</th><th colspan="3">Primary Group</th><th>Supportive Group</th></tr>
<tr><th>Paltusotine (N=84)</th><th>Placebo (N=85)</th><th>Total (N=169)</th><th>Paltusotine (N=233)</th></tr>
<tr><td><6.5% (not diabetic)</td><td>74 (88.1)</td><td>78 (91.8)</td><td>152 (89.9)</td><td>199 (85.4)</td></tr>
<tr><td>≥6.5% (diabetic)</td><td>10 (11.9)</td><td>7 (8.2)</td><td>17 (10.1)</td><td>33 (14.2)</td></tr>
<tr><td>Missing</td><td>0</td><td>0</td><td>0</td><td>1 (0.4)</td></tr>
</table>
HbA1c=haemoglobin A1c
Source: ISS Table 14.1.2.1, ISS Table 14.1.2.2
Primary Group Data Cut: Studies CRN00808-09: 05 Dec 2023; CRN00808-08: 20 Jan 2024.
Supportive Group Data Cut: Studies CRN00808-08: 01 Sep 2024; CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.</td></tr>
<tr><td>• Immunocompromised patients</td><td>Patients with active malignant disease within the last 5 years or known history of hepatitis B or human immunodeficiency virus, or active hepatitis C infection were excluded from participation in Studies CRN00808-08 and CRN00808-09 (Module SIV.1). Use of paltusotine in immunocompromised patients was not evaluated in the clinical development programme.</td></tr>
<tr><td>• Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Not included in the clinical development programme.
The proposed indication is for the medical treatment of adult patients with acromegaly is supported by data from the clinical studies.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>Clinical trial exposure data by ethnicity are presented for participants treated with paltusotine in the Primary Group and Supportive Group in Part II: Module SIII.
In the Primary Group, the majority of participants treated with paltusotine were Not Hispanic or Latino (n=48, 57.1%); followed by Hispanic or Latino (n=29, 34.5%) and unknown (n=7, 8.3%) (Table Part II: Module SIII.10). Likewise, in the Supportive Group, the majority of participants treated with paltusotine were Not Hispanic or Latino (n=144, 61.8%); followed by Hispanic or Latino (n=77, 33.0%), unknown (n=11, 4.7%), and not reported (n=1, 0.4%) (Table Part II: Module SIII.11).</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development programme.</td></tr>
</table>

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Not applicable.

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Paltusotine was designed to exhibit peripheral action only. As paltusotine is a P-gp substrate, it poorly penetrates the brain as demonstrated in nonclinical tissue distribution studies. There were no effects on functional observation parameters in nonclinical neurobehavioural safety pharmacology studies, and no evidence of clinical or ancillary observations indicative of the potential for abuse or dependence liability in the nonclinical toxicology programme.

While paltusotine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence, paltusotine does not target any of the relevant neuronal systems (such as dopamine, serotonin, GABA or Opioid systems) related to typical drugs of abuse and is not a salt, isomer, salt of isomer, or prodrug of any controlled substance. Unlike other indications (eg, acute or chronic pain, anxiety disorders, substance use disorders), the therapeutic indication of paltusotine (acromegaly) is not associated with a drug class that is reliably abused by any known population. Approved somatostatin agonists are not associated with drug abuse or dependence.

The safety profile of paltusotine does not exhibit a potential for abuse as evidenced by the AEs reported in the clinical studies. Chronic use of paltusotine is not associated with physical dependence or psychological dependence.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Gastrointestinal events

GI events are an identified risk of paltusotine.

In nonclinical GLP studies, emesis and abnormal stool (characterised by soft, loose, or watery stools) were observed in the dog at all dose levels up to 75 mg/kg/day (Table Part II: Module SIII.1). A loss of appetite accompanied by decreased body weight was also noted, which were improved by offering regular canned food. Emesis was dose-dependent but sporadic (not in all animals and not after each dose), and generally resolved over repeated dosing. Diarrhoea resolved upon cessation of dosing.

Gastrointestinal TEAEs for the Primary Group and Supportive Group are presented in Table Part II: Module SVII.1.

In the Primary Group, GI TEAEs that occurred with a higher incidence (either twice the incidence or a greater than 10% difference and occurring at an incidence of at least 5%) with paltusotine compared to placebo were diarrhoea (n=25, 29.8% vs n=14, 16.5%), abdominal pain (n=11, 13.1% vs n=5, 5.9%), nausea (n=9, 10.7% vs n=4, 4.7%) and abdominal discomfort (n=5, 6.0% vs n=1, 1.2%), respectively (ISS Table 14.3.1.3). The GI events were predominately mild in severity and none were serious (ISS Table 14.3.1.11, ISS Table 14.3.1.13). The majority of GI events did not require medication (ISS Listing 16.2.7.1). An analysis of the first 14 days of treatment at 20 mg paltusotine in Study CRN00808-08 found that most events of diarrhoea and nausea occurred in the first 14 days in this study (ISS Table 14.101.6). The majority of events of diarrhoea (23/40) lasted ≤3 days (ISS Listing 16.2.7.1).

Table Part II: Module SVII.1: Gastrointestinal TEAEs in the Primary Group and Supportive Group (Safety Populations)

	Primary Group			Supportive Group
	Paltusotine (N=84)	**Placebo (N=85)**	**Total (N=169)**	**Paltusotine (N=233)**
Gastrointestinal events, n (%)				
TEAEs	43 (51.2)	31 (36.5)	74 (43.8)	118 (50.6)
Related TEAEs	28 (33.3)	15 (17.6)	43 (25.4)	68 (29.2)
TEAEs by Severity[a]:				
Diarrhoea	25 (29.8)	14 (16.5)	39 (23.1)	57 (24.5)
Severe	0	0	0	0
Moderate	1 (1.2)	3 (3.5)	4 (2.4)	5 (2.1)
Mild	24 (28.6)	11 (12.9)	35 (20.7)	52 (22.3)
Abdominal pain	11 (13.1)	5 (5.9)	16 (9.5)	25 (10.7)
Severe	0	0	0	1 (0.4)
Moderate	2 (2.4)	1 (1.2)	3 (1.8)	5 (2.1)
Mild	9 (10.7)	4 (4.7)	13 (7.7)	19 (8.2)
Nausea	9 (10.7)	4 (4.7)	13 (7.7)	19 (8.2)
Severe	0	0	0	0
Moderate	1 (1.2)	2 (2.4)	3 (1.8)	2 (0.9)
Mild	8 (9.5)	2 (2.4)	10 (5.9)	17 (7.3)
Serious TEAEs	0	0	0	4 (1.7)
Serious Related TEAEs	0	0	0	1 (0.4)
TEAEs Leading to Treatment Discontinuation:				
Nausea	1 (1.2)	0	1 (0.6)	1 (0.4)

TEAE = treatment-emergent adverse event
Notes: MedDRA version 24.1. Percentages are calculated based on the number of participants in the Safety Population.
[a] The three gastrointestinal TEAEs with the highest incidence are presented.
Source: ISS Table 14.3.1.3, ISS Table 14.3.1.4, ISS Table 14.3.1.7, ISS Table 14.3.1.8, ISS Table 14.3.1.11, ISS Table 14.3.1.12, ISS Table 14.3.1.13, ISS Table 14.3.1.14, ISS Table 14.3.1.15, ISS Table 14.3.1.16, ISS Table 14.3.1.25, ISS Table 14.3.1.26, ISS Table 14.3.1.20
Primary Group Data Cut: Studies CRN00808-09: 05 Dec 2023; CRN00808-08: 20 Jan 2024.
Supportive Group Data Cut: Studies CRN00808-08: 01 Sep 2024 CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

The GI events did not appear to be dose dependent. There was no increase in frequency of the most common TEAEs in the paltusotine group when comparing the 2 maximum doses of paltusotine (40 mg vs 60 mg: diarrhoea [n=9, 30.0% vs n=16, 29.6%], abdominal pain [n=5, 16.7% vs n=6, 11.1%], nausea [n=4, 13.3% vs n=5, 9.3%], and abdominal discomfort [n=2, 6.7% vs n=3, 5.6%]) (ISS Table 14.100.2).

In the Primary Group, there was 1 study drug discontinuation due to nausea in the paltusotine group in Study CRN00808-08; a participant with a history of large intestine polyp had multiple TEAEs leading to discontinuation in addition to nausea (ISS Table 14.3.1.25, Study CRN00808-08 CSR Listing 16.2.7.4).

In the Supportive Group, the most common GI TEAEs (diarrhoea [n=57, 24.5%], abdominal pain [n=25, 10.7%], nausea [n=19, 8.2%], and abdominal distension [n=14, 6.0%]) occurred most frequently in the first 3 months of treatment (ISS Table 14.3.1.4, ISS Table 14.3.1.23). The GI events were predominately mild in severity and nonserious (ISS Table 14.3.1.12, ISS Table 14.3.1.14). Treatment was only discontinued in 1 participant due to nausea (ISS Table 14.3.1.26), which is the same participant described above.

In summary, there is adequate evidence to support a causal relationship between paltusotine and GI events of diarrhoea, abdominal pain, nausea, and abdominal discomfort, consistent with approved SRL therapies (Sandostatin LAR SmPC 2022; Somatuline Autogel SmPC 2024). There was no evidence to support a causal relationship with other GI TEAEs.

Gastrointestinal events are not an important risk of paltusotine as most gastrointestinal adverse reactions occurred within the first two months of paltusotine initiation, had a median duration ranging between 4 to 12 days, were non serious, predominantly mild in severity, and improved with continued treatment. There were no discontinuations due to gastrointestinal adverse reactions. Gastrointestinal events will be managed in clinical practice through the SmPC guidance that advises healthcare professionals of the gastrointestinal adverse reactions that occurred including diarrhoea with a frequency of very common (≥1/10) and abdominal pain, nausea, abdominal discomfort, abdominal distension, and vomiting with frequencies of common (≥1/100 to <1/10).

Gastrointestinal events will continue to be monitored using routine pharmacovigilance activities.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Drug-drug interactions

Drug-drug interactions are an identified risk of paltusotine.

The potential drug interactions between paltusotine and carbamazepine, metformin, cyclosporine, midazolam, and lansoprazole were evaluated in clinical studies with healthy participants. Additionally, results from PBPK modelling were used along with the dedicated clinical studies to define the clinical implications of paltusotine drug interactions.

An overview of the drug interaction evaluations, the clinical impact, and proposed recommendations is presented in Table Part II: Module SVII.2.

Table Part II: Module SVII.2: Overview for Drug-Drug Interactions with Paltusotine

Interaction	Assessment[a]	Clinical Impact	Recommendation
Victim-Based Drug Interaction Potential			
Carbamazepine (CYP3A4/5, UGT1A1, and P-gp inducer)	Clinical Study CRN00808-15 Cohort 1	Approximately 40% and 70% decreases in C_{max} and AUC, respectively, of paltusotine	Paltusotine dose may need to be increased
Weak CYP3A4 inducer	PBPK modelling (Inducer: dexamethasone)	No interaction with dexamethasone	Paltusotine dose adjustment is not necessary
Moderate CYP3A4 inducer	PBPK modelling (Inducer: efavirenz)	Approximately 5% and 30% decreases in C_{max} and AUC, respectively, of paltusotine	Paltusotine dose may need to be increased
Cyclosporine (CYP3A4/5, P-gp, and BCRP inhibitor)	Clinical Study CRN00808-15 Cohort 3	Approximately 2-fold increase in both C_{max} and AUC of paltusotine	Paltusotine dose adjustment is not necessary
Weak, moderate, strong, and mechanism-based CYP3A4/5 inhibitors	PBPK modelling (Inhibitors: cimetidine, fluconazole, itraconazole, erythromycin)	Little or no interaction (<25% increase in C_{max} and AUC of paltusotine)	Paltusotine dose adjustment is not necessary
Dual CYP3A4 and P-gp inhibitors	PBPK modelling (Inhibitor: itraconazole or verapamil)	62% and 91% increase in both C_{max} and AUC of paltusotine (using verapamil)	Paltusotine dose adjustment is not necessary
UGT1A1 inhibitors	PBPK modelling (Inhibitor: atazanavir)	Up to 8% and 44% increases in C_{max} and AUC, respectively, of paltusotine	Paltusotine dose adjustment is not necessary
Lansoprazole (PPI)	Clinical Study CRN00808-07	Dose-dependent decreases in paltusotine AUC, approximately 20% and 40% for 20 mg and 60 mg dose levels, respectively	Paltusotine dose may need to be increased
Perpetrator-Based Drug Interaction Potential			
CYP3A4/5 Inhibition	Clinical Study CRN00808-15 Cohort 4 (Clinical substrate: midazolam)	Paltusotine 60 mg QD at steady state showed no impact on midazolam C_{max} and approximately 30% increase in midazolam AUC	Dose adjustment for CYP3A4 substrate is not necessary
CYP2D6 Inhibition	PBPK modelling (Substrate: dextromethorphan)	Little or no interaction (<25% increase in dextromethorphan C_{max} and AUC)	Dose adjustment for CYP2D6 substrate is not necessary
P-gp inhibition	PBPK modelling (Substrates: digoxin and dabigatran etexilate)	No interaction with digoxin Weak interaction with dabigatran etexilate (approximately 33% and 17% increases in dabigatran etexilate C_{max} and AUC, respectively)	Dose adjustment for P-gp substrate is not necessary

Interaction	Assessment[a]	Clinical Impact	Recommendation
CYP1A2, CYP2B6 or CYP3A4 induction	In vitro	None	Dose adjustment for CYP1A2, CYP2B6 or CYP3A4 substrate is not necessary
MATE1 inhibition	Clinical Study CRN00808-15 Cohort 2 (Clinical substrate: metformin)	120 mg single dose of paltusotine with metformin resulted in approximately 40% and 20% decreases in metformin C_{max} and AUC, respectively	Dose adjustment for MATE1 substrate is not necessary
Cyclosporine[b]	Clinical Study CRN00808-15 Cohort 3	40 mg single dose of paltusotine with cyclosporine resulted in approximately 50% and 35% decreases in cyclosporine C_{max} and AUC in whole blood, respectively	Adjustment of cyclosporine dose to maintain therapeutic levels may be necessary. Follow recommended therapeutic drug monitoring in cyclosporine prescribing information.

AUC=area under the concentration time curve, BCRP=breast cancer resistance protein, C_{max}=maximum (peak) plasma drug concentration, CYP=cytochrome P450, MATE1=multidrug and toxin extrusion protein 1, P-gp=P-glycoprotein, PBPK=physiologically-based pharmacokinetic(s), PK=pharmacokinetic(s); PPI=proton pump inhibitor, QD=once daily, UGT1A1=uridine 5'-diphospho-glucuronosyltransferase family 1 member A1

[a] Model-based assessments.

[b] Paltusotine may affect cyclosporine PK by the same mechanism that parenteral somatostatin analogs have been suggested to decrease effectiveness of cyclosporine by reducing its bioavailability.

Source: Module 2.7.2 Section 3.5 Table 38

Drug-drug interactions are not considered an important risk as they can be managed in clinical practice by adhering to the SmPC guidance in Section 4.5 Interaction with other medicinal products and other forms of interaction.

Drug-drug interactions will continue to be monitored using routine pharmacovigilance activities.

Known risks that do not impact the risk-benefit profile:

- Cholelithiasis and complications of cholelithiasis

Cholelithiasis and complications of cholelithiasis are an identified risk of paltusotine.

There were no relevant nonclinical findings related to cholelithiasis (Section Part II: Module SII). Based on the mechanism of action, paltusotine may inhibit gallbladder contractility and decrease bile acid secretion, which may lead to gallbladder stones or sludge, consistent with approved SRL treatments (Sandostatin LAR SmPC 2022; Somatuline Autogel SmPC 2024).

Patients with symptomatic cholelithiasis were excluded from participation in Studies CRN00808-08 and CRN00808-09 as their inclusion could have impacted the safety assessment of paltusotine (Module SIV.1). Some study participants had a medical history of cholelithiasis; this was balanced between paltusotine and placebo groups for the FAS in Study CRN00808-08 (18.5% vs 19.3%, respectively) (Study CRN00808-08 CSR Table 14.1.2.8). In Study CRN00808-09, participants in the paltusotine group had a higher

incidence of medical history of cholelithiasis compared to placebo (40.0% vs 25.0%, respectively) in the FAS (Study CRN00808-09 CSR Table 14.1.2.5).

Cholelithiasis and complications of cholelithiasis TEAEs for the Primary Group and Supportive Group are presented in Table Part II: Module SVII.3.

Table Part II: Module SVII.3: Cholelithiasis and Complications of Cholelithiasis TEAEs in the Primary Group and Supportive Group (Safety Populations)

	Primary Group			Supportive Group
	Paltusotine (N=84)	**Placebo (N=85)**	**Total (N=169)**	**Paltusotine (N=233)**
Cholelithiasis, n (%)				
TEAEs	2 (2.4)	3 (3.5)	5 (3.0)	13 (5.6)
Related TEAEs	2 (2.4)	1 (1.2)	3 (1.8)	12 (5.2)
TEAEs by Severity				
Severe	0	0	0	0
Moderate	0	1 (1.2)	1 (0.6)	3 (1.3)
Mild	2 (2.4)	2 (2.4)	4 (2.4)	10 (4.3)
Serious TEAEs	0	0	0	4 (1.7)
Serious Related TEAEs	0	0	0	3 (1.3)
Bile duct stone, n (%)				
TEAEs	0	0	0	1 (0.4)
Related TEAEs	0	0	0	1 (0.4)
TEAEs by Severity				
Severe	0	0	0	0
Moderate	0	0	0	1 (0.4)
Mild	0	0	0	0
Serious TEAEs	0	0	0	1 (0.4)
Serious Related TEAEs	0	0	0	1 (0.4)
Biliary colic, n (%)				
TEAEs	0	0	0	2 (0.9)
Related TEAEs	0	0	0	2 (0.9)
TEAEs by Severity				
Severe	0	0	0	0
Moderate	0	0	0	2 (0.9)
Mild	0	0	0	0
Serious TEAEs	0	0	0	1 (0.4)
Serious Related TEAEs	0	0	0	1 (0.4)

	Primary Group			Supportive Group
	Paltusotine (N=84)	**Placebo (N=85)**	**Total (N=169)**	**Paltusotine (N=233)**
Cholecystitis acute, n (%)				
TEAEs	0	1 (1.2)	1 (0.6)	1 (0.4)
Related TEAEs	0	0	0	0
TEAEs by Severity				
Severe	0	0	0	0
Moderate	0	1 (1.2)	1 (0.6)	1 (0.4)
Mild	0	0	0	0
Serious TEAEs	0	1 (1.2)	1 (0.6)	1 (0.4)
Serious Related TEAEs	0	0	0	0
TEAEs Leading to Treatment Discontinuation	0	0	0	0

TEAE = treatment-emergent adverse event
Notes: MedDRA version 24.1. Percentages are calculated based on the number of participants in the Safety Population.
Source: ISS Table 14.3.1.3, ISS Table 14.3.1.4, ISS Table 14.3.1.7, ISS Table 14.3.1.8, ISS Table 14.3.1.11, ISS Table 14.3.1.12, ISS Table 14.3.1.13, ISS Table 14.3.1.14, ISS Table 14.3.1.15, ISS Table 14.3.1.16, ISS Table 14.3.1.25, ISS Table 14.3.1.26, ISS Table 14.3.1.20
Primary Group Data Cut: Studies CRN00808-09: 05 Dec 2023; CRN00808-08: 20 Jan 2024.
Supportive Group Data Cut: Studies CRN00808-08: 01 Sep 2024 CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

In the Primary Group, there was a similar incidence of cholelithiasis TEAEs between paltusotine (n=2, 2.4%) and placebo (n=3, 3.5%) groups. Both events on paltusotine occurred in Study CRN00808-08, with none reported in the paltusotine group of Study CRN00808-09 (ISS Table 14.100.1). 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 (ISS Table 14.100.2). Both were considered related to study treatment, mild in severity and nonserious. The paltusotine dose was not changed in either participant and did not lead to treatment withdrawal. One of the participants had a history of elevated ALT and ALP prior to study entry (Study CRN00808-08 CSR Listing 16.2.4.4). At study entry, the participant had a normal ALT (11 U/L) and ALP (71 U/L).

There were no notable differences in incidences of biliary-related TEAEs between the paltusotine and placebo groups for bile duct stone (0 vs 0), biliary colic (0 vs 0), or cholecystitis acute (0 vs n=1, 1.2%), respectively (Table Part II: Module SVII.3).

In the Supportive Group of all exposed participants in Phase 2 and 3 studies, 13 participants (5.6%) experienced cholelithiasis TEAEs and in 12 participants (5.2%), cholelithiasis was considered related to paltusotine (Table Part II: Module SVII.3). The TEAEs were mild (n=10, 4.3%) or moderate (n=3, 1.3%) in severity. Four participants (1.7%) experienced a serious cholelithiasis TEAE and the majority of these were considered related to paltusotine (n=3, 1.3%). None of the TEAEs led to study discontinuation.

Overall in the Supportive Group, there were 7 biliary-related SAEs: cholelithiasis (n=4, 1.7%), bile duct stone (n=1, 0.4%), biliary colic (n=1, 0.4%) and cholecystitis acute (n=1, 0.4%) (Table Part II: Module SVII.3). Most participants were receiving 40 mg at the time of the event (M2.7.4 Section 5.4).

Five participants experienced treatment-related (possibly or probably related) SAEs:
3 participants experienced 1 SAE of cholelithiasis each (2 mild and 1 moderate, all with no change in dose), 1 participant experienced biliary colic (moderate) and sinus arrest (severe) which resulted in study drug interruption; 1 participant for whom study drug was already interrupted prior to the onset of the SAE experienced bile duct stone (moderate) (ISS Table 14.3.1.16, ISS Listing 16.2.7.2, ISS Listing 16.2.7.9). All participants subsequently continued paltusotine, indicating that this event can be managed safely by healthcare professionals.

There were no deaths and no study drug discontinuations due to cholelithiasis (ISS Table 14.3.1.26, ISS Listing 16.2.7.1, ISS Listing 16.2.7.9).

An analysis of the data by time on treatment including participant incidence of cholelithiasis TEAEs and the exposure-adjusted incidence/year showed that the majority of events occurred later in treatment; ≤3 months (n=1, 0.4%, 0.003), >3 to ≤6 months (n=1, 0.4%, 0.003), >6 to ≤9 months (n=8, 3.4%, 0.02), >9 to ≤12 months (n=1, 0.4%, 0.003), >12 to ≤18 months (0), >18 months (n=2, 0.9%, 0.01) (ISS Table 14.3.1.23).

Gallbladder ultrasound results from the RC Phase showed an increased incidence of new gallbladder sludge or gallstones in paltusotine-treated versus placebo participants for Study CRN00808-08 but not Study CRN00808-09. Exposure-safety analyses for gallbladder sludge in Study CRN00808-08 found no trend with paltusotine exposure but the new sludge incidence appeared elevated at only the highest quintile of exposure (Module 2.7.2, Section 3.6.2). There was no relationship between new gallstone cases and paltusotine exposure.

In summary, there is sufficient evidence to support a causal association of cholelithiasis with paltusotine, consistent with approved SRL treatments, based on the observed cholelithiasis events that occurred later in treatment and on the gallbladder ultrasound results. 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. Accordingly, cholelithiasis is an identified adverse reaction of paltusotine that may occur later in treatment.

Cholelithiasis is not an important risk of paltusotine as the cholelithiasis events did not result in treatment discontinuations, indicating that this event can be managed safely by healthcare professionals. The risk of cholelithiasis will be minimised in clinical practice through the SmPC guidance that warns healthcare professionals that Palsonify may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder stones or sludge and that cholelithiasis and its complications have been reported with the use of paltusotine. Healthcare professionals are advised that if complications of cholelithiasis are suspected, evaluation and appropriate treatment should be initiated, and benefit-risk should be considered in determining whether or not to continue treatment with paltusotine. Cholelithiasis and bile duct stone are adverse reactions of paltusotine with frequencies of common (≥1/100 to <1/10) and uncommon

(≥1/1000 to <1/100), respectively. In randomised studies, cholelithiasis occurred between 6 and 9 months after the start of paltusotine. No patients discontinued paltusotine due to cholelithiasis.

Cholelithiasis and complications of cholelithiasis will continue to be monitored using routine pharmacovigilance activities.

- Sinus bradycardia

Sinus bradycardia is an identified risk of paltusotine.

Cardiovascular safety pharmacology studies with paltusotine in dogs showed a transient nondose-dependent decrease in heart rate and increase in blood pressure, which were considered small in magnitude and within normal biological variation (Table Part II: Module SII.1). There were no ECG abnormalities such as QT prolongation or arrhythmias observed in the cardiovascular safety pharmacology study or repeat-dose toxicity studies (up to 9 months) in dogs at the highest doses tested, which provide safety margins of 5.5-fold (at 10 mg/kg) and 50-fold (at 75 mg/kg/day), respectively, for the highest dose used in clinical trials, 60 mg for acromegaly.

Patients with abnormal heart rates including resting (at least 10 minutes) palpated pulse rate <45 bpm or >105 bpm during Screening were excluded from participation in Studies CRN00808-08 and CRN00808-09 as their inclusion could have impacted the safety assessment of paltusotine (Module SIV.1).

A small number of study participants had a medical history of sinus bradycardia or bradycardia. In Study CRN00808-08 this was balanced between the paltusotine and placebo groups for the FAS (sinus bradycardia: 2 participants in each group; bradycardia: 1 participant in each group) (Study CRN00808-08 CSR Table 14.1.2.8). In Study CRN00808-09, there was a small imbalance with 3 participants in the paltusotine group having a medical history of bradycardia (2 sinus bradycardia and 1 bradycardia) compared with 1 participant in the placebo group (bradycardia) in the FAS (Study CRN00808-09 CSR Table 14.1.2.5).

Sinus bradycardia and bradycardia TEAEs for the Primary Group and Supportive Group are presented in Table Part II: Module SVII.4.

Table Part II: Module SVII.4: Sinus Bradycardia and Bradycardia TEAEs in the Primary Group and Supportive Group (Safety Populations)

	Primary Group			Supportive Group
	Paltusotine (N=84)	**Placebo (N=85)**	**Total (N=169)**	**Paltusotine (N=233)**
Sinus bradycardia, n (%)				
TEAEs	4 (4.8)	0	4 (2.4)	10 (4.3)
Related TEAEs	3 (3.6)	0	3 (1.8)	8 (3.4)
TEAEs by Severity				
Severe	0	0	0	0
Moderate	1 (1.2)	0	1 (0.6)	1 (0.4)
Mild	3 (3.6)	0	3 (1.8)	9 (3.9)

	Primary Group			Supportive Group
	Paltusotine (N=84)	**Placebo (N=85)**	**Total (N=169)**	**Paltusotine (N=233)**
Serious TEAEs	0	0	0	0
Serious Related TEAEs	0	0	0	0
Bradycardia, n (%)				
TEAEs	1 (1.2)	0	1 (0.6)	4 (1.7)
Related TEAEs	1 (1.2)	0	1 (0.6)	4 (1.7)
TEAEs by Severity				
Severe	0	0	0	1 (0.4)
Moderate	0	0	0	0
Mild	1 (1.2)	0	1 (0.6)	3 (1.3)
Serious TEAEs	0	0	0	0
Serious Related TEAEs	0	0	0	0
TEAEs Leading to Treatment Discontinuation	0	0	0	0

TEAE = treatment-emergent adverse event
Notes: MedDRA version 24.1. Percentages are calculated based on the number of participants in the Safety Population.
Source: ISS Table 14.3.1.3, ISS Table 14.3.1.4, ISS Table 14.3.1.7, ISS Table 14.3.1.8, ISS Table 14.3.1.11, ISS Table 14.3.1.12, ISS Table 14.3.1.13, ISS Table 14.3.1.14, ISS Table 14.3.1.15, ISS Table 14.3.1.16, ISS Table 14.3.1.25, ISS Table 14.3.1.26, ISS Table 14.3.1.20
Primary Group Data Cut: Studies CRN00808-09: 05 Dec 2023; CRN00808-08: 20 Jan 2024.
Supportive Group Data Cut: Studies CRN00808-08: 01 Sep 2024 CRN00808-09: 15 Aug 2024; CRN00808-03: 31 Aug 2020; CRN00808-02: 12 Aug 2020; CRN00808-05: 01 Aug 2024.

In the Primary Group, a reduction in heart rate was observed in the paltusotine group but not in the placebo group; sinus bradycardia (n=4, 4.8% vs 0) and bradycardia (n=1, 1.2% vs 0), respectively (Table Part II: Module SVII.4). The TEAEs reported in the 5 participants were all nonserious and the participants were asymptomatic. Of the 5 events, 4 were of mild severity and 1 was of moderate severity. Three of the participants had a history of hypertension and 1 had a history of intermittent sinus bradycardia at baseline (medically naïve group). One participant received prior and concomitant calcium antagonists, and 1 participant received prior and concomitant beta-blockers and a calcium antagonist; both of these participants had a history of hypertension (Study CRN00808-08 CSR Listing 16.2.4.4, Study CRN00808-09 CSR Listing 16.2.4.4).

One participant was receiving 20 mg paltusotine which was subsequently increased to 40 mg, 2 participants were receiving 20 mg and the dose remained unchanged, and 2 participants were receiving 40 mg. No participants were receiving 60 mg of paltusotine at the time of the event. In all 5 participants, the first events of bradycardia occurred in the first 3 months of treatment. The duration of the events ranged from 14-36 days. Of the 5 participants, 1 had a dose reduction. No participants discontinued paltusotine because of bradycardia.

In the Supportive Group of all exposed participants in Phase 2 and 3 studies, 10 participants (4.3%) experienced sinus bradycardia TEAEs and sinus bradycardia was considered related to paltusotine in 8 participants (3.4%) (Table Part II: Module SVII.4). The majority of TEAEs were of mild severity (n=9, 3.9%); 1 participant (0.4%) experienced sinus bradycardia of moderate

severity. A further 4 participants (1.7%) experienced bradycardia TEAEs; all were considered related to paltusotine. Three of these participants (1.3%) had mild bradycardia and 1 participant (0.4%) experienced severe bradycardia. The severe bradycardia occurred in a participant from Study CRN00808-03 treated with 20 mg paltusotine who experienced asymptomatic bradycardia at Week 11 (baseline heart rate in the 50's found to be in the 40's) which was reported as asymptomatic but severe (Study CRN00808-03 CSR Section 12.5.4). Paltusotine was interrupted temporarily and within a week, the participant's heart rate improved (in the 50's) and stabilised. Paltusotine treatment was restarted at a reduced dose (10 mg) for the remainder of the treatment period without sequelae. This AE was assessed by the Investigator to be possibly related to paltusotine.

None of the sinus bradycardia or bradycardia TEAEs were serious or led to treatment discontinuation (Table Part II: Module SVII.4).

An analysis of the data by time on treatment presenting participant incidence of sinus bradycardia TEAEs and the exposure-adjusted incidence/year showed that the majority of events occurred within the first 3 months of treatment: ≤3 months (n=6, 2.6%, 0.02), >3 to ≤6 months (n=1, 0.4%, 0.003), >6 to ≤9 months (n=1, 0.4%, 0.003), >9 to ≤12 months (0), >12 to ≤18 months (n=2, 0.9%, 0.01), >18 months (0) (ISS Table 14.3.1.23). Similarly most events of bradycardia occurred within the first 3 months of treatment: ≤3 months (n=3, 1.3%, 0.01), >3 to ≤6 months (0), >6 to ≤9 months (n=1, 0.4%, 0.003), >9 to ≤12 months (0), >12 to ≤18 months (0), >18 months (0) (ISS Table 14.3.1.23).

A review of potentially significant heart rate changes based on ECG data was undertaken. Upon review of ECG data during the RC portion of Study CRN00808-08, there was a higher incidence of participants with shifts from a baseline of ≥50 bpm to <50 bpm in the paltusotine group vs placebo (medically naïve [7 of 21 vs 3 of 24] and previously treated groups [6 of 17 vs 2 of 18]) but not in the washout group (2 of 13 vs 2 of 15), respectively (M2.7.4 Section 4.4.3.1), and not in Study CRN00808-09 (M2.7.4 Section 4.4.3.2).

Seven participants in the Supportive Group had a mean heart rate drop of 20 bpm or more at any time (M2.7.4 Section 5.5.3). In general, there was a fluctuation in heart rate and not persistent significant drops. There were no associated TEAEs of dizziness, syncope or hypotension and no significant drops in blood pressure readings. Three of the participants had a history of hypertension and were receiving amlodipine (one participant) and amlodipine and metoprolol (2 participants). For participants who developed a heart rate of less than 50 bpm, there were no adverse outcomes such as syncope.

In summary, paltusotine is associated with a reduction in heart rate (mean reduction of 6 bpm in Study CRN00808-08 at Week 24), consistent with approved SRL treatments. A similar change was not seen in the ECG results for Study CRN00808-09 as these participants were switched straight from another SRL therapy and therefore had been exposed to the initial bradycardia effect.

Sinus bradycardia is not an important risk of paltusotine as all the events were nonserious, asymptomatic, did not lead to treatment discontinuation, did not lead to intervention and were not associated with adverse cardiovascular outcomes. The majority of events occurred in the first three months of treatment.

The risk of sinus bradycardia will be minimised in clinical practice through the SmPC guidance that warns healthcare professionals that cardiac conduction abnormalities and other ECG changes such as PR interval prolongation and bradycardia have occurred during treatment with paltusotine in clinical studies. These ECG changes may occur in patients with acromegaly. Dose adjustments of concomitantly used medicinal products that have bradycardia effects (eg, beta blockers) may be necessary. Sinus bradycardia (combined term of sinus bradycardia and bradycardia) is an adverse reaction of paltusotine with a frequency of common (≥1/100 to <1/10). The events of bradycardia in patients treated with paltusotine were asymptomatic and did not lead to the discontinuation of the medicinal product. The events occurred in patients with and without a history of bradycardia, occurred in the first three months of treatment and there was no clear dose association. The mean reduction in heart rate was 6 bpm.

Sinus bradycardia will continue to be monitored using routine pharmacovigilance activities.

Other reasons for considering the risks not important:

- None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no important identified risks or important potential risks for paltusotine.

Missing information 1: Long-term safety

To support the safety of paltusotine for the medical treatment of adult patients with acromegaly, the clinical development programme includes 2 pivotal studies (Studies CRN00808-08 and CRN00808-09) and 3 Phase 2 studies (Studies CRN00808-02, CRN00808-03, and CRN00808-05). Analyses were performed for the Primary Group and Supportive Group including duration of exposure (Part II: Module SIII).

In the Primary Group, 84 participants in the paltusotine group (54 from Study CRN00808-08 and 30 from Study CRN00808-09) and 85 participants in the placebo group (57 from Study CRN00808-08 and 28 from Study CRN00808-09) received at least 1 dose of study treatment (M2.7.4 Section 1.1.3.1.1 Table 2). Overall, the median duration of exposure was 24.2 weeks in the paltusotine group and 24.0 weeks in the placebo group (ISS Table 14.1.3.1). A total of 78 participants (92.9%) in the paltusotine group and 54 participants (63.5%) in the placebo group received >6 to ≤9 months of study treatment (ISS Table 14.1.3.1).

In the Supportive Group, 233 participants received at least 1 dose of paltusotine treatment. In total, 5.2% (n=12), 6.9% (n=16), 18.9% (n=44), 40.3% (n=94), 13.3% (n=31), and 15.5% (n=36) of participants received >0 to ≤3 months, >3 to ≤6 months, >6 months to ≤12 months, >12 to ≤24 months, >24 to ≤36 months, and >36 months of paltusotine treatment, respectively (Table Part II: Module SIII.3). The median duration of exposure was 65.4 weeks in participants treated with paltusotine (ISS Table 14.1.3.2). The longer exposure in the Supportive Group compared with the Primary Group was due to the longer exposure in Study CRN00808-05 and OLE Phases of Studies CRN00808-08 and CRN00808-09.

Paltusotine continues to be generally well tolerated across all clinical studies in the clinical development programme, with no new safety signals detected (M2.7.4 Appendix E Executive Summary). The analysis of data to date demonstrates a consistent safety profile in the

Supportive Group with longer exposure similar to what was observed in the Primary Group (RC Phases of the pivotal Phase 3 Studies CRN00808-08 and CRN00808-09).

Long-term safety data are 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.

Risk-benefit impact:

The benefit of paltusotine as the first novel, oral, targeted, and selective SST2 agonist for the medical treatment of adult patients with acromegaly is considered to outweigh long-term safety, an area of missing information where data are limited but where the safety profile of paltusotine associated with long-term use is not expected to differ from the established safety of paltusotine from the clinical development programme.

Long-term safety will be further characterised using additional (Section Part I:III.2) and routine pharmacovigilance activities (Section Part I:III.1).

Ongoing OLE Study CRN00808-05 will provide long-term safety data. In addition, safety data will continue to be collected from the ongoing OLE Phases of Studies CRN00808-08 and CRN00808-09 (Part II: Module SIII) and findings, including any new long-term safety findings, will be discussed in the PSUR or other relevant procedures as part of routine pharmacovigilance activities.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the Missing Information

Missing Information: Long-term Safety

Evidence source:

The assessment of safety of paltusotine for the medical treatment of adult patients with acromegaly is based primarily on pooled data from the RC Phases of the pivotal Phase 3 studies (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 (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.

Results of the safety data from these clinical studies demonstrated that paltusotine was generally well tolerated (M2.5 Section 5.3.12). 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 (ISS Table 14.3.1.23). 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 as discussed in Module SVII.1.1.

No unexpected safety signals were identified with long-term paltusotine treatment. However, long-term safety data are 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 safety profile of paltusotine associated with long-term use is not expected to differ from the established safety of paltusotine from the clinical development programme. While the number of patients is limited, this reflects the rare disease with an estimated prevalence of acromegaly in the EU and 3 EEA Member States of approximately 1.1 cases per 10,000, equating to 50,257 cases (Orphan Drug Designation EMA/OD/0000234998).

Long-term safety will be further characterised using additional (Section Part I:III.2) and routine pharmacovigilance activities (Section Part I:III.1). Ongoing OLE Study CRN00808-05 will provide long-term safety data. As of 31 Aug 2025, 77% of study participants have ≥4 years of exposure, including 20 patients with ≥5 years, and all remaining participants will have ≥3 years of data by Feb 2026.

In addition, safety data will continue to be collected from the ongoing OLE Phases of Studies CRN00808-08 and CRN00808-09 (Part II: Module SIII) and findings, including any new long-term safety findings, will be discussed in the PSUR or other relevant procedures as part of routine pharmacovigilance activities.

PART II: MODULE SVIIISUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

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:

Safety data will continue to be collected from the ongoing OLE Phases of Studies CRN00808-08 and CRN00808-09 (Part II: Module SIII) and findings, including any new long-term safety findings, will be discussed in the PSUR or, if applicable, communicated to the EEA regulatory authorities through other relevant procedures as part of routine pharmacovigilance activities.

III.2 Additional Pharmacovigilance Activities

Study CRN00808-05 is an ongoing Phase 2 long-term OLE study evaluating the safety and efficacy of paltusotine in participants with acromegaly who were previously enrolled in Study CRN00808-02 or Study CRN00808-03 (Part II: Module SIII).

Study CRN00808-05

Study short name and title:

OLE Study CRN00808-05

An Open Label, Long-term Extension study to Evaluate the Safety and Efficacy of CRN00808 in Subjects with Acromegaly (ACROBAT ADVANCE)

Rationale and study objectives:

- To evaluate the long-term safety and tolerability of paltusotine in acromegaly subjects
- To evaluate the efficacy of paltusotine in acromegaly subjects.

Study design:

Study CRN00808-05 is a Phase 2, open label exploratory study designed to evaluate the long-term safety and efficacy of paltusotine in adult subjects with acromegaly that completed either Studies CRN00808-02 or CRN00808-03 (parent studies). It is planned that up to approximately 60 subjects who completed the parent studies in approximately 22 centres in the US, Europe, and South America will be involved.

The expected duration of study participation for each subject is up to 320 weeks consisting of the following periods:

- Screening Period (0 to 4 weeks);
- Treatment Period (up to 312 weeks [6 years]; including a titration period of approximately 12 weeks);
- Follow-up Period (up to 4 weeks).

Study population:

Up to approximately 60 adult male and female subjects with a confirmed acromegaly diagnosis who completed either Studies CRN00808-02 or CRN00808-03 and have an acceptable benefit-risk assessment based on the opinion of the Investigator are planned to be enrolled in the study (Groups 1, 2a, and 2b):

- Group 1: Subjects who are not currently enrolled in Studies CRN00808-02 or CRN00808-03, but have completed Studies CRN00808-02 or CRN00808-03 and now have resumed standard acromegaly medications (eligible subjects should be screened for Study CRN00808-05 within 6 months of regulatory approval of protocol version 3.0);
- Group 2a: Subjects who are completing Studies CRN00808-02 or CRN00808-03 and have not resumed standard acromegaly medication;
- Group 2b: Subjects who are defined as completers of Studies CRN00808-02 or CRN00808-03 by receiving a rescue injection of long-acting somatostatin agonist during the Follow-up Period of the parent studies.

Milestones:

FPFV: 26 Feb 2020

LPLV: Jun 2026

Final study report: Jan 2027

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and 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) Ongoing	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

FPFV=first patient first visit; LPLV=last patient last visit

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

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

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety (missing information)	Routine risk minimisation measures: • *SmPC Section 4.8* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *PSUR reporting of any new long-term safety findings from the ongoing OLE Studies CRN00808-08 and CRN00808-09* Additional pharmacovigilance activities: • *OLE Study CRN00808-05*

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR PALSONIFY (PALTUSOTINE)

This is a summary of the risk management plan (RMP) for Palsonify. The RMP details important risks of Palsonify, how these risks can be minimised, and how more information will be obtained about Palsonify's risks and uncertainties (missing information).

Palsonify's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Palsonify should be used.

This summary of the RMP for Palsonify should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Palsonify's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Palsonify is authorised for the medical treatment of adult patients with acromegaly (see SmPC for the full indication). It contains paltusotine as the active substance and it is given by oral route.

Further information about the evaluation of Palsonify's benefits can be found in Palsonify's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Palsonify, together with measures to minimise such risks and the proposed studies for learning more about Palsonify's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment - so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Palsonify is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Palsonify are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Palsonify. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

II.B Summary of Important Risks

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • OLE Study CRN00808-05 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Palsonify.

II.C.2 Other Studies in Post-Authorisation Development Plan

OLE Study CRN00808-05

An Open Label, Long-term Extension Study to Evaluate the Safety and Efficacy of CRN00808 in Subjects with Acromegaly (ACROBAT ADVANCE)

Purpose of the study:

To evaluate the long-term safety and tolerability of paltusotine in acromegaly subjects;

To evaluate the efficacy of paltusotine in acromegaly subjects.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table Part VII.1: Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
CRN00808-05 An Open Label, Long-term Extension Study to Evaluate Safety and Efficacy of CRN00808 in Subjects with Acromegaly (ACROBAT ADVANCE) Category 3	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	Study CRN00808-05 FPFV: 26 Feb 2020 LPLV: Jun 2026 Final study report: Jan 2027

FPFV=first patient first visit; LPLV=last patient last visit

Table Part VII.2: Completed Studies

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
None			

ANNEX 3 PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Table of contents

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Approved protocols:

Not applicable

Final protocols not reviewed or not approved:

Study CRN00808-05

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 5 PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable.