11 December 2025
EMA/1407/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aumseqa

International non-proprietary name: aumolertinib

Procedure No. EMEA/H/C/006069/0000

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First-line
AAS	Atomic Absorption Spectrometry
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active substance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
CDISC	Clinical Data Interchange Standards Consortium
CDx	Companion Diagnostics
CE	Conformité Européenne
CEP	Certificate of Suitability of the EP
cfDNA	Cell-free DNA
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMS	Concerned Member State
CNS	Central nervous system
CoA	Certificate of Analysis
CPK	Creatine phosphokinase
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRF	Case Report Form
CRS	Chemical Reference Substance (official standard)
CSCO	Chinese Society of Clinical Oncology
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVMP	Committee for Medicinal Products for Veterinary use
DCR	Disease control rate
DepOR	Depth of response
DoE	Design of experiments
DoR	Duration of response
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry

Abbreviation	Definition
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic common technical document
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EP	European Pharmacopoeia
E-R	Exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
EU	European Union
Ex19del	Exon 19 deletion of the epidermal growth factor receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FFPET	Formalin-fixed paraffin-embedded tissue
FMEA	Failure mode effects analysis
FPM	Finished Product Manufacturer
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HEK	Human embryonic kidney
hERG	Human ether-a-go-go-related Gene
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRMS	High resolution mass spectrometry
IASLC	International Association for the Study of Lung Cancer
IC	Ion chromatography
ICH	International Council for Harmonisation
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICR	Independent central review
IFU	Instructions for Use
ILAP	Innovative Licensing and Access Pathway
ILD	Interstitial lung disease
IPC	In-process control
IR	Infrared
IU	International Units

Abbreviation	Definition
IUPAC	International Union of Pure and Applied Chemistry
IVD	In vitro diagnostics
KF	Karl Fischer titration
L858R	Point mutation in which leucine at amino acid 858 is replaced by arginine
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
LOA	Letter of Access
LOD	Loss on drying
LoD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
LVEF	Left ventricular ejection fraction
MA	Marketing Authorisation
MAA	Marketing Authorization Application
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Mass Spectrometry
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ND	Not detected
NDA	New Drug Application
NICE	National Institute for Health and Clinical Excellence
NIR	Near Infrared Spectroscopy
NLT	Not less than
NMPA	National Medical Products Administration
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
NSCLC	Non-small cell lung cancer
OOS	Out of Specification
ORR	Objective response rate
OS	Overall survival
PAR	Proven Acceptable Range
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase chain reaction
PCTFE	Polychlorotrifluoroethylene
PD	Progressive disease
PDE	Permitted Daily Exposure
PE	Polyethylene
PFS	Progression-free survival
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet

Abbreviation	Definition
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PP	Polypropylene
PPS	Per Protocol Set
PR	Partial response
PR interval	Time from the beginning of the P wave until the beginning of the QRS complex in an electrocardiogram
PS	Performance status
PT	Preferred term
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QC	Quality Control
QD	Once daily
QOS	Quality Overall Summary
QP	Qualified person
QRS	Time from beginning of the Q wave to the end of the S wave in an electrocardiogram
QT	Time from the start of the Q wave to the end of the T wave in an electrocardiogram
QTc	QT corrected for heart rate
QTcF	Corrected QT interval using the Fridericia formula
QTPP	Quality target product profile
QWP	Quality Working Party
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System organ class
T790M	Point mutation that substitutes methionine for threonine at amino acid position 790
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse event
TGA	Thermo-Gravimetric Analysis
TKI	Tyrosine kinase inhibitor
TLC	Thin layer chromatography
tmax	Time to achieve Cmax
TSE	Transmissible Spongiform Encephalopathy

Abbreviation	Definition
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
uHPLC	ultra-high performance liquid chromatography
UK	United Kingdom
ULN	Upper limit of normal
US	United States (of America)
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
WBC	White blood cell
WT	Wild-type
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SFL Pharmaceuticals Deutschland GmbH submitted on 12 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Aumseqa, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 January 2022.

The applicant applied for the following indication: as monotherapy for:

- the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.
- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0010/2022 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request for consideration

1.5.1. New active substance status

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

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 October 2021	*EMA/SA/0000063938*	*Pierre Demolis* *Rune Kjeken*

The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- The proposed commercial container closure system film-coated tablets;
- The non-clinical safety pharmacology and toxicology data package to support an MAA in the proposed indication(s);
- The overall clinical pharmacology package, proposed QT assessment plan, and PK approach to support extrapolation from Asian to European patient populations via a PK bridging study and PopPK analysis;
- The planned safety database to support an MAA;
- The proposed plan for a companion diagnostic to support an MAA.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Boje Kvorning Pires Ehmsen

The application was received by the EMA on	12 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	08 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2023
The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 3 investigator sites and one sponsor site in China between 26 February 2024 and 15 March 2024. The	31 May 2024

outcome of the inspection carried out was issued on:	
– A GMP inspection at one manufacturing site in China between 17 and 20 July 2023 . The outcome of the inspection carried out was issued on.	22 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aumseqa on	11 December 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)>	11 December 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication wording is as follows:

Aumolertinib as monotherapy is indicated for:

1. The first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

2. The treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Locally advanced NSCLC is defined as stage III NSCLC patients according to International Association for the Study of Lung Cancer (IASLC)/ Union for International Cancer Control (UICC) TNM staging classification. The treatment of such patients may be a challenge because of their local presentation, especially in the case of an advanced primary tumour (T4 situation) with local infiltration of vital mediastinal organs or involvement of locoregional mediastinal lymph nodes (N2 or N3 nodes) and the risk of metastatic recurrence. Subset IIIB includes either unresectable T4 or unresectable N3. (ESMO)

Metastatic NSCLC is defined as stage IV NSCLC patients according to IASLC/ UICC TNM staging classification.

2.1.2. Epidemiology

Lung cancer is the third most common cancer in Europe; NSCLC represents 85–90% of all lung cancers. (ESMO)

The frequency of EGFR TKI-sensitizing mutations in NSCLC patients is correlated to several pathologic, demographic, and epidemiologic factors. These mutations are largely limited to the non-squamous pathologic subtype of NSCLC, and are exceedingly rare in squamous subtype [1]. These mutations also occur more frequently in never-smoker patients[2] and in Asian patients (approximately 30% incidence) versus Caucasian patients (approximately 7% incidence)[3]. Additionally, these mutations occur more frequently in female patients than in male patients (an approximate 60:40 ratio)[4].

2.1.3. Biologic features

Molecular characterisation has led to the definition of new subgroups. Somatic alterations in NSCLC can lead to oncogenic activation through several mechanisms, including point mutations, insertions/deletions and rearrangements. Broadly, actionable mutations guiding targeted therapy can be classified according to gene rearrangements (e.g. ALK, ROS1, RET, NTRK, FGFR1/2/3, NRG1) or

[1] Chiu CH, Chou TY, Chiang CL, et al. Should EGFR mutations be tested in advanced lung squamous cell carcinomas to guide frontline treatment? Cancer Chemother Pharmacol. 2014;74(4):661-665.
[2] Ren JH, He WS, Yan GL, et al. EGFR mutations in non-small-cell lung cancer among smokers and non-smokers: a meta-analysis. Environ Mol Mutagen. 2012;53(1):78-82.
[3] Zhou W, Christiani DC. East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. Chin J Cancer. 2011;30(5): 287-292.
[4] Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014;9(2):154-162.

variants including point mutations, insertions/deletions and amplifications (e.g. EGFR, BRAF, mitogen-activated protein kinase [MEK], KRAS, MET, ERBB2/HER2)[5].

Clinically-relevant EGFR gene mutations in NSCLC include substitutions, deletions and insertions in exons 18-21 that activate the tyrosine kinase and variably confer sensitivity or resistance to available EGFR tyrosine kinase inhibitors (TKIs) or other drugs. The most common alterations conferring sensitivity to first- to third-generation TKIs are the exon 21 L858R substitution and exon 19 deletion mutations. The next most common alteration is a large group of exon 20 insertions mostly resistant to first- and second-generation EGFR-TKIs but sensitive to third-generation EGFR TKIs. The most frequent mechanisms of resistance for EGFR inhibitors are T790M mutation, and less frequently Met amplification or HGF over-expression, small-cell transformation and others. Other mutations, including in exon 18, variably sensitise, while some mutations confer resistance and may drive disease relapse. (ESMO)

2.1.4. Clinical presentation, diagnosis and stage

There are two main types of primary lung cancer: Small-cell lung cancer (SCLC) and Non-small-cell lung cancer (NSCLC). NSCLC is the more common type of lung cancer, and accounts for 80–90% of all lung cancers [6]

NSCLC presents a heterogeneity in terms of tumour histopathology, tumour location and extension and individual patient risk profile (long-term smokers still representing the majority of lung cancer patients). (ESMO)

The three main histological subtypes of NSCLC are:

- Adenocarcinoma: About 40% of all lung cancers are adenocarcinomas.
- Squamous cell carcinoma (SCC): About 25–30% of all lung cancers are SCC. This type of cancer is usually caused by smoking.
- Large cell (undifferentiated) carcinoma: This type makes up around 10–15% of all lung cancers.

Around 70% of NSCLC patients are diagnosed with advanced disease at diagnosis. Imaging of the central nervous system (CNS) should be considered at diagnosis for all patients with metastatic disease and is required for patients with neurological symptoms or signs.

2.1.5. Management

The treatment landscape of NSCLC is becoming increasingly biomarker driven with new targeted therapies used in concert with companion molecular diagnostics.[5]

As per ESMO guideline[6], patients with metastatic NSCLC harbouring sensitizing EGFR mutations should receive first-line EGFR TKIs, including, gefitinib (Iressa, EMEA/H/C/1016, first authorised in June 2009), erlotinib (Tarceva, EMEA/H/C/618 first authorised in September 2005), afatinib (GIOTRIF, EMEA/H/C/2280 first authorised in September 2013) and dacomitinib (Vizimpro, EMEA/H/C/4779, first

[5] Keith M. Kerr, Frédéric Bibeau, Erik Thunnissen, Johan Botling, Aleš Ryška, Jürgen Wolf, Katarina Öhrling, Peter Burdon, Umberto Malapelle, Reinhard Büttner,
The evolving landscape of biomarker testing for non-small cell lung cancer in Europe,
Lung Cancer,Volume 154,2021,Pages 161-175,ISSN 0169-5002,
[6] Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Hendriks, L.E. et al. - Annals of Oncology, Volume 34, Issue 4, 339 - 357

authorised in April 2019) and osimertinib (TAGRISSO, EMEA/H/C/4124, first authorised in February 2016) with osimertinib being considered the preferred option (Recommendation I,A).

The first-generation EGFR TKIs, gefitinib and erlotinib, are reversible inhibitors that have activity against both mutated and WT EGFR. The second-generation, small-molecular mass EGFR TKIs, afatinib and dacomitinib, are distinct from the first-generation inhibitors, as these agents are irreversible and also have activity towards other EGFR family members.

The frequency of T790M mutation as the mechanism of acquired resistance after treatment with first- and second-generation EGFR TKIs prompted the development of third-generation EGFR TKIs which are active towards both EGFR T790M and EGFR TKI-sensitizing mutations in exons 19 or 21. Osimertinib is also the standard therapy for patients with tumours that tested positive for the T790M mutation[7].

2.2. About the product

Aumolertinib is a novel, irreversible, small-molecule inhibitor with potent activity against EGFR with the EGFR TKI-sensitizing mutations Ex19del and L858R and the EGFR TKI resistance mutation T790M.

The finally agreed indications are:

Aumseqa as monotherapy is indicated for:

- the first line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (for biomarker based patient selection, see section 4.2).
- the treatment of adult patients with advanced EGFR T790M mutation positive NSCLC (for biomarker based patient selection, see section 4.2).

Treatment with Aumseqa should be initiated by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose of Aumseqa is 110 mg (2 tablets of 55 mg) once a day.

This medicinal product should be continued until disease progression or unacceptable toxicity.

Method of administration

This medicinal product is for oral use.

Two 55 mg tablets should be swallowed whole with water without chewing or crushing.

Aumseqa should be taken approximately at the same time each day. It can be taken with or without food.

Missed dose

If a dose of Aumseqa is missed, it should be taken within the same day as soon as the patient remembers. However, if the next scheduled dose is due within 12 hours, then the missed dose must be skipped. The patient should not take two doses together to make up for a missed dose.

Dose modifications for adverse reactions

[7] Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-125.

Dosing interruption and/or dose reduction or permanent discontinuation may be required based on individual safety and tolerability.

If dose reduction is necessary, then the dose should be reduced from 110 mg (2 tablets) to 55 mg (1 tablet) taken once daily.

Dose modification guidelines for adverse reactions are provided in Table 1.

Table 1 Recommended Aumseqa dose modifications due to adverse reactions

Adverse reaction	Severity	Dose modification
Interstitial lung disease	Any grade	Permanently discontinue Aumseqa.
QTc interval prolongation	QTc interval prolongation > 480 to ≤ 500 msec (Grade 2)	Withhold Aumseqa for up to 2 weeks. If QTc interval has not recovered to ≤ 480 msec, permanently discontinue Aumseqa. If QTc interval recovers to ≤ 480 msec or within 30 msec of baseline, resume treatment at 110 mg. Monitor ECGs at least weekly for 2 weeks following return to ≤ 480 msec. Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see SmPC section 4.5).
	QTc interval prolongation > 500 msec or > 60 msec from baseline (Grade 3)	Withhold Aumseqa for up to 2 weeks. If QTc interval has not recovered to ≤ 480 msec or within 30 msec of baseline, permanently discontinue Aumseqa. If QTc interval recovers to ≤ 480 msec: • resume treatment at 110 mg dose for the first occurrence. • resume treatment at 55 mg dose for the second occurrence or the first occurrence in patients with risk factors (see section 4.4). Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg). Monitor ECGs at least weekly for 2 weeks following return of QTc interval to ≤ 480 msec. Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see SmPC section 4.5).

Adverse reaction	Severity	Dose modification
	Prolongation associated with torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of other serious arrhythmias	Permanently discontinue Aumseqa.
Cardiac failure	Asymptomatic, absolute decrease in LVEF > 10% from baseline or to below 50%	Withhold Aumseqa for up to 2 weeks. If LVEF returns to baseline or ≥ 50%: • resume treatment at 110 mg dose for the first occurrence. • resume treatment at 55 mg dose for the second occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg).
	Symptomatic congestive heart failure	Permanently discontinue Aumseqa.
Blood creatine phosphokinase (CPK) increased / rhabdomyolysis	Grade 3 with muscular symptoms (e.g. muscle tenderness, muscle twitches or myalgia)	Withhold Aumseqa for up to 2 weeks. If muscular symptoms resolve and blood CPK increase is ≤ Grade 3: • resume treatment at 110 mg dose for the first occurrence. • resume treatment at 55 mg for the second occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg). If muscular symptoms do not resolve and CPK increase does not improve to ≤ Grade 2, permanently discontinue Aumseqa.
	Grade 4 with or without muscular symptoms (e.g. muscle tenderness, muscle twitches or myalgia)	Withhold Aumseqa for up to 2 weeks. If muscular symptoms resolve and blood CPK increase is ≤ Grade 3, resume treatment at 55 mg dose for the first occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on this dose. If muscular symptoms do not resolve and CPK increase remains ≥ Grade 3, permanently discontinue Aumseqa.
Other adverse reactions	≥ Grade 3	Withhold Aumseqa for up to 2 weeks. If adverse reaction recovers to ≤ Grade 2: • resume treatment at 110 mg dose for the first occurrence • resume treatment at 55 mg dose for the second occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg).

Adverse reaction	Severity	Dose modification
		If adverse reaction does not recover to ≤ Grade 2, permanently discontinue Aumseqa.

Grade = Severity graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) CPK = creatine phosphokinase, ECG = electrocardiogram, LVEF = left ventricular ejection fraction, QTc = corrected QT

Paediatric population

The safety and efficacy of Aumseqa in children or adolescents under the age of 18 years have not been established. No data are available.

2.3. Type of Application and aspects on development

Summary of CHMP answers to the Scientific advice request and interactions with Rapporteurs:

The sought indications are supported by 2 pivotal studies; 1 for 1st line treatment (HS-10296-03-01) and 1 for patients with T790M mutation (predominantly resistance mutation to 1st and 2nd generation EGFR TKI, 2nd line study HS-10296-12-01).

Study HS-10296-03-01 is a Phase 3, randomized, controlled, double-blind, multicenter study conducted in China only. The study was designed to evaluate the safety and efficacy of aumolertinib versus gefitinib as first line treatment in subjects with locally advanced or metastatic NSCLC harbouring EGFR mutations. The primary efficacy endpoint was PFS as assessed by the Investigator.

Study HS-10296-12-01 is a Phase 1/2, open-label, multicenter study conducted in China, Taiwan, and the US (however, only 7 patients were included in the US, none of them in part 3). The study was designed to assess the efficacy and safety of aumolertinib in patients with NSCLC and locally advanced or metastatic disease who progressed following prior therapy with EGFR TKIs. The primary efficacy endpoint was confirmed ORR evaluated by ICR.

The preferred basis for an MAA in the EU would have been to demonstrate non-inferiority of aumolertinib against the EU approved third-generation EGFR TKI, osimertinib, in a randomised trial enrolling an adequate number of European subjects.

In principle, the proposed bridging strategy based on PK analysis from formal study to compare aumolertinib PK in populations with different race and ethnicity with a supportive analysis-based population PK analysis might be acceptable, provided PK in healthy subjects and in NSCLC patients are comparable.

In order to compare aumolertinib PK properties in different populations (i.e. in different ethnicities), it is expected PK in these two populations to be compared not only based on AUCs and Cmax but also on distribution and elimination as well.

In principle the planned population PK analysis of a combined parent metabolite model was supported.

In case of successful demonstration of PK comparability between populations with different ethnicity/race background, if no clinical differences in the PD response and safety issue expected, and if the planned covariate analysis on the exposure-response using population PK modelling does not identify ethnicity as a significant covariate, then the proposed approach could be acceptable.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 55 mg of aumolertinib (as mesilate) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E460), sodium starch glycolate (type a), lactose, sodium stearyl fumarate (E485), magnesium stearate (E572).

Film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), iron oxide yellow (E172).

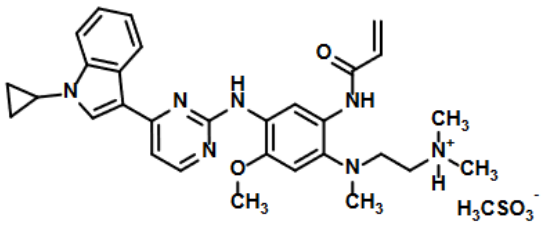
The product is available in a white, high density polyethylene (HDPE) bottle with an aluminium heat - induction sealed child resistant closure, a silica gel desiccant cannister inside, and a white polypropylene (PP) cap.

2.4.2. Active substance

General information

The chemical name of aumolertinib (as mesilate) is *N*-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4 methoxyphenyl)acrylamide methanesulfonate corresponding to the molecular formula $C_{30}H_{35}N_7O_2 \cdot CH_4SO_3$. It has a molecular mass of 621.76 g/mol (free base 525.66 g/mol) and the following structure:

Figure 1: active substance structure



The chemical structure of aumolertinib mesilatewas elucidated by a combination of elemental analysis, UV/Visible spectroscopy, IR spectroscopy, NMR spectroscopy (^{1}H NMR,^{13}C NMR) and mass spectrometry. The solid state properties of the active substance were measured by XRPD, thermogravimetric analysis, DSC and single crystal X-ray analysis.

The active substance is a non-hygroscopic, white to light yellow powder, crystalline in nature.

Aumolertinib has a non - chiral molecular structure.

Aumolertinib exists in only one stable polymorph, designated as Form I. Polymorphism has only been observed for aumolertinib under experimental conditions, which are not foreseen during the manufacture of the active substance. It has been demonstrated that aumolertinib Form I is the only form generated with the proposed manufacturing process, even when using several alternative solvents at a range of temperatures; it is stable to micronisation and under long-term stability conditions for the proposed retest period.

Manufacture, characterisation and process controls

Aumolertinib mesilateis synthesised in seven main steps using well defined starting materials (SM) with acceptable specifications. There are isolated intermediates in the manufacturing process of aumolertinib active substance.

The specifications and control methods for starting materials, intermediates and reagents have been presented, some impurities limits were tightened during the procedure, as requested by CHMP. An assay test was also included in the specification for an intermediate, as requested by the CHMP.

Adequate in-process controls are applied during the synthesis.

Normal operating ranges (NORs) and proven acceptable ranges (PARs) have been defined for each step of the synthesis. During the procedure NORs have been tightened to be in line with the definition given in the Questions and Answers EMA/CHMP/CVMP/QWP/354895/2017. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. No design space is claimed.

The manufacturing process development for the active substance contains QbD elements. The active substance critical quality attributes (CQAs) are described.

The manufacturing development has been evaluated through the use of risk assessment, using the failure mode effect analysis (FMEA) method, and design of experiments (DOE) to identify the critical process steps and process parameters that may have an influence on the active substance quality attributes. The critical process parameters have been adequately identified.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. To improve the purity profile of the active substance, additional IPCs have been introduced in the proposed commercial manufacturing process, if compared to the process used for the manufacture of the batches used in pivotal clinical studies. The reaction scale of several steps has been increased to improve the overall process throughput. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Process impurities have been discussed and evaluated for mutagenic potential.

Specification

The active substance specification includes tests for appearance (visual inspection), identification (HPLC and FTIR -Ph. Eur.-), assay (HPLC), related substances (HPLC), residual solvents (acetone, acetonitrile, ethyl acetate by GC), water content (Karl Fischer, Ph. Eur.), residue on ignition (Ph. Eur.), methanesulfonic acid (titration) and particle size (laser diffraction).

The active substance specifications are based on the active substance CQAs.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Specifications for residual solvents are in compliance with ICH guideline Q3C.

The absence of control of microbial control, elemental impurities, solvent content and polymorphic form have been adequately justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Results of forced degradation studies performed demonstrated that the HPLC method for determination drug-related impurities was stability indicating. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on production scale batches of active substance, manufactured at the commercial site according to the proposed commercial route and process have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on pilot scale batches of active substance from the proposed manufacturer using the proposed commercial process, stored in a container closure system representative of that intended for the market under long term and accelerated conditions according to ICH guidelines were provided.

The parameters tested are the same as for release, with the exclusion of identification by FTIR, solvents and methanesulfonic acid; as these parameters are not stability indicating, this is acceptable. The analytical methods used were the same as for release and were stability indicating. Additionally, polymorphism, particle size, and microbial limits have been tested in the primary stability batches.

All tested parameters during stability studies conducted at long term and accelerated conditions were within the specification limits.

Photostability testing following the ICH guideline Q1B was performed, confirming that the active substance is stable to light in the solid state.

Results on stress conditions were also provided. The results indicate that the tests are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when stored at the proposed storage conditions in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as a light yellow, 7 mm, round immediate-release film-coated tablet debossed with “E1” on one side and plain on the reverse containing 55 mg of aumolertinib (as mesilate) as active substance. The film-coating is non-functional.

The percentage of active substance is >2% of composition, hence the dosage form is considered standard.

The physico-chemical characteristics of the active substance have been adequately discussed. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except for iron oxide yellow colorant contained in the coating that comply with EU food legislation. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The functions of the excipients in the formulation have been satisfactorily described. Compatibility of the active substance with the chosen excipients has been demonstrated by compatibility studies and justified by stability data. The specification for each excipient has been revised to include relevant functionality-related characteristics. The analytical methods used for the excipients have been adequately described and non-compendial methods have been appropriately validated, in accordance with the ICH guidelines.

The pharmaceutical development of the finished product contains QbD elements. No design space has been claimed for the manufacturing process of the finished product.

The quality target product profile (QTPP) was defined as an immediate release oral dosage form (rapid onset), which allows to achieve the 110 mg daily dose, that meets compendial and other relevant quality standards, and is packaged in a suitable container to achieve the desired shelf life (zones I to IVa).

The CQAs identified were identification, assay, uniformity of dosage units, dissolution, degradation products, and microbial limits.

The manufacturing development has been evaluated through the use of risk assessment and DoE to identify the high-risk steps that may affect the CQAs of the finished product. The potentially high-risk process variables that could impact the identified finished product CQAs were investigated to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch. The critical process parameters have been adequately identified.The effect of the manufacturing process of the finished product on the active substance polymorphism was investigated and no changes were observed.

The formulation used during the phase 3 clinical studies is the same as that intended for marketing.

The development of the dissolution method has been described in detail. . In consideration of the high solubility of the active substance, the proposed QC dissolution method was accepted, despite that its discriminatory power was not fully demonstrated; this is in line with the recommendations of CPMP/EWP/QWP/1401/98.

The primary packaging is a white, high density polyethylene (HDPE) bottle with an aluminium heat - induction sealed child-resistant closure, a silica gel desiccant cannister inside, and a white polypropylene (PP) cap. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process. Satisfactory shipping data from simulation studies have also been provided.

NORs and PARs have been described and their definition is in line with EMA/CHMP/CVMP/QWP/354895/2017. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

A bulk holding time for the final blend and the core tablets, respectively, and bulk holding time for the film-coated tablets have been justified.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (HPLC), assay (HPLC), degradation products (HPLC), nitrosamine impurity (LC-MS), Dissolution, water content (Karl Fischer, Ph. Eur.), uniformity of dosage units (Ph. Eur.) and microbial limits (Ph. Eur.).4

The finished product is released on the market based on the above release specifications, through traditional final product release testing. Overall, the finished product specification has been adequately set in accordance with guidance, and the limits are supported by batch data. During the procedure, the finished product release and shelf-life specifications were revised to include a reference number with revision and effective date.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches was provided, confirming that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Six potential nitrosamines impurities which may be derived from aumolertinib under ideal conditions for N-nitrosamine formation were identified. Two of them were commercially available two were successfully synthetized , and two could not be synthetized . The extensive experiments to try to synthetize these two impurities have been described in detail; therefore, as mentioned in Q&A no. 8 and/or 14 in EMA/409815/2020, it is acceptable to conclude that these two nitrosamine impurities are not formed. During the procedure, the applicant provided validated analytical procedures for each of the four synthesised nitrosamine impurities. Confirmatory testing was performed on the three PPQ batches; all impurities, except for one impurity , were not detected . The specified impurity was detected in two PPQ batches , and the proposed control limit in the finished product specification. Since the product is indicated for advanced cancer only, hence it falls under the scope of ICH S9 guideline, the proposed limit is acceptable as it is below the acceptable limit of NMT 0.2% as set by ICH Q3B(R2). Therefore, no additional specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The same reference standards used for the active substance testing are also used for the finished product.

Batch analysis results are provided for six full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for three production scale batches of the finished product stored under long term and accelerated conditions according to the ICH guidelines. The batches were manufactured at the commercial site and were packaged in container closure system representative of the one proposed for commercial use.

Samples were tested in line with the shelf-life specification presented4. Stability data for all quality attributes complied with specifications. However, during the procedure additional stability data were provided showing an increase in total impurities at long-term conditions. This justifies the temperature restriction 'Do not store above 30°C'.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study confirmed that finished product is stable to light.

Aumolertinib tablets were subjected to stress conditions including heat, heat/humidity, and treatment under acidic, basic, and oxidative conditions. Degradation was monitored by analyzing the resulting samples for assay and impurities by HPLC. In all cases, mass balance between 90.0 and 110.0% was achieved and the peak purity data for the main peak in the HPLC degradation products method was acceptable, demonstrating specificity of these stability-indicating analytical methods. Some degradation was observed in the samples under all stress conditions.

In-use stability studies have been completed for the bottle commercial package configuration to evaluate the stability of the proposed multi-dose package after opening. The study was conducted for a total duration of 60 days to evaluate the stability over twice the intended life of the bottle to accommodate the unlikely scenario where two containers are used in parallel. Water was observed to slightly increase over the 60 days period, but it remained within the specification. This justifies the restriction 'Store in the original bottle in order to protect from moisture'.

Based on available stability data, the proposed shelf-life of 36 months with the storage condition "Do not store above 30°C. Store in the original bottle in order to protect from moisture" has been justified.

Adventitious agents

It has been confirmed that lactose has been produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

TSE/BSE statements for magnesium stearate as well as talc (used in the Opadry ready-to-use material) were provided, upon request of the CHMP, justifying that the excipients are not of animal origin.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a

satisfactory and uniform performance in clinical use. The control of nitrosamine impurities is considered adequate.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Aumolertinib is a novel, selective, irreversible EGFR TKI, with activity against the T790M resistance mutations and common EGFR activating mutations and reduced inhibitory activity against WT EGFRs.

The proposed indication for this application is first-line monotherapy treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations; and the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

The recommended dose of Aumseqa is 110 mg (2 tablets of 55 mg) taken orally once a day.

This application follows the ICH S9 guideline, with a non-clinical package including more studies than required for ICHS 9.

In vitro pharmacology studies assessed the inhibitory activity and selectivity of aumolertinib towards EGFR-resistant mutant kinases, EGFR-activating mutations, and WT EGFR. In vivo efficacy of aumolertinib was tested in NSCLC xenograft or patient-derived PDX models with EGFR-resistant or -activating mutations or wild type EGFR. Safety pharmacology studies assessed the effects of aumolertinib on the CNS, cardiovascular, and respiratory systems.

Nonclinical pharmacokinetic studies evaluated the absorption of aumolertinib after single and repeated doses, organ distribution, protein binding, excretion, and in vitro and in vivo metabolism studies. Metabolic pathways were identified in both rats and dogs and showed that the major circulating metabolite of aumolertinib, HAS-719, is formed via an N-demethylation pathway. In vitro studies evaluated the potential of aumolertinib to inhibit or induce various cytochrome (CYP) P450 enzymes and assessed permeability in human carcinoma colon-2 (Caco-2) cells.

The toxicity and toxicokinetics of aumolertinib was assessed in pivotal single- and repeat-dose toxicology studies in rats (13 and 26 weeks) and dogs (13 and 39 weeks). These studies were preceded by single-dose and 4-week repeat-dose range-finding studies to support dose selection. The genotoxic potential of aumolertinib was tested in both, in vitro and in vivo assays. The effects of aumolertinib on reproductive performance and early embryonic development were evaluated in rats. Potential embryo-foetal development effects were evaluated in rats and rabbits. Furthermore, a study to investigate the phototoxic potential of aumolertinib was conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies

Table 2: Inhibition of Wild Type and Mutant EGFR by various compounds

EGFR Type	IC_{50} (nM)				
	Aumolertinib	HAS-719	Osimertinib	Gefitinib	Afatinib
T790M	0.37 ± 0.04	0.73 ± 0.10	0.54 ± 0.07	> 100	0.79 ± 0.09
Wild Type	3.39 ± 0.53	11.30 ± 0.12	5.55 ± 0.86	0.13 ± 0.04	0.05 ± 0.01
L858R	1.50 ± 0.32	5.08 ± 0.71	2.26 ± 0.25	0.88 ± 0.15	0.08 ± 0.01
Del 19 (Del E746-A750)	0.88 ± 0.31	2.84 ± 0.19	1.21 ± 0.31	0.17 ± 0.04	0.05 ± 0.02
T790M/L858R	0.29 ± 0.10	0.69 ± 0.18	0.46 ± 0.18	> 100	2.37 ± 0.43
T790M/Del	0.21 ± 0.10	0.48 ± 0.25	0.29 ± 0.15	> 100	2.48 ± 0.33

Abbreviations: IC_{50}=50% inhibitory concentration.
IC_{50} and standard deviations were calculated from 3 separate tests.

The activity of aumolertinib was also examined in cellular assays.

Table 3: Anti-Proliferation Activity of Aumolertinib, HAS-719 and Other EGFR Inhibitors in Various Cancer Cell Lines

Cell Line (EGFR Mutation)	Cancer Type		IC_{50} (nM) (Mean ± SD)			
		Aumolertinib	HAS-719	Osimertinib	Gefitinib	Afatinib
NCI-H1975 (T790M/L858R)	Human lung cancer	3.3 ± 0.18	12.6 ± 1.32	4.0 ± 0.79	> 1000	119.8 ± 10.50
PC9-GR (T790M/Del 19)	Human lung cancer	2.7 ± 0.42	13.6 ± 5.60	4.1 ± 2.26	> 1000	19.7 ± 9.06
HCC827 (Del 19)	Human lung cancer	3.3 ± 1.04	12.3 ± 1.04	2.6 ± 0.52	5.0 ± 0.69	0.6 ± 0.12
PC9 (Del 19)	Human lung cancer	4.1 ± 0.83	19.9 ± 4.23	4.3 ± 1.95	10.7 ± 2.38	0.4 ± 0.06
A431 (Wild type)	Human epidermoid carcinoma	596.6 ± 225.27	1338.3 ± 205.71	249.2 ± 91.84	137.6 ± 44.65	11.4 ± 4.02

Abbreviations: IC_{50} = 50% inhibitory concentration. The IC_{50} and SD were calculated from 3 separate tests.

Western Blot analysis in the NCI-H1975 cell line with EGFR T790M and L858R double mutations showed that Aumolertinib concentration-dependently inhibited EGFR phosphorylation in both EGFR T790M mutant and EGFR-activating mutant NSCLC tumours, resulting in inhibition of downstream AKT and ERK1/2 signalling pathways.

The selectivity of aumolertinib was tested in vitro in a kinase panel of 38 closely related tyrosine kinases using staurosporine (a broad-spectrum kinase inhibitor) as reference compound (CPB-P15-5267). The metabolite HAS-719 was not included in the test.

Table 4: Potency of Aumolertinib Against 38 Closely Related Tyrosine Kinases

Kinase Name	IC_{50} (nM)		Kinase Name	IC_{50} (nM)	
	Aumolertinib	Staurosporine		Aumolertinib	Staurosporine
ALK	490	6.1	IGF1R	1732	69
AXL	3405	3.1	INSR	2179	43
AURA	>10,000	2.4	ITK	260	71
BTK	339	61	JAK1	>10,000	1.4
BLK	691	5.3	JAK2	>10,000	0.20
BRK	103	952	JAK3	16	0.21
CKIT	9628	3.1	KDR	3900	6.2
CHK2	>10,000	29	LTK	377	2.9
FAK	782	8.7	MET	>10,000	121
FGFR1	8802	8.5	MUSK	>10,000	4.6
FGFR2	6985	4.6	PDGFRa	390	0.48
FGFR3	7641	10	PDGFRb	226	0.64
FGFR4	7065	96	RET	7513	5.8
FLT1	9725	3.1	RON	>10,000	102
FLT3	113	0.24	ROS	32	0.37
FLT4	1006	0.58	TRK-A	>10,000	0.28
FES	2707	8.2	TIE2	>10,000	53
HER2	60	416	TYK2	>10,000	0.34
HER4	6.5	23	YES	7403	3.9

Abbreviations: IC_{50}=50% inhibitory concentration.

In vivo studies

The effect of oral dosing of aumolertinib across different EGFRm (HCC827 cell lines), EGFRm/T790M (NCIH1975 and LU1868) and wild-type EGFR (A431) xenograft mice models was determined *in vivo*.

In female nude mice implanted with human xenografts derived from NSCLC cell line NCIH1975 with the EGFR T790M mutation, aumolertinib dose-dependently inhibited phosphorylation of both EGFR and its downstream signalling molecules AKT and ERK1/2. The inhibitory activity correlated with drug concentrations in tumour tissues. At 5 mg/kg (low dose), the plasma Cmax was 190 ng/mL at 2 hours post-dose. Potent pEGFR inhibitory effects were noted 6-16 hours post-dose, correlating with a tumour Cmax of 332 ng/g at 6h. However, this did not fully correlate with pAKT and pERK inhibition that was most obvious at 4-6 h post-dose. At 20 mg/kg (high dose), inhibition of these signalling proteins lasted for 24 hours and aumolertinib concentration in tumours was higher than that measured in plasma. At this dose, the plasma Cmax was 905 ng/mL at 2 hours post- dose, the tumour Cmax was 1454 ng/g at 4 hours post-dose, and the 24-hour tumour concentration was 432 ng/g aumolertinib.

In female nude mice inoculated with the NSCLC cell line HCC827 with the EGFR exon 19 deletion activating mutation, EGFR phosphorylation was potently inhibited at the lowest dose evaluated (5 mg/kg, plasma concentration of 96 ng/mL at 6 hours post-dose). Phosphorylation of AKT was also significantly inhibited, to a greater degree than phosphorylation of ERK. PK data 6 h post-dosing

showed higher aumolertinib concentration in tumour tissue compared to plasma. Aumolertinib inhibited growth of HCC827 tumours xenograft. Tumour regression was observed at all doses (5, 10, and 20 mg/kg).

In female nude mice inoculated with human xenografts of NCI-H1975 tumours with EGFR T790M-resistant mutation, aumolertinib showed dose-dependent tumour growth inhibition and tumour regression.

Table 5: Anti-Tumour Activity of Aumolertinib in the NCI-H1975 Xenograft Tumour Model

Treatment	Tumour Volume (mm^3) Mean ± SEM	Tumour Volume (mm^3) Mean ± SEM	T/C	TGI	*P* Value [a]	Tumour Regression
	Day 0	Day 14	Day 14	Day 14	Day 14	
Vehicle	297.6 ± 19.4	1912.2 ± 194.20	-	-	-	0
Osimertinib 20 mg/kg	297.7 ± 23.4	7.0 ± 1.14	-97.6%	197.6%	< 0.0001	8/8 PR
Aumolertinib 5 mg/kg	297.8 ± 19.6	518.3 ± 112.39	13.7%	86.3%	< 0.0001	2/8 PR
Aumolertinib 10 mg/kg	297.8 ± 23.9	222.7 ± 44.98	-25.2%	125.2%	< 0.0001	5/8 PR
Aumolertinib 20 mg/kg	297.6 ± 23.2	16.8 ± 5.85	-94.4%	194.4%	< 0.0001	8/8 PR

N=8 females/group
Abbreviations: SEM = standard error, TGI = tumour growth inhibition, PR = partial regression.
[a] *P* value was from one-way ANOVA analysis when compared to vehicle group.

Aumolertinib inhibited growth of the patient-derived primary LU1868 xenografts that carry the EGFR T790M-resistant mutation and induced almost complete tumour regression at a dose of 20 mg/kg.

Anti-Tumour Activity of Aumolertinib in the A431 Tumour Model with Wild Type EGFR

Table 6: Anti-Tumour Effect of Aumolertinib in Nude Mouse A431 Xenografts

Treatment	Tumour Volume (mm^3) Mean ± SEM	Tumour Volume (mm^3) Mean ± SEM	T/C	TGI	*P* Value [a]	Tumour Regression
	Day 0	Day 14	Day 14	Day 14	Day 14	
Vehicle	202.67 ± 27.72	928.62 ± 95.92	-	-	-	0
Gefitinib 6.25 mg/kg	202.89 ± 17.95	553.01 ± 57.46	48.2%	51.8%	0.0038	0
Afatinib 7.5 mg/kg	203.14 ± 23.33	344.02 ± 65.33	19.4%	80.6%	< 0.0001	0
Osimertinib 5 mg/kg	202.86 ± 21.03	468.75 ± 38.99	36.6%	63.4%	0.0003	0
Aumolertinib 5 mg/kg	202.95 ± 18.97	711.37 ± 77.10	70.0%	30.0%	0.1728	0

Aumolertinib 10 mg/kg	202.87 ± 23.17	656.15 ± 96.34	62.4%	37.6%	0.0542	0
Aumolertinib 20 mg/kg	202.94 ± 20.10	417.65 ± 64.61	29.6%	70.4%	< 0.0001	0

SEM=standard error, TGI=tumour growth inhibition.
[a]*P* value was from one-way ANOVA analysis when compared to vehicle group.

Brain penetrance

To explore the efficacy of aumolertinib against EGFR mutant tumours in the brain, an orthotopic brain xenograft study was performed using NCI-H1975-luc NSCLC cells in mice. Tumour growth inhibition in the brain and prolonged survival of animals were observed in aumolertinib dosed at 20 mg/kg and 40 mg/kg groups and osimertinib dosed at 25 mg/kg group , supporting the capacity of aumolertinib to cross the blood-brain barrier.

2.5.2.2. Secondary pharmacodynamic studies

Aumolertinib was not tested in an exploratory secondary pharmacological panel.

Aumolertinib was tested across a cell kinase assays (see in vitro primary pharmacodynamic studies, Table 4) and results indicated that aumolertinib is a selective EGFR mutant kinase inhibitor with weak inhibition of most of its closely related kinases. Secondary pharmacology studies against other non-kinase receptors, enzymes and ion channels were not conducted for aumolertinib. The Applicant justification of the absence of in vitro secondary pharmacology studies was based on: i) The safety profile of the substance as determined from in vitro and in vivo safety pharmacology studies, ii) the weak to none inhibition of 38 closely related kinases suggesting that it was a selective EGFR mutant kinase inhibitor with limited potential for off-target adverse effects. iii) The availability of safety data from clinical trials and several years of post-marketing experience with aumolertinib.

2.5.2.3. Safety pharmacology programme

Aumolertinib has been evaluated in a panel of nonclinical safety pharmacology studies.

In a non GLP compliant study, aumolertinib inhibited the human ether-a-go-go related gene (hERG)-mediated potassium current with an IC50 of 2.958 μM, which indicated that aumolertinib mildly inhibits hERG current. The main metabolite of aumolertinib, HAS-719 inhibited hERG-mediated potassium current in a concentration-dependent manner, with an IC50 of 2.45 μM. Taking into account the Cmax adjusted for free component of aumolertinib at the clinically dose of 110 mg for both aumolertinib and HAS-719, the safety margin is almost 900-fold and 2175, respectively.

In vivo GLP compliant studies were conducted with aumolertinib but not with the pharmacologically active metabolite HAS719 which is formed in rats and dogs.

Aumolertinib had no effect on body temperature, cardiovascular, or respiratory parameters at clinically relevant doses of up to 20 mg/kg in telemetered dogs.

No effects on CNS function were noted in an assessment of behaviour using a functional observational battery test in Sprague-Dawley rats administered aumolertinib up to 250 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

No studies were submitted.

2.5.3. Pharmacokinetics

Methods of analysis

Four validation reports on LC-MS/MS methods used to determine aumolertinib and HAS-719 concentrations in plasma from rats, dogs and rabbits were submitted by the Applicant. These methods were used in the non-GLP-compliant pharmacokinetic studies in the rat and dog (validation report: RP-HS10296-ADME-Bioanalysis-MV) and in the pivotal GLP-compliant toxicology studies in rats, dogs and rabbits (validation reports R14-S145-2MV, D14-S145-2MV, Q14-S145-MV, respectively). In line with ICH M10 guideline on bioanalytical method validation (EMEA/CHMP/ICH/172948/2019), the validations of methods used in the pivotal toxicology studies were performed according to GLP standards.

Absorption

The permeability of aumolertinib was assessed as low to moderate in a series of in vitro studies in Caco-2 cells with aumolertinib concentrations of 2, 10, 50 and 100 µM (RP-HS10296-ADME-1_PB, 401380-20180704-CAPGPS). Efflux ratios ranged from 0.4 to 3.1 across experiments,. In vivo bioavailability was later determined to be low (male rats) to high (in female rats and dogs, see further below).

Single-dose pharmacokinetics of aumolertinib was determined in Sprague Dawley rats and beagle dogs by intravenous and oral routes to determine the oral absolute bioavailability.

Aumolertinib exposure was higher (approximately 8 to 14-fold) in female rats as compared to male rats following oral (gavage) administration. Following intravenous administration, aumolertinib exposure was slightly higher (approximately 1.8-fold) in female rats as compared to male rats. Following oral or intravenous administration, no gender differences were apparent in aumolertinib exposure in dogs.

Aumolertinib was rapidly absorbed after a single oral dose in all species tested.

Bioavailability after oral dosing at 10 to 40 mg/kg of aumolertinib was low in male rats (12 to 18%) and high in female rats (84 to 104%). Bioavailability ranged from 59 to 83% in dogs.

Following single increasing oral doses of aumolertinib in rats and dogs in the toxicology studies the increase in exposure (AUC) was generally dose proportional.

Repeat dose oral pharmacokinetics of aumolertinib was determined in Sprague Dawley rats and Beagle dogs.

In rats, aumolertinib exposure was significantly higher (approximately 12-fold) in females as compared to males. In comparison to single dose pharmacokinetic data, aumolertinib exposure (AUC) increased 1.7 and 1.4-fold in male and female rats, respectively, indicating no significant accumulation following once daily dosing for 7 days. Similarly, no significant accumulation was observed for HAS-719 exposure following once daily dosing. Aumolertinib and HAS-719 concentrations appeared to achieve steady-state after 5 days of once daily dosing.

In dogs, aumolertinib exposure was similar in male and female dogs. In comparison to single dose pharmacokinetic data, aumolertinib and HAS-719 exposures (AUC) did not accumulate following once daily dosing in dogs. Aumolertinib and HAS-719 concentrations appeared to achieve steady-state after 5 days of once daily dosing.

The systemic exposure to HAS-719 was 50% of the parent compound in male rats, 7% in female rats, and 57% in dogs, respectively.

Distribution

Aumolertinib and its metabolite HAS-719, are extensively bound to plasma proteins in a non-concentration-dependent manner across species and the bound fraction is similar across species (≥99.5).

Tissue distribution was evaluated in the albino rat and in the Long Evans rat.

In albino rats, [^{14}C]-aumolertinib was rapidly absorbed and widely distributed throughout a variety of tissues. With the exception of the testes (9.2%), aumolertinib concentrations in rat tissues at 24-hours post-dose were <5% of those at 2 hours post-dose, indicating low tissue retention of aumolertinib. In all tissues evaluated, aumolertinib concentrations were higher than plasma concentrations. Similar to plasma exposures, significant sex-related differences were observed. The tissue exposures (AUC) of aumolertinib were approximately 2.3- to 9.1-fold higher in female rats as compared to male rats. Lung, adrenal gland, spleen, marrow, and liver were the preferred sites for distribution. Aumolertinib exhibited a high distribution in the brain (brain:plasma AUC ratio=7.4 (female) and 7.6 (male)). The blood:plasma ratio of aumolertinib indicated that the parent drug partitions to red blood cells. After oral administration of aumolertinib, relatively high concentrations of HAS-719 were observed in tissues. The tissue exposure (AUC) of HAS-719 in female rats was similar to that in the male rats. The exposure of HAS-719 in the tissues was approximately 72% of the parent compound in male rats and 13% of the parent compound in female rats. The mean brain:plasma exposure ratio was 1.5 across measured time points, indicating a lower potential for the metabolite to cross the blood-brain barrier. The mean blood:plasma ratio of HAS-719 was approximately 2, indicating that the metabolite partitions to red blood cells.

In Long-Evans rats, results showed rapid absorption of [^{14}C]-aumolertinib which distributed in the ocular, endocrine, and secretory tissues, as well as the tissues of the gastrointestinal tract and metabolic/excretory system. The brain:plasma ratio of radioactivity detected was 0.38 at its maximum, 4 hours post-dose. In addition, there was significant distribution of radioactivity to the melanin-containing tissues, such as the uveal tract. However, the exposure (AUC) to [^{14}C]-aumolertinib in pigmented skin was similar when compared to the exposure of the non-pigmented skin. The tissue:plasma AUC ratios for [^{14}C]-aumolertinib were greater than 1.0 in the majority of tissues, indicating that aumolertinib preferentially portioned to tissues.

Placental transfer: Based on the pivotal EFD study in rabbits (Q14-S145-2RP), both aumolertinib and HAS-719 plasma exposure was detectable in pregnant rabbits and live foetuses 2-3 hours after last maternal dosing on GD29 (total dosing schedule: GD6 through GD29, n=2), indicating that aumolertinib and HAS-719 both cross the placenta. The maternal:foetal exposure ratios in rabbits (based on single-point concentration determinations) were 1.23 for aumolertinib and 5.51 for HAS-719.

Milk transfer was not investigated for aumolertinib or HAS-719.

<u>Metabolism</u>

An in vitro metabolic stability study in hepatic microsomes from mice, rats, dogs, monkeys, and humans demonstrated an intermediate hepatic intrinsic clearance of aumolertinib in dogs and humans, and a high hepatic clearance of aumolertinib in mice, rats, and monkeys.

The studies with recombinant human enzymes further indicated that aumolertinib is mainly metabolized by CYP3A4.

A cross-species metabolic comparison of aumolertinib in mouse, rat, dog, monkey, and human hepatocytes demonstrated that aumolertinib is extensively metabolized without any unique human metabolites. The major metabolic pathway determined for mouse and human hepatocytes was N-

demethylation (M5-2 = HAS-719); in rats it was N-demethylation and glutathione conjugation and in dogs, N-oxidation, glutathione conjugation, and N-demethylation.

The metabolite HAS-719 was formed and detected in the plasma of all species. In rats, exposure measures (AUC and Cmax) were at approximately similar levels between sexes. As such, a much higher proportion of drug exposure was contributable to HAS-719 in male rats (AUCmetabolite:parent0-24h:0.6-0.9) compared to female rats (AUCmetabolite:parent0-24h:0.08-0.1), due to marked difference in aumolertinib exposure between sexes as noted above. Overall, systemic exposure to HAS-719 was approximately 9 to 70% of the parent compound in rats and 41 to 53% in dogs.

The in vivo metabolism of aumolertinib was studied in rat, dog, and human. After oral administration of aumolertinib, the N-demethylated metabolite (M5-1) and the N-dealkylated and N-demethylated metabolite (M1) were the predominant circulating species detected in plasma of male rats, followed by the parent drug, the N-dealkylated metabolite (M2), and N-demethylated metabolite HAS-719 (see Figure 4). In contrast, the main circulating species in females was unchanged aumolertinib. In urine, the N-dealkylated and N-demethylated metabolite (M1) and the N-acetylcysteine conjugate (M25) were the major metabolites identified in male rats, while the cysteine conjugate (M23) was mainly found in female rat urine. In bile from male rats, the major species detected were the sulphite adduct (M18), cysteine conjugate (M23), and mono-oxidized (M10-2). In bile from females, the mono-oxidized (M10-2) and cysteine conjugate (M23) were the main species detected. Unchanged parent drug, the sulphite adduct (M18), and the cysteine conjugate (M23) were the major metabolites identified in rat faeces. The major Phase I metabolic routes of aumolertinib in rats include: 1) O-demethylation, 2) N-demethylation, and 3) mono-oxidation at multiple positions. Glucuronidation, sulfation, and glutathione were the main Phase II metabolic pathways. In rats, unchanged aumolertinib was the predominant circulating component identified (10 to 38% of total radioactivity in plasma). HAS-719 accounted for approximately 5% and 8% of total radioactivity in female and male rats, respectively.

In dogs, unchanged aumolertinib was the predominant circulating component identified (84% of total plasma exposure 2 hours post-dose). The major metabolite HAS-719 accounted for 11% of total plasma and the N-dealkylated metabolite (M2) for 3%.

The main metabolic pathways of aumolertinib in the human body are first N-demethylacetamide, then N-demethylation that forms HAS-719. The secondary metabolic pathways are oxidation and N-dealkylation.

Excretion

The excretion profile of aumolertinib was characterized in male and female rats and showed that the main excretion path assessed was via faeces (99.89%) with urinary elimination being a minor component (1.95%), and with similar excretion between sexes.

Pharmacokinetic interaction studies

Aumolertinib as a victim drug

- ***Potential for interactions related to aumolertinib as metabolism:***

Aumolertinib undergoes metabolism through one main enzyme CYP3A4 leading to one main metabolite, HAS-719. This major circulating metabolite represents more than 10% of total drug-related exposure at steady-state in humans (37.4%). Other minor pathways involved CYP3A5, CYP1A2 and CYP2A6, in a lesser extent.

The Applicant had carried out PBPK analyses and in vivo DDI studies with a strong CYP3A4 inhibitor and inducer, itraconazole and rifampicin, respectively to evaluate the effect of CYP3A4

inhibitors/inducers on the PK of aumolertinib. Results showed a significant effect of these drugs on aumolertinib exposure, confirm that aumolertinib is a CYP3A4 substrate, consistent with in vitro data (see section 2.6.2.1. in vivo DDI).

- ***Potential for interactions related to* aumolertinib transport**

Based on in vitro studies results drug-drug interactions between OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K modulators and aumolertinib as a substrate are not anticipated as Rs/Ri ratios were <2 for aumolertinib in all transporter systems (study 401380-20180704-OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-KU).

The Applicant conducted an in vitro assay to assess the potential for HAS-719 to be a substrate of drug transporters. The results demonstrate that HAS-719 is a substrate of P-gp and a weak substrate of BCRP.

Nevertheless, it is unknown whether aumolertinib is or not a BSEP and OCT1 substrates. Neither, if the active metabolite HAS-719 is or not BSEP, MATE1, OATP1B1, and OATP1B3 substrate.

Aumolertinib as a perpetrator drug

- ***Potential for interactions related to enzymes (CYPs, UGTs and CES): Aumolertinib, and HAS-719 as inhibitors***

The ability of aumolertinib (HS-10296) and its main metabolite HAS-719 to be direct inhibitors of CYP1A2, 2B6, CYP2C8, CYP2C9, 2C19, 2D6 and 3A4 was assessed as part of two assays: RP-HS10296 and 401380-20180704-DDIM.IC50>100 μM) on activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 (with midazolam as substrate) and CYP3A4/5 (with testosterone as substrate) over a concentration range of 0.1 to 100 μM (RP-HS10296-ADME-1_Inhib). HAS-719 exhibited no inhibition on CYP2C9 (IC50>50 μM), weak inhibition on CYP1A2 (IC50=29 μM)m CYP2B6 (IC50=19.7 μM), CYP2C8 (IC50=21.8 μM), CYP2C19 (IC50=22.5 μM), CYP2D6 (IC50=25.7 μM), CYP3A4 (testosterone, IC50=10.1 μM), and moderate inhibition on CYP3A4 (midazolam, IC50=8.8 μM) over a concentration range from 0.03 to 50 μM. The ability of aumolertinib (HS-10296) and its main metabolite HAS-719 to be direct inhibitors of CYP1A2, 2B6, CYP2C8, CYP2C9, 2C19, 2D6 and 3A4 was assessed as part of two assays: RP-HS10296 and 401380-20180704-DDIM.

The study setups used an appropriate system, human liver microsomes (HLM), the ranges of concentrations, from (0.10~100 μM) for aumolertinib and (0.03 to 50 μM) for HAS-719 were covering the worst expected at systemic and intestinal level (i.e. 0.33 μM and 70 μM), control substrates and inhibitors. Results from these studies show that, at the highest tested concentrations of 100μM and 50μM aumolertinib did not exert any direct inhibition towards the tested CYPs.

As regards the metabolite HAS-719, a reversible inhibition occurred on CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4 (with testosterone as substrate) (IC50 was 29.7, 19.7, 21.8, 22.5, 25.7 and 10.1 μM, respectively), moderately inhibited CYP3A4 (with midazolam as substrate) (IC50 was 8.81 μM). These IC50 values and their corresponding Ki values are higher than the estimated systemic concentration of HAS-719, i.e. 0.12 μM. Then, clinically relevant drug-drug interactions due to the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4 by HAS-719 can be ruled out.

The Applicant has conducted time-dependent inhibition (TDI) studies with aumolertinib and HAS-719 on CYP450 enzymes in HLM. The results indicate that the IC50 values are 19.9 μM and 15 μM when midazolam and testosterone are used as substrates for CYP3A4, respectively.

Aumolertinib effect on midazolam (a sensitive CYP3A substrate) was investigated in a clinical study (see clinical pharmacology section 2.6.2.1.).

Table 7 In Vitro rUGT Inhibition for EQ143 and HAS-719

rUGT	EQ143 IC_{50}(μM)	HAS-719 IC_{50}(μM)
1A1	7.38	13.4
2B7	50.1	37.7

- ***Potential for interactions related to CYP1A2, 2B6 and CYP3A4: Aumolertinib, and HAS-719 as inducers***

The Applicant conducted an in vitro CYP450 induction assay with aumolertinib on CYP450 enzymes in HLM. The results revealed that aumolertinib induced CYP3A4 mRNA expression by over 2-fold across the concentration ranges studied in all donors. Furthermore, aumolertinib also caused a more than 2-fold increase in CYP1A2 mRNA in all three donors.

- ***Potential inhibition of transporters:***

Aumolertinib inhibited the efflux transporters P-gp and BCRP and MATE1 an IC50 of 0.33, 4.94 and 0.098μM, respectively. These IC50 values are lower than the estimated intestinal concentration (i.e. 83.6μM). In a clinical drug-drug interaction study, aumolertinib increased the Cmax and AUC of fexofenadine (sensitive P-gp substrate) by 86% and 67%, respectively. No clinical studies have been performed to investigate interactions with MATE1 substrates and therefore the potential clinical effect of MATE1 inhibition by aumolertinib is unknown.

Additional in vitro assays investigating the potential for aumolertinib to be a substrate of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) were performed in multidrug resistant protein 1 (MDR1)- Madin-Darby Canine Kidney (MDCK)II and BCRP-MDCKII cells. The concentrations of aumolertinib tested were 0.1, 1, and 10 μM, which span the maximum aumolertinib concentration at steady state ($C_{max,ss}$) following a 110 mg dose in humans. After incubation with 10 μM aumolertinib in MDR1-MDCKII cells, the total recovery of aumolertinib in A>B and B>A direction was 21.6% and 85.2%, respectively. The efflux ratio was 4.58, which was reduced to 1.15 in the presence of the P-gp inhibitor, ketoconazole (50 μM).

After incubation with 10 μM aumolertinib in BCRP-MDCKII cells, the total recovery of aumolertinib in A>B and B>A direction was 32% and 84.4%, respectively. The efflux ratio was 3.05 which was reduced to 1.89 in the presence of the BCRP inhibitor, Ko-143 (10 μM).

Aumolertinib inhibited the uptake transporters OATP1B1, OAT1, OCT2 and MATE1 with IC50 values of 26.0 μM, 97.9 μM, 26.2 μM, and 0.098 μM, respectively but did not inhibit OATP1B3, OAT3, or MATE2-K (IC50 > 100 μM).

Aumolertinib did not inhibit OATP1B3, OAT3, MATE2-K, or bile salt export pump (BSEP).

2.5.4. Toxicology

Table 8 Overview of toxicology studies

Test Article: Aumolertinib					
Type of Study Species/Strain	**Method of Administration**	**Duration of Dosing**	**Daily Dose (mg/kg)[a]**	**GLP**	**Study Number**
Single-Dose Toxicity					

Rat/Sprague-Dawley	PO	Single dose	0, 100, 300, and 900	Yes	R14-S145-SD
Dog/Beagle	PO	Single dose	0, 20, 60, and 200	Yes	D14-S145-SD
Repeat-Dose Toxicity					
Rat/Sprague-Dawley	PO	Escalating dose (5 days)	10→30→90→270→ 810	No	R14-S145-DR
Rat/Sprague-Dawley	PO	4 to 6 weeks	Aumolertinib: 0, 30, 100→200, 300	No	R14-S145-2DR
Rat/Sprague-Dawley	PO	13 weeks + 4-week recovery	0, 20, 60 (F), and 120 (M)	Yes	R14-S145-RD
Rat/Sprague-Dawley	PO	26 weeks + 4-week recovery	0, 10, 30, and 90	Yes	R14-S145-2RD
Dog/Beagle	PO	Escalating dose (5 days)	5→15→45→135→ 270	No	D14-S145-DR
Dog/Beagle	PO	4 weeks	Aumolertinib: 0, 10, 25, 75	No	D14-S145-2DR
Dog/Beagle	PO	13 weeks + 4-week recovery	0, 4, 10, and 25	Yes	D14-S145-RD
Dog/Beagle	PO	39 weeks + 4-week recovery	0, 1, 3, and 10	Yes	D17-130-CD

[a] For Repeat-Dose Toxicity, the highest non-severe toxic dose (HNSTD)/maximum tolerated dose (MTD) is underlined.
Abbreviations: GD = Gestation Day; PO = oral administration; S9 = metabolic activator; NA = Not Applicable

2.5.4.1. Single dose toxicity

Single oral gavage doses of aumolertinib up to 900 mg/kg in rats and 200 mg/kg in dogs were tolerated.

Single doses ≥300 mg/kg to rats resulted in rough hair and/or decreased motor activity, and a dose of 900 mg/kg to male rats produced observations of piloerection, prostration, eyelids closed, hunched back, loose/soft stools, and/or dirty anal area.

Soft, loose, and/or bloody stool were seen in dogs at ≥20 mg/kg and emesis occurred at 200 mg/kg. The maximum tolerated single dose of aumolertinib in rats and dogs was 900 mg/kg and 200 mg/kg, respectively.

Overall, the GI tract appeared to be the major target organ of toxicity in the single-dose studies in both species. The maximum tolerated single dose of aumolertinib in rats and dogs was 900 mg/kg and

200 mg/kg, respectively. NOAELs was 100 mg/kg for rats and not possible to determine in dogs, due to clinical symptoms of diarrhoea at the lowest tested dose of 20 mg/kg.

2.5.4.2. Repeat dose toxicity

Non-pivotal studies

-Dose-range finding studies in rats by oral gavage were conducted for 5 days up to 810 mg/kg [10 mg/kg (Day 1), 30 mg/kg (Day 2), 90 mg/kg (Day 3), 270 mg/kg (Day 4), and 810 mg/kg (Day 5)] and for 4 weeks up to 300 mg/kg. In the 5-day dose escalating study, one male died after the 810 mg/kg dose. Clinical observations were seen at 810 mg/kg only and consisted of salivation, lethargy, decreased spontaneous motor activity, closed eyelid and dyspnoea. Except for lethargy and decreased spontaneous motor activity in 2 males, all clinical observations resolved by 3 hours post-dose.

The MTD was determined as 270 mg/kg in rats.

During the 4-week repeat-dose study in rats, mortality occurred at ≥ 200 mg/kg and clinical observations included nasal and ocular discharge, rough hair, emaciated, hunched back, pale, loose stool, and dirty anal area. Clinical signs in the 100 mg/kg dose group included decreased body weight gain, ocular changes (discharge, eyelid swelling and redness), altered clinical pathological parameters and rough hair. No treatment-related gross pathologic findings were noted at the end of the treatment periods.

In general, the majority of the findings seen in the 5-day study were also seen following 4 weeks of dosing.

A NOAEL = 30 mg/kg were determined and provided an exposure margin of 0.29 and 2,59-fold in male and females, respectively, due to difference in exposure levels (2-9 fold higher in females). No findings were noted at the NOAEL level. More than 90% mortality (20/22) were observed at doses of 300 mg/kg aumolertinib.

-Dose-range finding studies in dogs by oral gavage were conducted for 5 days up to 270 mg/kg and for 4 weeks up to 75 mg/kg. No deaths occurred during the 5-day study. Observations included salivation, emesis and loose stool. No aumolertinib related macroscopic findings were noted at necropsy. The MTD was set to 270 mg/kg but the NOAEL is estimated to be 15 mg/kg in male and female dogs.

During the 4 week repeat-dose study, 3 animals treated with 75 mg/kg were found dead and one was euthanized in moribund condition. Prior to death, decreased body weights, emesis, loose, soft, and/or bloody stool, reduced or lack of defecation, ulceration (oral cavity/lower lip), lethargy, prostration, quivering, and discharge (eye, nasal) were observed. For the remaining animals, observations of salivation, soft stool, skin flush, and ulceration (oral cavity) occurred at ≥ 10 mg/kg and emesis, loose stool, and ulceration (lower lip) occurred at 25 mg/kg. Treatment-related ophthalmologic changes occurred, conjunctival congestion ≥ 10 mg/kg, and abnormal cornea, miosis at 25 mg/kg. Except for findings in the eye, which generally correlate with the ophthalmologic findings, no aumolertinib-related macroscopic findings were noted at necropsy. There were no significant changes in body weight or food consumption data at ≤ 25 mg/kg, and no effects were noted in body temperature or in ECG parameters. No NOAEL could be established in the study and the lowest dose of 10 mg/kg provided an exposure margin of 5-fold.

Pivotal studies in rats

-In rats treated daily for 13-weeks with oral doses aumolertinib up to 120 mg/kg, mortality was observed at 120 mg/kg. Aumolertinib-related clinical signs occurred at ≥ 60 mg/kg providing none to

narrow exposure margins of 0.72-1.88 in males and females, respectively. Clinical signs were generally associated with effects to the GI tract and skin. These findings recovered, or where in the path to recovery after a 4-week post-dose observation period. Ophthalmoscopic findings including lens turbidity/opacity and/or corneal ulceration were noted. Decreases in body weight and body weight gain, which often correlated with decreases in food consumption, were noted for males at 120 mg/kg and for females at ≥ 60 mg/kg. Reversible changes occurred in clinical pathology parameters at 120 mg/kg and correlated with reversible histopathologic changes of inflammatory responses seen in the lung, lymph nodes, and skin and with bile duct vacuolation in the liver. Aumolertinib-related histopathologic changes in rats occurred in the liver, the lungs, mesenteric lymph nodes, skin, the mammary glands, and/or vagina at ≥60 mg/kg. Complete recovery of these microscopic findings occurred in the lungs, mesenteric lymph nodes, mammary glands, and vagina; while partial recovery was observed for the liver and skin findings. The NOAEL for aumolertinib administered to rats daily for 13 consecutive weeks was 20 mg/kg.

-In rats treated 26-week daily with oral doses aumolertinib up to 90 mg/kg, mortality was observed at 90 mg/kg. Clinical observations occurred at ≥30 mg/kg and provided no safety margins to human relevant exposure (0.35- and 0.99-fold in respectively males and females). Clinical findings were generally associated with effects to the GI tract and skin. Clinical observations recovered or were in the process of recovery after a 4-week recovery period. At 90 mg/kg, turbidity/opacity in both eyes was observed in one male and one female. There were reversible changes in clinical pathology parameters at ≥ 30 mg/kg, which correlated with reversible histopathologic changes of inflammatory responses in the lung, lymph nodes, and skin and with bile duct vacuolation in the liver. At the terminal necropsy, aumolertinib-related findings were seen in the liver, lung, mammary glands, skin, and vagina. Bile duct vacuolation was seen in most males and a few females receiving 90 mg/kg; interstitial inflammatory cell infiltration in lung at ≥ 30 mg/kg, atrophy of mammary glands in males ≥ 30 mg/kg; folliculitis accompanied in most cases by disruption of the growth pattern of the hair follicles at 90 mg/kg; and mucification of the vaginal epithelium at ≥ 30 mg/kg. The NOAEL was 10 mg/kg. Mortality was higher among female animals (3/15 F 120 mg/kg in 13-week rat, 7/15 F in 90 mg/kg in 26-weeks).

An increased incidence of changes in epididymis and testes was noted in the high dose group (90 mg/kg) but not at lower doses (10 and 30 mg/kg) in the histopathological evaluations of the individual animals in the 26-week rat study. Similar changes but less frequent and less severe was noted in the control group. An increased incidence of inflammatory cell infiltrations in the epididymides at the high dose following terminal (90%) and recovery (100%) necropsies was observed, at markedly increased levels compared to controls (50% and 40%, respectively).

Mammary gland atrophy was seen in male rats from doses of 60 mg/kg in the 13-week study and 30 mg/kg in the 26-week study (safety margin 0.35-0.72-fold).

Pivotal studies in dogs

-In dogs treated 13-week daily with oral doses aumolertinib up to 25 mg/kg, lesions in the skin, mouth mucosa and GI tract were seen at ≥ 4 mg/kg. Two animals at the high dose group were euthanized because of the severity of ulceration in the oral mucosa and skin. Clinical observations noted during the dosing period resolved or were partially recovered during the 4-week recovery period. Ophthalmologic changes occurred in dogs at ≥ 10 mg/kg with no correlative microscopic findings, except for conjunctival congestion in a single 10 mg/kg female. These findings were reversible. Reversible increases in TCH occurred in dogs at ≥ 4 mg/kg and reversible decreases in ALB and A/G were seen at ≥10 mg/kg. There were no correlative microscopic findings for these transient clinical chemistry changes. Aumolertinib-related histopathologic changes occurred in the tongue, skin, oral cavity, and thymus. The histopathological changes were reversible after cessation of dosing. A NOAEL

was not defined for the study and the lowest dose of 4 mg/kg provided an exposure margin of 1.48-fold. The 25 mg/kg dose produced lethality (2/10 dogs). The HNSTD or MTD in dogs administered aumolertinib for 13 consecutive weeks was 10 mg/kg.

-In dogs treated 39-week daily with oral doses aumolertinib up to 10 mg/kg, no mortality was observed. Clinical signs included flushing of gums and emaciation, as well as lesions in the skin and mouth mucosa and GI tract were seen in animals at ≥ 3 mg/kg. Opaque right lens was seen in 1 animal at 10 mg/kg group. Histopathological findings of ulcers and mucosal atrophy or proliferation were seen at 10 mg/kg. The MTD for aumolertinib administered to dogs daily for 39 consecutive weeks was 10 mg/kg and the NOAEL was 3 mg/kg, providing an exposure margin of 1.75-fold. The 39 week dog study was not considered GLP compliant but the observed effects were not different from those of the 13-weeks study in dogs nor in the rat studies and the chronic dosing regimen in animals follows the clinical drug administration schedule.

General organs of toxicity

Thus, target organs identified in the repeated dose toxicology studies were the GI tract, skin, oral mucosa, eyes, liver, and lung. Findings in these organs are monitorable in clinical studies.

Gastrointestinal System

In the rat, drug-related GI toxicity, as evidenced by saliva secretion, soft, loose, or bloody stools, and a dirty or soiled anal area, was observed when aumolertinib was administered ≥ 60 mg/kg. Similarly, in the dogs, drug-related GI toxicities included vomiting, excessive salivation, soft stools, loose stools, blood in the stools, other stool abnormalities, and/or decreased bowel movements. The GI symptoms of all treatment groups gradually recovered during the post dose observation period.

Skin

In the 26-week rat study at a dose of 90 mg/kg, microscopic findings of folliculitis, skin granuloma, and disruption of follicular growth pattern were observed in approximately half of the animals. After 4-weeks recovery, these observations were partially recovered in females and fully recovered in males.

In the 39-week dog study, aumolertinib-related histopathological changes at ≥ 10 mg/kg, included of folliculitis, dermal/subcutaneous inflammation, epidermal ulceration of the foot pad, and abscesses. Other skin related observations (e.g. sparse hair) were seen at ≥ 60 mg/kg in rats and ≥ 4 mg/kg in dogs. After a 4-week post dose observation period, all skin related findings recovered.

Mouth

In the 13-week rat study, ulceration around the mouth was observed at the high dose of 120 mg/kg.

In the 13-week dog study, 2 of 10 animals administered 25 mg/kg/were euthanized due to aumolertinib-related ulceration in the oral mucosa and skin. These findings were associated with oral cavity rupture, erosion, ulceration, and inflammation. Ulceration and erosion of the tongue occurred in dogs that received 25 mg/kg, and was associated with inflammatory cell infiltrates in the epithelium and submucosa of the tongue. These findings were partially reversed after the 4-week reversal phase.

In the 39-week study, pink oral mucosa, flushing of inner walls of oral cavity and gums, and swelling of gums was associated with histopathological observations of ulcers and mucosal atrophy or proliferation. Flushing of the gums was also observed at 3 mg/kg. After the 4-week post dose observation period, 1/4 animals in the 10 mg/kg group had subacute inflammation and mucosal hyperplasia under the oral mucosa. The dog was the most sensitive species for oral findings.

Ocular

Ocular findings were present in the dog studies, and in the 13-week study in rats. In the dog studies, conjunctival congestion was seen at all doses, and corneal and lens opacity, reflective media turbidity and photophobia were observed at 25 mg/kg. In the 39-week dog study one animal in the 10 mg/kg group had opacity of the right vitreous body at the end of the study.

In rats ophthalmoscopic findings were noted at 120 mg/kg in 2 males (lens turbidity/lens reflective media turbidity) and 1 female (abnormal pupil). A second 120 mg/kg female had multiple eye lesions during treatment that were not reversible, and an irregular agglomerate in the lens was noted for a 120 mg/kg female at the recovery examination only In rats, findings were consistent with lens turbidity/opacity and/or corneal ulceration whereas conjunctival hyperaemia, photophobia, lacrimation, myosis, corneal oedema, and opacity of the reflective media were noted in dogs. Safety margins to human clinical exposure were 1.27- and 3.5-fold in male and female rats, respectively, and 6.67-fold in dogs.

Hepatic

In the 13- and 26-week toxicity studies in rats, ALT, AST, ALP, GGT, TBil, and/or blood urea nitrogen were elevated, and the total protein, ALB, and triglycerides were decreased at 60 mg/kg.

Bile duct vacuolation of the liver was associated with the increases in ALT, AST, ALP, TBil, and GGT. There was a dose related increase in the incidence and severity of bile duct vacuolation at ≥ 60 mg/kg group, which was partially recovered after a 4-week post dose observation period. There were no hepatic findings in the dog in doses up to 10 mg/kg administered for 39 weeks.

Pulmonary System

In the 13- and 26-week studies in rats, a dose related increase in the accumulation of foamy macrophages in the lung alveolar cavities was observed microscopically at ≥ 30 mg/kg. Increases in WBC, absolute lymphocyte and neutrophil counts were observed and are considered as related to inflammatory reactions in the lungs. All lung findings were reversed after a 4-week post dose observation period. There were no lung findings in the dog in doses up to 10 mg/kg administered for 39 weeks.

2.5.4.3. Genotoxicity

Table 9 Genotoxicity tabular summary

Type of test (study ID) GLP	Test system (strain)	Concentration/ Dose	Results
In vitro			
Gene mutations in bacteria (Ames test) (Study O14-S145-AM) **GLP**	*S.typhimurium* (TA97a, TA98, TA100, TA102, and TA1535)	12.8, 32, 80, 200, and 800 µg/plate Precipitation at 800 µg/plate. Cytotoxicity for TA97a, TA98, TA100, and TA1535, with and without metabolic activation at ≥ 200 µg/plate.	Negative
Chromosomal Aberration Study (Study O14-S145-CA) **GLP**	Chinese Hamster Lung Fibroblast	2.4, 6, or 15 µg/mL for 4 h 0.96, 2.4, or 6 µg/mL for 24 h	Negative

In vivo			
Micronucleus test (Study M14-S145-MN) **GLP**	ICR mice	single oral gavage doses 100, 300, or 1000 mg/kg Evidence of exposure was noted by the incidence of wet hair, rough hair, and/or lethargy at 1000 mg/kg aumolertinib. One of the 1000 mg/kg females was found dead on Day 2.	Negative

2.5.4.4. Carcinogenicity

As this application is for the use of aumolertinib for the treatment of patients with advanced NSCLC, in accordance with ICH S9, no carcinogenicity studies have been conducted.

2.5.4.5. Reproductive and developmental toxicity

Potential aumolertinib-related effects on fertility and early embryonic development were evaluated in rats dosed orally by gavage at doses ranging from 10 to 100 mg/kg/day. No effect on male fertility was observed at any dose level, whereas the NOAEL for female fertility and early embryonic development was set at 30 mg/kg/day due to treatment-related decrease of the number of corpora lutea, and increase of post implantation loss, respectively, at 100 mg/kg/day.

Fertility indices appeared low in all groups (72%, 76%, 52%, 84% at 0, 10, 30, 100 mg/kg/day, respectively), but were within the historical control range of 72-100%. The decrease at the mid dose level was considered unrelated to treatment in view of the results in other groups and absence of effects on reproductive organs, sperm parameters and oestrous cycles. An increased post implantation loss was observed in the fertility study. A treatment-related effect on gametes and/or early embryos in the fertility study was hypothesized as the underlying cause. Taking into account the toxicokinetic data obtained in 13- and 26-week rat studies over the 10-120 mg/kg dose range, it is estimated that exposure levels (AUC) at the NOAELs determined in male and female animals are within the clinical AUC levels.

Embryo-foetal development toxicity studies were conducted in rats and rabbits dosed orally by gavage at doses ranging from 10 to 100 mg/kg/day and 5 to 30 mg/kg/day [which corresponded to exposure levels ranging from 0.6- to 4.1-fold (rat) and 0.1- to 0.5-fold (rabbit) those reached in patients at the maximum recommended dose], respectively. In rats, aumolertinib was shown to be devoid of embryo-foetal toxicity up to the high maternotoxic dose level.

In rabbits, maternal toxicity was noted at all dose levels with dose-dependent increase in incidence and earlier onset of mortality and abortions at ≥15 mg/kg. This resulted in limited numbers of dams and litters subjected to ovarian/uterine and foetal examinations, respectively, at 30 mg/kg. At caesarean section, embryo lethality was observed at 30 mg/kg as shown by increases in early resorptions and post implantation loss, resulting in a decrease in number of live foetuses. In addition, the number of dead foetuses was increased in all treated groups compared to the concurrent control group and historical controls. Regarding foetal examinations, there were treatment-related effects on sternal development, i.e. decreases in ossification rate at all doses and in sternum (likely sternebrae) number at ≥15 mg/kg. An increased incidence of bipartite sternum was also observed at ≥15 mg/kg. At visceral examination, a dose-related increase in abnormality of artery arborisation was observed.

2.5.4.6. Local Tolerance

Since the oral route has been used for the repeat dose toxicology studies and this is the intended clinical route of administration, no local tolerance studies have been conducted.

2.5.4.7. Other toxicity studies

Phototoxicity

Table 10 Phototoxicity study tabular summary

In vitro Neutral Red Uptake assay/ BALB/c 3T3 mouse fibroblasts (Study 19006NG01)		
Preliminary test	Concentration: 7.81 µg/mL to 750 µg/mL ± light	Cytotoxicity was observed at 15.62 µg/mL
Definitive test. -DMSO: negative control -Chlorphenazine hydrochloride (CPZ) positive control	Concentration : 0.49 µg/mL to 62.5 µg/mL	In the two tests, the **IC50 (-UV):** -Assay 1: 12.336 µg/mL -Assay 2: 7.977 µg/mL **IC50 (+UV):** -Assay 1: 11.810 µg/mL -Assay 2:9.072 µg/mL **Photo irritation factor (PIF):**0.882 **Mean photo irritation (MPE)**: -0.02. Therefore, as the PIF value was less < 2 and MPE value was < 0.1, aumolertinib is not expected to be phototoxic.

Impurities:

An in-silico assessment of the mutagenic potential of aumolertinib impurities was conducted. Based on these results a follow-up study, was run.

The mutagenic potential of two impurities was evaluated using S. typhimurium strains TA97a, TA98, TA100, TA102, and TA1535. The impurities were not mutagenic.

2.5.5. Ecotoxicity/environmental risk assessment

Table 11 Summary of main study results

Substance (INN): Aumolertinib			
CAS-number (if available): 1899921-05-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	3.88 at pH7	Potential PBT: N
PBT-assessment : NA			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence)	0.0065 µg/L.	µg/L	> 0.01 threshold: no

The lack of solubility above pH 8.8 makes the measurement of logDow for the neutral molecule utilizing OECD 107 and/or OECD 123 challenging and inaccurate. So, the applicant provided predicted logPow/logD values over the three ionic states of the molecule. However, an OECD 107 Experimental

Determination of logDow for aumolertinib was also conducted, showing an ion-corrected logDow at pH 7.0 of 3.88. So, as logDow was less than the trigger limit, a PBT assessment was not necessary.

Concerning the PECsw, the prevalence-based Fpen refinement taking into account the population of NSCLC patients with EGFR mutations (worst case scenario in Europe) is acceptable. As aumolertinib PECsw value is below the action limit of 0.01 µg/L, Phase II testing is therefore not required in agreement with the guidelines.

2.5.6. Discussion on non-clinical aspects

Aumolertinib is a selective, irreversible EGFR TKI.

Overall, primary pharmacodynamic studies provided evidence that aumolertinib can inhibit EGFR - resistant mutant kinases and EGFR-activating mutations, with less inhibitory activity toward WT EGFR. Selectivity and limited potential for off-target adverse effects was stated based on an in vitro kinase assay. In vivo studies using murine xenograft tumour models showed aumolertinib efficacy against several tumour cell lines. The justification for the absence of provision of secondary pharmacodynamics data (other non-kinase receptors, enzymes, ion channels) is considered acceptable.

Non-clinical in vitro and in vivo safety pharmacology studies did not show any concern. The results of the hERG assay indicate minimal clinical cardiovascular risk under the conditions of this assay. However, none of the assays were GLP compliant. As cardiac effects were reported in humans, non-clinical results are less relevant and repetition of the hERG studies to GLP were considered not meaningful, and a statement that non-clinical data indicate that aumolertinib and its metabolite (HAS-719) inhibit the h-ERG channel, and QTc prolonging effects cannot be excluded was included in section 5.3 of the SmPC. The pharmacokinetics of aumolertinib were assessed in in-vitro studies, single-dose PK studies after oral and IV administration and in repeat-dose toxicity studies in rats and dogs. This is appropriate as the clinical route of administration is oral.

Milk transfer was not investigated for aumolertinib or HAS-719, a related warning was included in section 4.6 of the SmPC.

Based on in vitro data aumolertinib is not a CYP450 direct inhibitor. However, a time-dependent inhibition (TDI) study indicates that the IC50 values are 19.9 µM and 15 µM when midazolam and testosterone are used as substrates for CYP3A4, respectively. This suggests the possibility of a TDI effect of aumolertinib on CYP3A4 substrates at the intestinal level since these IC50 values are lower than the worst-case intestinal concentration estimated i.e., 83.6µM.

Based on in vitro data aumolertinib induced CYP3A4 mRNA expression by over 2-fold across the concentration ranges studied in all donors. A clinical DDI study with a CYP3A4 probe substrate was conducted to investigate the magnitude of the TDI or induction effect of aumolertinib that is discussed in the clinical section below. Furthermore, aumolertinib also caused a more than 2-fold increase in CYP1A2 mRNA in all three donors. In three in vitro studies assessing aumolertinib potential to induce CYP1A2 in human hepatocytes, including mechanistic modelling (Emax, EC50, RIS) per ICH M12 were provided (data not shown). While a modest ≈2-fold mRNA increase was observed in only one of three donors at concentrations > 100-fold above the Cmax,u (≈ 0.007 µM), the response was not clinically meaningful, as the calculated induction risk index (R = 0.752) falls below the regulatory threshold of 0.8, indicating a negligible risk of CYP1A2 induction in patients.

Aumolertinib inhibited the efflux transporters P-gp and BCRP and MATE1 an IC50 of 0.33, 4.94 and 0.098µM, respectively. These IC50 values are lower than the estimated intestinal concentration (i.e. 83.6µM). Hence, the potential of aumolertinib to inhibit P-gp and BCRP and MATE1 cannot be ruled out.

Aumolertinib was found to be an inhibitor of UGT1A1 and UGT2B7 *in vitro*. Considering the steady-state C_{max} concentrations after 110 mg daily dose, this is not likely to be clinically relevant. Intestinal interactions cannot be ruled out, however, the clinical impact is unknown.

Aumolertinib inhibited the uptake transporters OATP1B1, OAT1, OCT2 with IC50 values of 26.0 µM, 97.9 µM, 26.2 µM. Since, these IC50 values are higher than the worst estimated systemic concentration (i.e. 0.33µM) or hepatocytes concentrations or at the portal vein (i.e. 3.39 µM) in vivo inhibition of OATP1B1, OAT1, OCT2 by aumolertinib can be ruled out. Aumolertinib did not inhibit OATP1B3, OAT3, or MATE2-K (IC50 > 100 µM).

It is not known whether aumolertinib is an inhibitor of BSEP and OCT1. It is also not known whether the active metabolite HAS-719 is an inhibitor of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, MATE1 or MATE2-K.

Aumolertinib undergoes a metabolism through one main enzyme CYP3A4 leading to one main metabolite, HAS-719. This major circulating metabolite represents more than 10% of total drug-related exposure at steady-state in humans (37.4%). Other minor pathways involved CYP3A5, CYP1A2 and CYP2A6, in a lesser extent.

In vitro studies have shown that aumolertinib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and MATE2-K, nor did inhibit OATP1B3, OAT3, MATE2K, or bile salt export pump (BSEP). Aumolertinib is a weak inhibitor of organic anion transporting polypeptide (OATP)1B1, organic anion transporter (OAT)1, and OCT2 *in vitro*. Considering the unbound human Cmax-values for aumolertinib and HAS-719 (0.003 and 0.001 µM) and the reported data on CYP inhibition, no significant drug interactions are expected in vivo through inhibitory action of aumolertinib/HAS-719 on CYP enzymes.

In vitro assays investigating the potential for aumolertinib to be a substrate of P-gp and BCRP in MDR1-MDCKII and BCRP-MDCKII cells were performed (data not shown). It was concluded that aumolertinib is a P-gp and BCRP substrate (study No EQR-R2047) which has been reflected in section 5.2 of the SmPC.

According to the ICH M12 guideline, the decision on whether the sponsor should conduct a clinical drug-drug interaction (DDI) study with an inhibitor or inducer of an enzyme or a transporter depends on various factors. These factors include the estimated fraction of formation or elimination of a metabolite mediated by an enzyme or transporter, the contribution of the metabolite to the clinical effect, the exposure-response relationship of the metabolite if known, and the potential impact of concurrent medications that affect the enzyme or transporter. Consequently, a clinical DDI study with inhibitors of BCRP and P-gp transporters is recommended to fully characterize the interaction potential **(REC)**. In the absence of clinical data, the following statement was included in the SmPC:

Based on in vitro data, aumolertinib is a substrate of P-glycoprotein (P-gp) and breast-cancer resistance protein (BCRP). Concomitant administration of aumolertinib with medicinal products that are inhibitors of these transporter proteins should be avoided, as it may result in increased aumolertinib plasma concentration. If co-administration with such inhibitors is unavoidable, clinical monitoring is recommended.

The toxicity of aumolertinib was evaluated in single and repeated-dose toxicology studies in rats and dogs. Overall, target organs identified were the GI tract, skin, oral mucosa, eyes, liver, and lung. The clinical studies monitored these organs and further confirmed this non-clinical toxicity profile (see discussion on clinical safety).

The determined NOAELs from the pivotal rat studies were found acceptable but do not provide safety margins to clinically relevant exposure (0.14-0.25 in males and 0.35-0.0.51). Observed toxic effects were therefore seen at clinically relevant doses or with a very narrow safety margin and appeared to

be pharmacologically driven to a large degree. The severity of toxicity was dose-dependent and reduction in NOAEL was noted with prolongation of the treatment duration. Overall, organs of toxicity in the rat included GI, skin, liver, lung, mammary gland, vagina and less commonly the eyes. Mortality was very high among female rats in the pivotal repeat-dose studies, which corelated with a significantly higher exposure in female animals. This was also reflected in a difference in severity of clinical and histopathological findings between the two sexes, and it appeared that female rats generally showed an increased incidence and/or severity of liver, lung and skin changes compared to male animals receiving the same dose of aumolertinib. GI changes, on the other hand, appeared with more similar incidence between the two sexes. This sex-related difference in rats was likely driven by a species-specific difference in the expression of sex-selective CYP isoforms used in the metabolism of aumolertinib in rats.

An increased incidence of inflammatory cell infiltrations in the epididymides at the high dose following terminal and recovery necropsies was observed, at markedly increased levels compared to controls, and even compared to the wide historical range (0-80%). The occurrence and type of inflammatory epididymis findings were further discussed but no clear treatment-related effect was seen across studies or species (data not shown). It is accepted that no clear treatment-related effect exists and that the clinical relevance therefore is considered limited. Mammary gland atrophy was seen in male rats. As the findings were observed at clinically relevant doses, considered related to aumolertinib treatment and the clinical significance is unknown, this finding was included in section 5.3 of the SmPC.

GI toxicity is a class-related toxicity associated with inhibition of the wild-type EGFR receptor in the gut. In the rat, drug-related GI toxicity, as evidenced by saliva secretion, soft, loose, or bloody stools, and a dirty or soiled anal area, was observed when aumolertinib was administered ≥ 60 mg/kg. However, in rats a high occurrence of intestinal parasites was noted by histopathology and a potential effect on background findings and/or exacerbation of GI symptoms cannot be excluded. In the dogs, drug-related GI toxicities included vomiting, excessive salivation, soft stools, loose stools, blood in the stools, other stool abnormalities, and/or decreased bowel movements. The GI symptoms of all treatment groups gradually recovered during the post dose observation period.

The skin is also a target organ of toxicity for EGFR based on the presence of wild type EGFR receptors.

Effects in the mouths were observed in the 2 species. The dog was the most sensitive species for oral findings.

Ocular findings of different severity were noted across species (i.e. in the dog studies, and in the 13-week study in rats) in both non-pivotal and pivotal repeat-dose studies at clinically relevant exposures. In rats, findings were consistent with lens turbidity/opacity and/or corneal ulceration whereas conjunctival hyperaemia, photophobia, lacrimation, myosis, corneal oedema, and opacity of the reflective media were noted in dogs. Safety margins to human clinical exposure were 1.27- and 3.5-fold in male and female rats, respectively, and 6.67-fold in dogs. As ocular findings have been seen with other EGFR tyrosine kinase inhibitors (TKIs), the ocular effects are considered to be a class effect consistent with inhibition of wild type EGFR in the eye. The findings were mostly reversible. Ocular adverse events (AEs) have also been observed in patients treated with aumolertinib. Ocular events have been included in the list of adverse events of clinical interest (AECI) and reflected in section 4.8 of the SmPC. The non-clinical findings of ocular toxicity are considered sufficiently covered in the clinical part of the SmPC.

Hepatic effects were reported in the 13- and 26-week toxicity studies in rats. There were no hepatic findings in the dog in doses up to 10 mg/kg administered for 39 weeks.

It should be noted that, based on plasma exposure levels at NOAEL and expected human exposure levels at intended therapeutic dose, there are no safety margins regardless of the tested species.

Aumolertinib is considered devoid of genotoxic potential, based on negative results in a standard battery of in vitro and in vivo genotoxicity studies.

As this application is for the use of aumolertinib for the treatment of patients with advanced NSCLC, no carcinogenicity studies have been conducted. The lack of carcinogenicity studies is considered acceptable in accordance with ICH S9.

Developmental and reproductive toxicity studies were conducted to investigate the potential effects of aumolertinib on fertility and early embryonic development in rats, and on embryo-foetal development in rats and rabbits. This is acceptable as per ICH S9. Although no effects were detected on male fertility, female fertility was affected at the high dose level and there is overall no safety margin.

EGFR deficiency in mice can cause death at various developmental stages according to the genetic background, including peri-implantation death (Threadgill et al., 1995). In addition, it was shown that mice lacking EGFR expression are severely sub fertile with pregnancy demise occurring shortly after blastocyst implantation due to defects in decidualization including decreased proliferation, cell survival, differentiation and target gene expression (Large et al., 2014). Therefore, increase in post implantation loss reported in the fertility study might have occurred as a result of an interference with endometrial function, which would also be in line with the decrease in implantation sites. The fact that female fertility may be impaired was reflected in section 4.6 and 5.3 of the SmPC.

There was no adverse developmental finding in rats observed in embryofoetal development studies whereas marked maternal toxicity, embryo-foetal lethality, effects on sternal development and visceral findings were observed in rabbits resulting in no developmental NOAEL.

Examination of foetuses showed decreases in ossification rate at all doses and in sternum (likely sternebrae) number at ≥15 mg/kg. An increased incidence of bipartite sternum was also observed at ≥15 mg/kg. According to the applicant, this was likely related to a delayed development of the sternum with decreased sternal ossification and number of sternebrae. This is in line with DeSesso and Scialli [8] who report that in rodents "if ossification is slightly delayed, the right and left ossification centres may appear as two sites (sometimes called bipartite sternebrae)". At visceral examination, a dose-related increase in abnormality of artery arborisation was observed. The findings reported by the applicant correspond to mispositioned carotid origin (from aortic arch or innominate artery) and absent innominate artery. Although they are not considered as visceral malformations, they could be viewed as anomalies. Therefore, these findings were reported in section 5.3 of the SmPC.

Finally, at the high dose levels investigated in embryo-development toxicity studies, the animal exposure were <4-fold (rat) and <1-fold (rabbit) the aumolertinib exposure achieved in patients at the maximum recommended dose, and <1-fold for the main human metabolite HAS-719. Therefore, a safety margin for embryo-foetal development could not be determined in any species regardless of the developmental NOAEL.

Based on in vitro data, aumolertinib is not expected to present phototoxic potential.

Aumolertinib $PEC_{surfacewater}$ value is below the action limit of 0.01 μg/L and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, aumolertinib is not expected to pose a risk to the environment.

[8] DeSesso JM, Scialli AR. Bone development in laboratory mammals used in developmental toxicity studies. Birth Defects Res. 2018;110(15):1157-1187.

2.5.7. Conclusion on the non-clinical aspects

Overall, the Applicant performed an adequate package of in vitro and in vivo non-clinical studies with aumolertinib. Primary in vitro and in vivo pharmacodynamic studies provided adequate evidence that aumolertinib presents inhibitory activity and selectivity towards EGFR resistant mutant kinases with less potent inhibition of WT EGFR. This is in accordance with the indication of treatment of patients with non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations and EGFR T790M mutation-positive NSCLC.

From the pharmacokinetic point of view, the package was considered adequate.

Overall, the toxicology programme revealed that target organs identified in the repeated dose toxicology studies were the GI tract, liver, lung, skin, oral mucosa, and eyes. Findings in these organs are monitorable in clinical studies. There are no safety margins at NOAELs regardless the tested species.

It is noted that the conducted hERG studies and the 39-week repeat-dose dog study were not GLP compliant but as effects were already observed in clinical studies or not different from other toxicological studies, no inspection nor repetition of those studies is requested.

Aumolertinib is not expected to pose a risk to the environment in the recommended conditions of use.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 12 Tabular overview of clinical studies

Study Identifier	Study Objectives (Primary and Secondary)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase 1 Studies						
HS-10296-102	• To evaluate the effect of food on the PK of aumolertinib and its metabolite, HAS-719 • Secondary: to evaluate the safety and tolerability of aumolertinib	Single center, open-label, randomized, double period, crossover	Aumolertinib 110 mg QD; PO	20	Healthy subjects	Sequence AB: D1 aumolertinib (fasted); D22 aumolertinib (fed) Sequence BA: D1 aumolertinib (fed); D22 aumolertinib (fasted)
EQ143-101	• To compare the PK of a single oral dose of aumolertinib • Secondary: to evaluate the safety and tolerability of a single oral dose of aumolertinib	Open-label, uncontrolled study	Aumolertinib 110 mg QD; PO	45	Healthy Caucasian, Black or African American, Hispanic or Latino, and ethnic Chinese subjects	Single dose
HS-10296-106	• To evaluate the effects of mild and moderate hepatic impairment on the PK of aumolertinib and its metabolite, HAS-719 • Secondary: To evaluate the safety of aumolertinib	Multicenter, open-label, uncontrolled, parallel administration	Aumolertinib 110 mg QD; PO	24	Patients with mild and moderate hepatic impairment and matched healthy subjects	Single dose

Study Identifier	Study Objectives (Primary and Secondary)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
HS-10296-107	• To evaluate the impact of aumolertinib (P-gp inhibitor) on the main PK of fexofenadine (P-gp substrate) • Secondary: To evaluate the safety and tolerability of aumolertinib and fexofenadine	Open-label, 2-period, 2-sequence, crossover	Aumolertinib 110 mg QD; PO Fexofenadine 120 mg QD; PO	12	Healthy subjects	Sequence AB: D1 fexofenadine (only); D22 fexofenadine + aumolertinib Sequence BA: D1 fexofenadine + aumolertinib; D22 fexofenadine (only)
HS-10296-105	• To evaluate PK of the total radioactivity of [^{14}C]-aumolertinib; to analyse quantitatively the total radioactivity [^{14}C]-aumolertinib in the excreta, and to obtain the material balance data and main excretion pathways • Secondary objective: To analyse quantitatively the concentration of aumolertinib in plasma using the validated LC/MS method and obtain PK parameters of aumolertinib in plasma; to observe the safety of [^{14}C]-aumolertinib	Single-center, single-dose, open-label	110 mg/50 μCi of [^{14}C]-aumolertinib QD; PO	4	Healthy Chinese adult male subjects	Single dose

Study Identifier	Study Objectives (Primary and Secondary)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
HS-10296-103	• To evaluate the effects of an oral potent inhibitor of CYP3A4 (itraconazole) on the PK of aumolertinib and its metabolite, HAS-719 • Secondary: to evaluate the safety and tolerability of aumolertinib	Single-center, open-label, double-period, single-sequence, crossover	Aumolertinib 110 mg QD; PO Itraconazole 200 mg BID; PO	32	Healthy subjects	Period 1, D1: aumolertinib (only); WO, D19-21: itraconazole (only); Period 2, D22: aumolertinib + itraconazole; D23-30: itraconazole (only)
HS-10296-104	• To evaluate the effect of a potent oral inhibitor of CYP3A4 (rifampicin) on the PK of aumolertinib and its metabolite, HAS-719 • Secondary: to evaluate the safety and tolerability of aumolertinib	Single-center, open-label, double-period, single-sequence, crossover	Aumolertinib 110 mg QD; PO Rifampicin 600 mg QID; PO	32	Healthy subjects	Period 1, D1: aumolertinib (only); WO, D16-21 rifampicin (only); Period 2, D22 aumolertinib + rifampicin; D23-30 rifampicin (only)

Study Identifier	Study Objectives (Primary and Secondary)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
EQ143-102	• To assess the effect of hepatic impairment on the PK of aumolertinib and HAS-719 • Secondary: To assess the safety and tolerability of aumolertinib in severely hepatically impaired participants and in matched healthy adults.	Open-label, single-dose, parallel-group, multicenter study	Aumolertinib 55 mg; PO	12	Severely hepatically impaired adults and matched healthy subjects	Single dose
HS-10296-108	• To Evaluate the Pharmacokinetics, Safety, and Tolerability of Aumolertinib in European Participants with Locally Advanced or Metastatic, EGFR-mutated Non-Small Cell Lung Cancer • Secondary: to evaluate the safety and tolerability of aumolertinib	Open-label, multicenter, multiple-dose study	Aumolertinib 110 mg QD; PO	19	Patients with locally advanced or metastatic NSCLC with EGFR sensitive mutations	Part A: 23 days; Part B: Continuous 21-day treatment cycles until pre-defined discontinuation criteria
HS-10296-109	• To evaluate the effect of multiple doses of aumolertinib on the pharmacokinetics of midazolam and 1-hydroxymidazolam in patients with NSCLC. • Secondary: To evaluate the pharmacokinetic profiles of aumolertinib, HAS- 719 and other major metabolites (if applicable) following multiple doses of aumolertinib. • Secondary: To evaluate the safety and tolerability of aumolertinib and midazolam in patients with NSCLC.	Open-label, fixed-sequence study	Aumolertinib 110 mg QD PO Midazolam hydrochloride syrup 2 mg; PO	20	Patients with locally advanced or metastatic NSCLC with EGFR sensitive mutations	25 days (including 2-day run-in period with midazolam administered on the first day)

Study Identifier	Study Objectives (Primary and Secondary)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase 1/2 Uncontrolled Study						
HS-10296-12-01	• To evaluate the safety, tolerability, and efficacy of aumolertinib • Secondary: o To explore the DLT, MTD, and RP2D after treatment with aumolertinib o To evaluate the PK of aumolertinib and its metabolite, HAS-719 after single-dose and multiple-doses of aumolertinib o To evaluate ORR, DCR, PFS, and DoR of aumolertinib (Parts 1 and 2) • To evaluate ORR, DCR, PFS, DoR, DepOR, and OS of aumolertinib (Part 3)	Open-label, multicenter	Aumolertinib Part 1: 55, 110, 220, and 260 mg QD; PO Part 2: 55, 110, and 220 mg QD; PO Part 3: 110 mg QD; PO	364 Total Part 1: 26 Part 2: 94 Part 3: 244	Patients with locally advanced or metastatic NSCLC for whom EGFR TKIs treatments have failed	Continuous basis, 21-day treatment cycles until disease progression
Phase 3 Controlled Study						
HS-10296-03-01	• To compare the PFS of aumolertinib vs gefitinib as 1st-line treatment • Secondary: o to compare OS, ORR, DoR, DCR, and DepOR (Depth of response) of aumolertinib vs gefitinib as 1st-line treatment o To compare the safety of aumolertinib and gefitinib	Randomized, Controlled, Double-blind, Multicenter	Aumolertinib 110 mg QD PO Gefitinib 250 mg QD; PO	429 Patients	Patients with locally advanced or metastatic NSCLC with EGFR sensitive mutations	Continuous basis, 21-day treatment cycles until disease progression

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Aumolertinib is a new chemical entity, and the pharmacokinetic studies should thus aim at describing the ADME characteristics and also to identify subgroups where an altered exposure can be expected based on the pharmacokinetic properties. Potential interactions should also be evaluated.

Aumolertinib is also known as N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide methanesulfonate. It is a highly soluble drug. Aumolertinib is a third-generation, irreversible, small-molecule TKI of EGFR that blocks the activity of mutant EGFR. It will be intended to treat some classes of NSCLC. The proposed posology is 110 mg (2 tablets of 55 mg) taken orally once a day.

To support this marketing application, the pharmacokinetics of aumolertinib and its metabolite, HAS-719, is investigated in 12 clinical studies, including 4 for DDI evaluation. In addition, 23 *in vitro* studies were also performed. All pharmacokinetic studies were conducted according to GCP. A population PK analysis and simulation are presented.

The qualitative and quantitative composition of the formulation used in first-in-man and all subsequent clinical studies have changed during development, with different non-homothetic tablets used, particularly in the study in NSCLC patients. This is discussed in the BE section below.

Methods

Quantification of aumolertinib and HAS-719

LC-MS/MS was used to measure plasma concentrations of aumolertinib and HAS-719. Five sites, 3 in China and 2 in the US were used for these analyses.

Several validated LC-MS/MS methods were used for quantification of aumolertinib and the metabolite HAS-719 using protein precipitation for sample preparation. Both analytes were measured simultaneously. Stable isotope labelled internal standards were applied for quantification of aumolertinib and HAS-719. The analytical ranges varied across the different methods but all methods were fully validated. A method for quantification fexofenadine was also validated.

Since 2 laboratories were used to generate data for the same study, HS-10296-12-01, a cross-validation study was also performed. Q2 Solutions prepared a total of 36 QC samples and aliquots were analysed in each laboratory. Q2 Solutions compared the results from each laboratory. All 36 results from each laboratory agreed within the pre-defined acceptance criteria for both analytes.

For Study EQ143-101, the Frontage Labs method validation proceeded normally as planned with all results meeting pre-defined acceptance criteria (2230R11353). The accompanying method was BTM-3245-R0. However, during study samples analysis, interference with HAS-719 was observed. The method was re-developed to mitigate the interference by modifying HPLC column and gradient in the original method. A partial validation on the modified method was then performed and met the pre-defined criteria (2230-R11353A2). The revised method BTM-3245-R1 was used for all sample analyses for this study.

Reports for analysis of radioactivity in plasma, and analysis for metabolites and radioactivity in plasma, urine and faeces were also provided.

Validations

Q2 Solutions (161171VSLJB_JSC_R1): This full validation included calibration ranges, 20-fold dilution, intra- and inter assay accuracy and precision, sample reinjection, sample stability (processed samples, bench-top, freeze/thaw, long term storage, whole blood at room temperature and on ice), carry-over, selectivity and matrix effect. Effect of haemolytic or lipemic plasma was not investigated. In this method LTS was determined to 822 days at -20 or -70 °C for both analytes.

Frontage Labs (2230-R11353): This full validation also included evaluation of haemolysed samples and lipemic samples. Dilution 10-fold was tested. LTS was determined to 105 days stored at -20 °C and for 237 days stored at -70 °C for both analytes.

Teddy Labs (DL-17011): This full validation investigated dilution 20-fold and documented LTS for 94 days for both analytes when stored at -20 or -70 °C.

WuXi AppTec (RTC01255): A full validation was performed in support of the human mass-balance study. Dilution 5-fold were tested. The internal standard solutions were stable for 21 hours at room temperature. LTS indicated that plasma samples can be stored for approximately 5 months when stored at -20 or -80 °C. In this validation aumolertinib at Upper limit of quantification (ULOQ) (2500 ng/mL) was shown to interfere with HAS-719 and accounted for 18.29% of the HAS-719 Lower limit of quantification (LLOQ).

Pharmacokinetic data analysis

Plasma concentrations of aumolertinib and HAS-719 were determined in Studies: 12-01, 101, 102, 103, 104, 105 and 106. Fexofenadine was measured in Study 107.

Non-compartmental methods and population pharmacokinetic analysis were used to evaluate the pharmacokinetics.

Population pharmacokinetic modelling

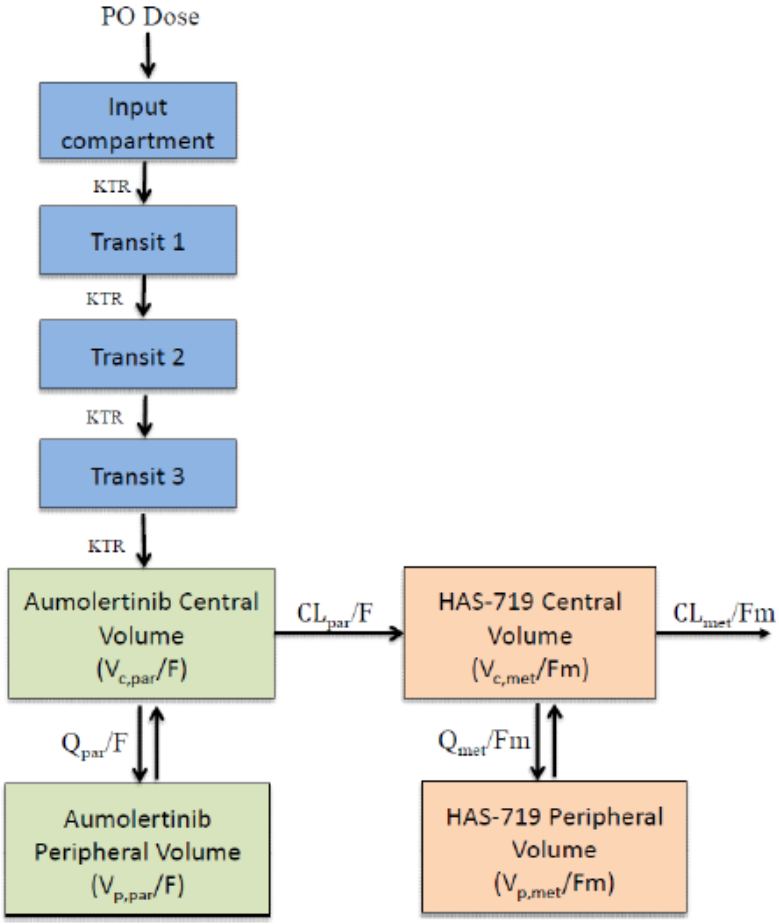
The population PK model was developed from plasma concentration-time data in both healthy subjects (Studies HS-10296-102, HS-10296-103, HS-10296-104 and EQ143-101) and subjects with NSCLC (HS-10296-12-01).

A total of 6980 aumolertinib and 7052 HAS-719 plasma concentration records were obtained from 491 subjects. Of these samples, 4862 aumolertinib and 4857 HAS-719 plasma concentrations were obtained from 362 subjects with NSCLC.

Covariates evaluated during the analysis included ethnicity, sex, weight, BSA, age, subject population (healthy subjects versus subjects with NSCLC), markers of renal function (CLCR), markers of liver function (AST, ALT, ALB, TBIL, NCI-ODWG hepatic impairment category), fed status (high-fat meal versus fasted), tablet formulation (minor grade change), and concomitant CYP3A4 inhibitors, CYP3A4 inducers, and proton pump inhibitors.

The final aumolertinib model was a two-compartment disposition model with absorption described by a series of transit compartments. HAS-719 was described by its own separate two-compartment model, assuming complete metabolism of aumolertinib with Fm fixed to 1.0.

Figure 2: schematic of the final population PK model



CL_{par}/F = apparent clearance for aumolertinib; CL_{met}/Fm = apparent clearance for HAS-719; KTR = absorption transit rate constant; PO = oral administration; Q_{par}/F = apparent intercompartmental clearance for parent drug; Q_{met}/Fm = apparent intercompartmental clearance for metabolite; $V_{c,par}$/F = apparent central volume of distribution for parent drug; $V_{c,met}$/Fm = apparent central volume of distribution for metabolite; $V_{p,par}$/F = apparent peripheral volume of distribution for parent drug; $V_{p,met}$/Fm = apparent peripheral volume of distribution for metabolite.
Source: PopPK/E-R Report, Figure 20.

Results are presented below.

Table 13: Parameters estimates for the final population PK model

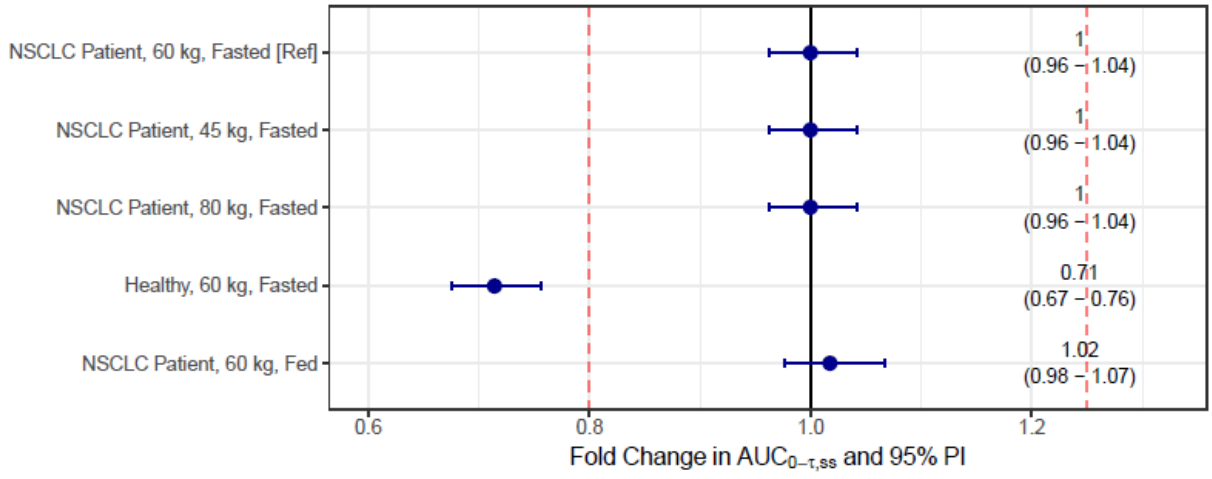
Parameter	Estimated Value (%RSE)	95% CI‡
Absorption rate constant (KTR) (/hr)	2.16 (4.1)	2.01 – 2.32
Absorption rate constant at Steady-state (KTR) (/hr)	1.21 (3.9)	1.07 – 1.28
Fold change of absorption rate constant with high-fat meal	0.78 (10.1)	0.65 – 0.95
Relative bioavailability on C0D1 (F_{C0D1})	1.26 (1.4)	1.23 – 1.29
Apparent clearance for aumolertinib (CL_{PAR}/F, L/h)	17.4 (2.2)	16.7 – 18.1
Increase in CL_{PAR}/F for HV (%)	40.4 (8.7)	32.9 – 48.4
Apparent central volume of distribution for aumolertinib ($V_{c,PAR}$/F, L)	875 (2.6)	835 – 911
Apparent intercompartmental clearance for aumolertinib (Q_{PAR}/F, L/h)	2.09 (11.6)	1.70 – 2.58
Apparent peripheral volume of distribution for aumolertinib ($V_{p,PAR}$/F, L)	79.8 (5.9)	71.8 – 89.3
Apparent clearance for HAS-719 (CL_{MET}/Fm, L/h)	45.8 (1.6)	44.6 – 47.0
Increase in CL_{MET}/Fm for HV (%)	23.3 (11.3)	18.2 – 28.5
Exponent for WT on CL_{MET}/Fm	0.50 (8.7)	0.43 – 0.58
Apparent central volume of distribution for HAS-719 ($V_{c,MET}$/Fm, L)	31.0 (4.7)	28.7 – 33.3
Apparent intercompartmental clearance for HAS-719 (Q_{MET}/Fm, L/h)	63.0 (2.0)	60.9 – 65.5
Apparent peripheral volume of distribution for HAS-719 ($V_{p,MET}$/Fm, L)	1377 (1.2)	1347 – 1408
Between-subject variability for CL_{PAR}/F (%CV)	45.8 (3.3)	43.4 – 48.3
Between-subject variability for $V_{c,PAR}$/F (%CV)	50.1 (4.1)	46.7 – 53.6
Between-subject variability for CL_{MET}/Fm (%CV)	33.2 (3.3)	31.2 – 34.9
Covariance between CL_{PAR}/F and $V_{c,PAR}$/F	0.186 (4.0)	0.162 – 0.212
Covariance between CL_{PAR}/F and CL_{MET}/Fm	0.134 (3.5)	0.117 – 0.149
Covariance between CL_{MET}/Fm and $V_{c,PAR}$/F	0.135 (4.0)	0.117 – 0.152
Between-subject variability for KTR fasted (%CV)	56.0 (5.0)	52.0 – 60.9
Between-subject variability for KTR fed (%CV)	39.9 (16.5)	30.0 – 53.4
Proportional residual unexplained variability for aumolertinib (%CV)	19.6 (1.0)	19.3 – 20.0
Proportional residual unexplained variability for HAS-719 (%CV)	16.0 (1.0)	15.6 – 16.2

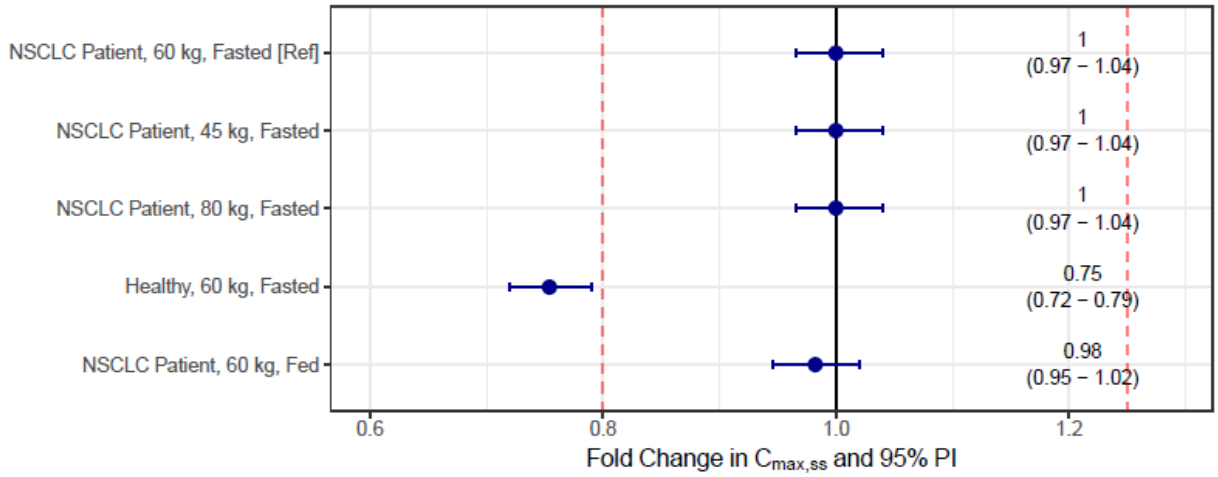
RSE = relative standard error, ‡derived from sampling imporatance resampling [1].
$CL_{PAR}/F = 17.4 \cdot 1.404$ (if HV), $CL_{PAR}/F = 45.8 \cdot (WT/60)^{0.5} \cdot 1.233$ (if HV)

Significant covariates were fed status on KTR, weight on CLmet/Fm, and subject population (healthy subject effect) on CLpar/F and CLmet/Fm. These covariates were included in the final PopPK model.

The influence of statistically significant covariates, including fed status and subject population on the expected aumolertinib exposure is presented below. None of the statistically significant covariates individually resulted in > 30% change in aumolertinib exposure. The covariate effect of subject population on CLpar/F was the most influential covariate and resulted in < 30% lower PK exposures in healthy subjects compared with subjects with NSCLC.

Figure 3: Model predicted fold change in Aumolertinib AUCtau,ss and Cmax,ss





Legend: The solid black line represents no impact of the covariate with the reference subject referring to NSCLC subject with median weight of 60 kg receiving 110 mg dose of aumolertinib QD in a fasted condition, sampled at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post dose at steady state.
Dashed red lines represent the 80-125% range of the reference subject. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals of the covariate effect, based on 1000 simulated subjects within each group including uncertainty on the fixed effect.
$AUC_{(0-\tau),ss}$ = area under the plasma concentration-time curve from time 0 to time τ at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; NSCLC = non-small cell lung cancer; PI = prediction interval; Ref = reference.

See discussion section for impact and conclusion of this modelling.

Exposure was markedly lower in Healthy Volunteers (25-29%) than in NSCLC patients. The GoF plots were shown for the overall Pop PK population.

Statistical analysis

Monte Carlo Mapped Power (MCMP) was used to quantify the power to detect an effect of race on aumolertinib PK, using population PK methods under the current sample size. With the current sample size (35 non-Asian subjects and 456 Asian subjects), the power was > 85% for all critical p-values (0.05, 0.01, 0.001) to detect a racial difference of ≥ 20%.

The following approach was taken to explore time-dependency in the PK of aumolertinib and HAS-719:

- Visualization of trough concentrations (defined as between 20 and 28 hours post dose) of aumolertinib (110 mg QD) and HAS-719 from the Phase 1 dose expansion portion (Part 2) of Study HS-10296-12-01.
- Comparison of AUC∞ following a single dose (healthy subjects as well as subjects with NSCLC from the Phase 1 dose escalation portion [Part 1] of Study HS-10296-12-01) and AUC(0-τ),ss at steady state (subjects with NSCLC).

Absorption

In study HS-10296-12-01 with NSCLC patients (group 1 (SD) and 3 (MD)) after 110 mg aumolertinib Single Dose, the aumolertinib mean Cmax was 318.5 ±185.9 ng/mL, and Multiple Dose mean Css,max was 352.51 ±185.33 ng/mL. Tmax ranged from 2 to 10 hours depending on studies and the median time to peak plasma concentration was 4 to 6 hours.

For HAS-719 in the same study, mean Cmax Single Dose was 36.52 ±16.74 ng/mL, mean Cmax Multiple Dose was 118.38 ± 43.34 ng/mL. Through studies, Tmax ranged from 3 to 48 hours, with a

median peak plasma concentrations observed at 4 to 6 hours post dose after multiple dosing. The mass-balance study HS-10296-105 enrolled 4 healthy male subjects. After oral elimination, 90.19% of the total dose was detected in urine and faeces, while 8.61% of aumolertinib was unchanged (see below the elimination section).

Aumolertinib undergoes first-order absorption with an estimated steady-state absorption rate of 1.2 hr^{-1} based on population PK modelling.

Table 14 Multiple dose PK parameters of aumolertinib and HAS 719 following oral administration of aumolertinib 110 mg in adults with NSCLC

Parameter*	**Aumolertinib Mean (% CV)** (N = 237)	**HAS-719 Mean (% CV)** (N = 237)
C_{max} (ng/mL)	353 (53)	118 (37)
AUC_{tau} (ng×h/mL)	6602 (53)	2468 (36)
C_{min} (ng/mL)	223 (58)	87.4 (38)

* Based on non-compartmental analysis from part 3, dose extension part, of the phase 1/2 study
AUC_{tau} = area under the plasma concentration-time curve from time zero to the endo the dosing interval, C_{max} = maximum concentration, C_{min} = lowest concentration, CV = coefficient of variation

Food intake (high-fat meal) had no effect on the Cmax of aumolertinib, but modestly increased the AUC∞ of aumolertinib by 20% (90% CI: [10, 30]) (Study HS-10296-102). In line with this, PopPK analyses showed a 0.8-fold change in the absorption rate constant with a high-fat meal. However, under steady-state conditions, PopPK analyses showed a minimal impact of food on Cmax,ss and AUC(0-τ),ss for both aumolertinib and HAS-719.

Distribution

In NSCLC patients (HS-10296-12-01), mean Vd/F was 554.20 ± 351.42 L. The aumolertinib population pharmacokinetic estimate for the volume of distribution in subjects with NSCLC at steady state was 875 L, indicating that aumolertinib distributes extensively outside of plasma which may indicate extensive tissue distribution, consistent with *in vivo* data in rats. Vp/F was estimated at 79.8 L for aumolertinib.

In vitro aumolertinib and HAS-719 are highly bound (≥99.5%) to human plasma proteins and bind to both albumin and AAG with no concentration dependence at clinically relevant concentrations in vitro.

The B/P ratio was close to 0.8 across 0.1-1 μM aumolertinib, independent of gender and subject population (HV/NSCLC patient).

Elimination

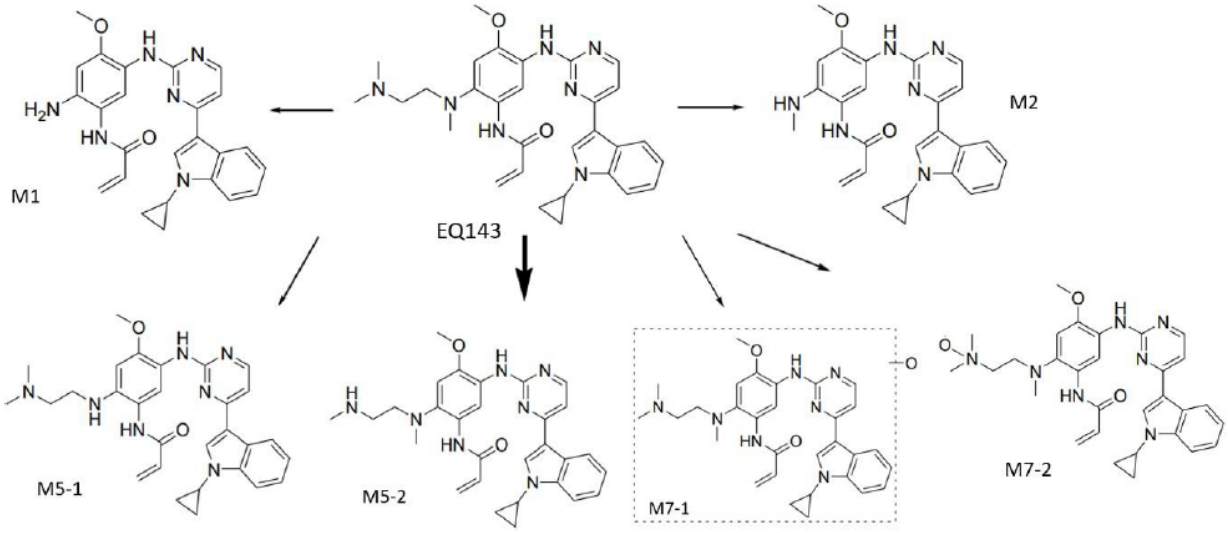
Aumolertinib and HAS-719 plasma concentrations decline in a mono-exponential manner. For aumolertinib in NSCLC subjects (HS-10296-12-01 group 1 SD patients) mean T1/2 was 30.62 ±9.34 h, and mean CL/F was 13.57±9.88 L/h. For HAS-719 in the same population, mean T1/2 was 55.36 ±19.95 h. In the Population pK modelling, the typical parameter values in subjects with NSCLC for CLpar/F, CLmet/Fm, were 17.4 L/h, 45.8 L/h, respectively.

After a single oral dose of [^{14}C]-aumolertinib, aumolertinib is primarily excreted in faeces with 85% of the total administered dose recovered in faeces. In Study HS-10296-105, unchanged aumolertinib

accounted for approximately 8.6% of the dose in faeces. HAS-719 was the most abundant metabolite in faeces, accounting for 12.3% of the dose. Unchanged aumolertinib constituted the majority (70%) of circulating total radioactivity in plasma. Renal excretion is a minor elimination pathway with 5.4% of the total dose recovered in urine. In Study HS-10296-105, approximately 0.5% and 1.2% of the administered dose is excreted in urine as aumolertinib and HAS-719, respectively.

The studies with recombinant human enzymes further indicated that aumolertinib is mainly metabolized by CYP3A4, with smaller contributions from CYP3A5, CYP1A2, and CYP2A6.

Figure 4: Proposed metabolic pathway for Aumolertinib in human hepatocytes



Note: EQ143 = HS-10296, aumolertinib; M5-2 = HAS-719

The main metabolic pathway of aumolertinib in humans is N-dimethylacetamide and demethylation; the secondary metabolic pathway is oxidation. CYP3A4 is the main enzyme involved.

HAS-719 is a major metabolite. The PK of metabolite HAS-719 has been detailed in each clinical study and presented in this report.

In plasma, aumolertinib accounts for 70%, after a single 110 mg dose to 4 healthy subjects in the mass balance study. Mean CL/F and t½ were determined to 36.8 L/h and 25 h for unlabelled aumolertinib and to 99.1 L/h and 41.8 h for HAS-719.

Measured CL/F was 13.57 L/h for aumolertinib after a single dose of 110 mg. Estimated CL/F values based on the population PK model of 17.4 L/h for aumolertinib and 45.8 L/h for HAS-719, respectively.

The mass balance study indicated aumolertinib is primarily excreted in faeces (85%), while renal excretion is a minor elimination pathway (5.4%). The mean recovery of radioactivity in the mass-balance study was 90%.

Data on metabolites in samples of plasma, urine and faeces identified by LC-RAM/HRMS were provided and abundance was based on radioactivity collected in plasma (0-48 h), urine (0-96 h), and faeces (0-240 h). Only plasma concentration profiles of aumolertinib and HAS-719 was measured.

From Table 15, other metabolites were detected in plasma with radioactivity abundances collected within the first 48 hours equal to or higher than HAS-719. This is HS-10296-M30 (M30), M440 and HS-10296-M2 (M2). M2 was detected in dogs in low amounts (2%).

Table 15: Radioactivity counts of 14C-Aumerlotinib and its metabolites in plasma following SD oral administration of 110 mg 14C-Aumerlotinib in healthy subjects in study HS-10296-105

Metabolic spectrum peak No.	Liquid Phase Time Rt (min)	Radioactivity Counts (Aumolertinib ng Eq/g)[a]						
		2 h	4 h	6 h	10 h	24 h	48 h	0 – 48 h
Total radioactivity concentration		329	464	373	361	325	282	2134
1	2.6-3.9	17.8	ND	ND	12.5	ND	ND	30.3
3	10.1-10.6	4.4	ND	ND	ND	ND	ND	4.4
5	12.1-13.1	ND	ND	ND	12.5	ND	ND	12.5
7	14.1-15.4	4.4	ND	ND	ND	ND	ND	4.4
9	16.9-17.9	ND	ND	ND	12.5	ND	ND	12.5
10 (M717)	18.3-18.9	4.4	ND	15.2	ND	ND	ND	19.6
17	27.1-29.6	ND	7.8	ND	ND	ND	ND	7.8
23 (M617 and M575)	41.1-42.6	4.4	ND	ND	ND	ND	ND	4.4
24 (M541a and M470a)	43.4-44.4	4.4	ND	ND	ND	ND	ND	4.4
29 (HS-10296-M30)	49.6-50.6	4.4	46.4	15.2	37.2	ND	ND	103.2
32 (M511a)	54.1-54.9	ND	ND	7.6	ND	ND	ND	7.6
33 (M470e)	55.4-56.1	8.9	7.8	ND	ND	ND	ND	16.6
34 (M440)	56.4-56.9	35.5	101	60.8	12.5	31.5	ND	241.3
35 (M497b)	56.9-57.4	4.4	7.8	ND	ND	ND	ND	12.2
36 (HAS-719)	57.9-58.4	8.9	ND	30.4	12.5	52.3	ND	104.1
37 (HS-10296-M2)	58.6-59.4	26.7	7.8	7.6	12.5	10.5	70.5	135.6
38 ([^{14}C]-HS-10296)	59.6-60.1	200	286	236	249	231	212	1414

[a]Concentration of [^{14}C]-aumolertinib and its metabolites in plasma (HS-10296 ng Eq/g) = percentage of [^{14}C]-HS-10296 and its metabolites in total radioactivity × total radioactivity concentration in plasma samples.
No radioactive metabolites were detected in 96-hour plasma samples due to very low radioactivity.
h = hours; HS-10296 = aumolertinib; ND = not detected; Rt = retention time.

Study HS-10296-108 in 18 patients of European origin provided PK samples following single-dose and multiple-dose administration of 110 mg aumolertinib for quantification of aumolertinib and selected circulating metabolites HAS-719, M2, M511a, M440, and M30.

Table 16: Contribution of Aumolertinib and metabolites to total measured exposure at C1D1 and C2D1 (Study HS-10296-108 CSR)

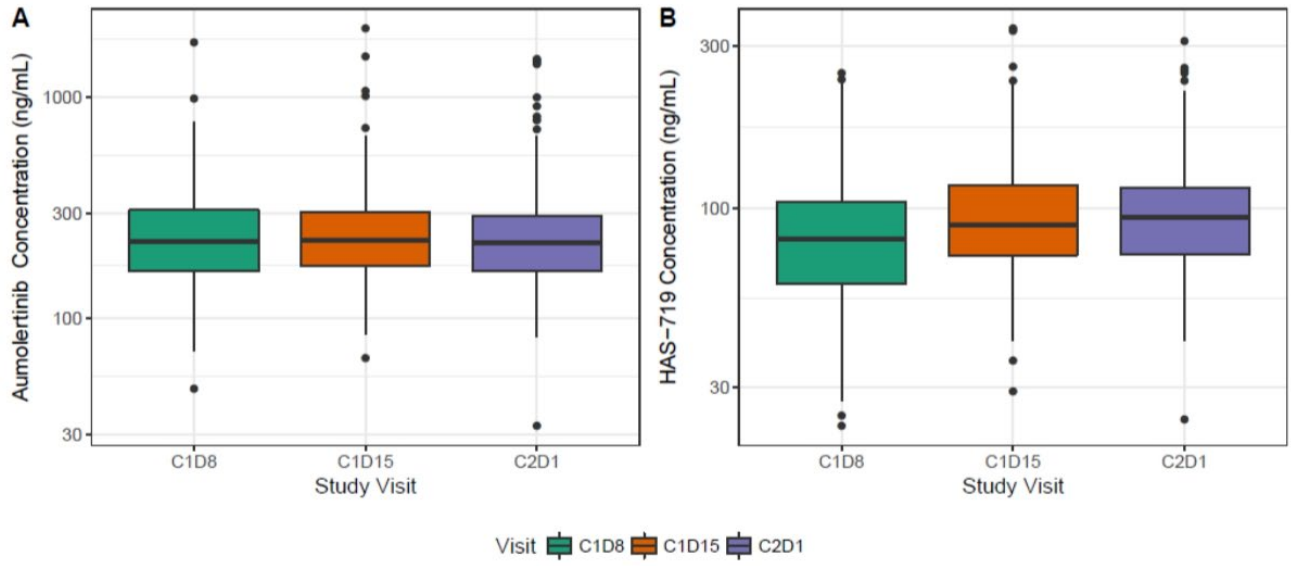
Analyte	MW	C1D1 AUC_{0-24h} (h·ng/mL)	C1D1 (h·µmol/L)	C1D1 M/Total	C2D1 AUC_{0-24h} (h·ng/mL)	C2D1 (h·µmol/L)	C2D1 M/Total
Aumolertinib	525.64	3370	6.41	0.741	6260	11.9	0.584
HAS-719	511.63	468	0.915	0.106	2270	4.44	0.218
M2	455.2	464	1.02	0.118	1160	2.55	0.125
M440	441.3	39.7	0.0900	0.0104	136	0.308	0.0151
M30	251.3	7.62	0.0303	0.00351	49.7	0.198	0.00970
M511a	512.3	93.9	0.183	0.0212	511	0.997	0.0489
Total			8.65			20.4	

Note: The total measured plasma exposure was calculated as the molar sum of AUC_{0-24h} of aumolertinib and the quantified metabolites: HAS-719, M2, M440, M30, and M511a. MW = molecular weight. AUC values are observed h·ng/mL. AUC values were converted to molar units (h·µmol/L) using molecular weight. Fractions

Dose proportionality and time dependencies

In Study HS-10296-12-01 aumolertinib exposures (AUC and Cmax) were approximately dose-proportional across the 55 mg – 220 mg dose range in first part.

Figure 5 Trough Concentrations: Subjects with NSCLC in Phase 1 Dose Expansion Part of Study HS-10296-12-01



CxDx = Cycle x Day x; NSCLC = non-small cell lung cancer.

Table 17: Study HS-10296-12-01, Proportional dose response relationship of PK parameters after SD part 1

PK Parameters (Unit)	Dose range	n	Estimated slope β1	90% confidence interval
C_{max}	55~ 260 mg	26	0.9301	(0.6281, 1.2321)
AUC_{0-t}	55~ 260 mg	26	1.0276	(0.7178, 1.3374)
$C_{ss\ max}$	55~ 260 mg	345	0.7865	(0.6618, 0.9111)
AUC_{ss}	55~ 260 mg	305	0.8095	(0.6845, 0.9345)

Aumolertinib exposure increased in a dose proportional manner from 55 mg to 110 mg. From 110 mg to 220 mg, aumolertinib exposure increased less than proportional to dose (Cmax increased by 34% and AUC by 43% based on mean values).

T½ for aumolertinib was determined to 30.62 h after a single dose 110 mg aumolertinib. Thus, the expected accumulation ratio would be 2.38. For HAS-719 with a t½ 55.36 h under the same conditions, the expected accumulation ratio would be 3.86. Rac, as estimated by t½ and Tau, was longer for aumolertinib and slightly shorter for HAS-719 compared to observed values following 110 mg QD dosing.

Considering the estimated elimination t1/2 of aumolertinib of 31 to 35 hours, steady-state conditions would be expected by Day 8 of dosing. The boxplot of aumolertinib trough concentrations displayed in Figure 5 demonstrates no significant changes in aumolertinib trough concentrations between Cycle 1 Day 8 and Cycle 2 Day 1 of dosing, indicating no time dependency in the PK. Additionally, the scatterplot of trough HAS-719 concentrations shows a minor increase occurring between Cycle 1 Day 8 and Cycle 1 Day 15 (~ 15%). There was no appreciable difference between the mean HAS-719 trough concentrations on Cycle 1 Day 15 (100.3 ng/mL) and Cycle 2 Day 1 (99.7 ng/mL). Aumolertinib AUC(0-τ),ss was lower than AUC∞ on C0D1 in subjects with NSCLC, with no apparent difference between AUC∞ and AUC(0-τ),ss for HAS-719.

Based on data from Study HS-10296-12-01, the accumulation ratio was approximately 1.4 for aumolertinib and 4 for HAS-719 following 110 mg QD dosing of aumolertinib, and the mean accumulation ratio across the dose range of 55 mg – 260 mg were approximately 1.8 and 4.6-fold for aumolertinib and HAS-719, respectively.

Based on Ctrough measurements between 8-22 days of dosing no time-dependency is expected. Steady-state was reached on Day 8 for aumolertinib and after 15 days for HAS-719.

Intra and inter-individual variability

From the population PK analysis, between-subject variability for CLpar/F, CLmet/Fm, and Vc,par/F was 45.8%, 33.2%, and 50.1% respectively, and residual unexplained variability for aumolertinib and HAS-719 was 19.6% and 16.0%, respectively.

Information on the intra- and inter-individual variability were also provided from the food interaction study (HS-10296-102, n=20). For AUC, the intra- and inter-individual variability was 15.41% and 26.86% for aumolertinib and 10.07% and 21.79% for HAS-719, respectively.

Target population

Subject population (NSCLC subjects versus healthy subjects) was identified as a significant covariate on aumolertinib PK.

Aumolertinib clearance and volume of distribution are approximately 2-fold higher in healthy subjects compared to subjects with NSCLC with half-life remaining similar (see Figure 3).

The effect of race was examined in a dedicated Phase 1 study (Study EQ143-101), as a covariate in the PopPK analysis, and in a separate PK study HS-10296-108. **Error! Reference source not found.** presents C2D1 (21-day cycle) exposure expressed as AUCtau and Cmax in Chinese patients (Study HS-10296-12-01, n=237) and in patients of European origin (Study HS-10296-108, n=18). Slightly higher exposure was observed in Europeans.

Table 18: Comparison of Aumolertinib and HAS-719 PK Parameters at Steady State (C2D1) between Study HS-10296-12-01 (Chinese Patients) and HS-10296-108 (European Patients)

Parameter	**HS-10296-12-01** (GeoMean, %CV) (n=237)	**HS-10296-108** (GeoMean, %CV) (n=18)	**% Difference** (108 vs 12-01)
Aumolertinib AUC (h·ng/mL)	5969.7 (45.4%)	6260 (38.3%)	4.9%
Aumolertinib C_{max} (ng/mL)	319.1 (44.7%)	368 (33.4%)	15.3%
HAS-719 AUC (h·ng/mL)	2325.2 (35.6%)	2270 (33.8%)	-2.4%
HAS-719 C_{max} (ng/mL)	111.4 (35.9%)	117 (34.4%)	5.0%

C2D1 = Cycle 2 Day 1 (steady-state assessment); CV = coefficient of variation.CV: coefficient of variation.

Special populations

Renal impairment:

In a population PK analysis, aumolertinib and HAS -719 exposures were similar in subjects with mild renal impairment (60 ≤ CLcr < 90 mL/min), subjects with moderate renal impairment (30 ≤ CLcr ≤ 60 mL/min), and patients with normal renal function (CLcr ≥ 90 mL/min). Aumolertinib has not been evaluated in subjects with severe renal impairment (CLcr < 30 mL/min) or end -stage renal disease.

Aumolertinib and HAS-719 pharmacokinetics were similar across varying degrees of renal function.

Hepatic impairment:

The exposure of aumolertinib and HAS-719 was lower in subjects with moderate hepatic impairment in Study HS-10296-106 compared to the control group with normal liver function

Table 19 Effect of Mild and Moderate Hepatic Impairment on the Pharmacokinetics of Aumolertinib Following Single Dosing of Aumolertinib 110 mg in Study HS-10296-106

Parameter	**Arithmetic Mean[a] ± SD**				**Geometric Mean Ratio (%) (90% CI)**	
	Mild Hepatic Impairment (Group 1, n = 6)	**Healthy Subjects (Group 3, n = 6)**	**Moderate Hepatic Impairment (Group 2, n = 6)**	**Healthy Subjects (Group 4, n = 6)**	**Mild Hepatic Impairment/Healthy Subjects (Group 3)**	**Moderate Hepatic Impairment/Healthy Subjects (Group 4)**
C_{max} (ng/mL)	123.8 ± 18.3	114.9 ± 22.1	78.9 ± 36.9	151.3 ± 23.0	108.5 (90.4 – 130.3)	46.2 (28.8 – 74.0)
$AUC_{(0-\tau)}$ (ng*h/mL)	4418.3 ± 1227.9	3136.8 ± 625.0	3342.9 ± 1012.6	4851.1 ± 1734.5	138.3 (106.2 – 180.1)	68.6 (48.6 – 97.0)

Parameter	Arithmetic Mean[a] ± SD				Geometric Mean Ratio (%) (90% CI)	
	Mild Hepatic Impairment (Group 1, n = 6)	**Healthy Subjects (Group 3, n = 6)**	**Moderate Hepatic Impairment (Group 2, n = 6)**	**Healthy Subjects (Group 4, n = 6)**	**Mild Hepatic Impairment/Healthy Subjects (Group 3)**	**Moderate Hepatic Impairment/Healthy Subjects (Group 4)**
AUC_{∞} (ng*h/mL)	4502.1 ± 1297.5	3173.2 ± 634.5	3443.5 ± 1028.5	4927.8 ± 1771.3	139.0 (106.1 – 182.0)	69.8 (49.7 – 98.0)
$t_{½}$ (h)	37.5 ± 6.7	27.8 ± 8.1	42.2 ± 6.7	36.9 ± 6.5	NA	NA
T_{max} (h)	4.5 (2 – 6) [a]	5.0 (5 – 6) [a]	2.5 (2 – 10) [a]	5.0 (2 – 5) [a]	NA	NA
CL/F (L/h)	26.4 ± 8.4	35.8 ± 7.1	35.3 ± 14.1	24.1 ± 6.1	NA	NA
Vz/F (L)	1388.0 ± 384.2	1395.7 ± 347.8	2228.7 ± 1300.3	1280.4 ± 397.0	NA	NA

[a] Values for Tmax are: Median (min – max).
AUC_{∞} = area under the plasma concentration-time curve from time 0 estimated to infinity; $AUC(0-\tau)$ = area under the plasma concentration-time curve from time 0 to time τ; CI = confidence interval; CL/F = apparent clearance; Cmax = maximum plasma concentration; NA = not available or not applicable; SD = standard deviation; t½ = half-life; Tmax = time to observed maximum concentration; Vz/F = apparent volume of distribution

Compared with the matched healthy subjects, aumolertinib AUC∞ and Cmax were increased by 39% and 9%, respectively, in subjects with mild hepatic impairment. The AUC∞ of the metabolite HAS-719 increased by approximately 7% and Cmax decreased by approximately 11%. Aumolertinib AUC∞ and Cmax were decreased by 31% and 54%, respectively, in subjects with moderate hepatic impairment relative to matched healthy control subjects. HAS-719 AUC∞ and Cmax decreased by approximately 62% and 72%, respectively.

In Study EQ143-102 subjects with severe hepatic impairment (Child-Pugh Class C) were compared to subjects with normal liver function. Subjects with severe hepatic impairment had notable lower total exposure than subjects with normal liver function but the unbound exposure seemed comparable. In severe hepatic impairment, total Cmax and AUCinf of aumolertinib were reduced by ~64% and 50%, respectively, and HAS-719 by ~80% and 70%.

Gender, weight, age effect:

Population PK analysis did not show any influence of gender, age over PK.

In the Pop PK model, weight was included as a significant covariate of HAS-719 CL, but was not included in the model for aumolertinib.

No paediatric study was performed as aumolertinib is not intended for paediatric populations.

A total of 362 subjects with NSCLC from the Phase 1/2 Study HS-10296-12-01 were included in the population PK analysis. Of these 362 subjects with NSCLC, 135 (37%) were ≥ 65 years of age.

A summary of the number of elderly subjects with NSCLC and the number of PK samples, presented by age category, is provided in Table 20.

Table 20: Summary of PK Data from Elderly Subjects (≥ 65 Years of Age) with NSCLC in Study HS-10296-12-01

	Age in Years		
	65 – 74	**75 – 84**	**≥ 85**
Number of elderly subjects/total number (% of total number)	96/362 (26.5%)	35/362 (9.7%)	4/362 (1.1%)
Number of aumolertinib PK samples (% of total number)	1301 (26.8%)	479 (9.9%)	51 (1%)
Number of HAS-719 PK samples (% of total number)	1298 (26.7%)	479 (9.9%)	51 (1.1%)

NSCLC = non-small cell lung cancer; PK = pharmacokinetic.

Studies HS-10296-108 and HS-10296-109 also included patients above 65 years of age:

Table 21: Elderly Subjects (≥ 65 Years of Age) in PK trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
HS-10296-109	5/20	0/20	0/20
HS-10296-108	6/19	2/19	0/19
Total	11/39	2/39	0/39

Pharmacokinetic interaction studies

In vitro – see section 2.5.3.

Aumolertinib as a victim drug

In silico

- **Aumolertinib PBPK model**

The PBPK model was established using a mixed approach combining physicochemical and *in vitro* data together with PK parameters derived from noncompartmental and PopPK analysis of data from clinical studies and itraconazole DDI study.

Simulations with the PBPK model were performed to predict how aumolertinib PK will be affected by coadministration fluconazole (moderate CYP3A4 inhibitor), erythromycin (moderate CYP3A4 inhibitor) or efavirenz (moderate CYP3A4 inducer) following a single dose of 110 mg aumolertinib in healthy subjects. The simulated AUC∞ and Cmax ratios for aumolertinib with and without the co-administration of moderate CYP3A4 inhibitor were 2.32- and 1.36-fold, respectively, for fluconazole and 2.41- and 1.39-fold, respectively for erythromycin. The simulated AUC∞ and Cmax ratios for aumolertinib with and without the co-administration of moderate CYP3A4 inducer (efavirenz) were 0.35- and 0.68-fold, respectively. The simulated AUC∞ and Cmax ratios for HAS-719 with and without the co-administration of moderate CYP3A4 inhibitor were 1.13- and 0.59-fold respectively, for fluconazole and 1.07- and 0.53-fold, respectively for erythromycin. The simulated AUC∞ and Cmax ratios for HAS-719 with and without the co-administration of moderate CYP3A4 inducer (efavirenz) were 0.52- and 1.22-fold, respectively.

Simulations with the PBPK model were performed to predict effect of aumolertinib on PK of dabigatran (P-gp substrate) or rosuvastatin (BCRP substrate) following administration of aumolertinib 110 mg QD. Aumolertinib was simulated under steady-state conditions. A sensitivity analysis on transporter Ki values was conducted. DDI simulations were repeated after reducing the Ki values by 10- or 15-fold. This analysis indicated that aumolertinib is likely to be a P-gp inhibitor *in vivo*, as the simulated GMRs of AUC∞ and Cmax for dabigatran (sensitive P-gp substrate) with and without co-administration of aumolertinib were between 1.2- and 2.1-fold, after accounting for the uncertainty in the *in vitro* Ki values.

Based on the in vitro Ki value, there is no DDI between aumolertinib and rosuvastatin. However, under the worst-case scenario, i.e., with a 15-fold reduction in the in vitro estimated Ki value (0.33 μM), the results showed a potential inhibition of aumolertinib on rosuvastatin since the AUC and Cmax GMR are 1.34 and 1.61, respectively.

Table 22 Simulated geometric mean AUC0-inf and Cmax values and corresponding GMRs for rosuvastatin in the absence and presence of aumolertinib in healthy subjects.

	Rosuvastatin PO		Rosuvastatin + Aumolertinib		GMR	
	$AUC_{0\text{-inf}}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$	C_{max}
***In vitro* K_i**	59.5	7.28	60.9	7.54	1.02	1.04
90% CI – Lower	49.9	6.23	51.1	6.46	1.02	1.03
90% CI – Upper	70.9	8.50	72.6	8.80	1.02	1.04
15x lower K_i	59.5	7.28	78.5	11.4	1.32	1.57
90% CI – Lower	49.9	6.23	66.0	9.92	1.30	1.53
90% CI – Upper	70.9	8.50	93.3	13.2	1.34	1.61

GMR: geometric mean ratio; CI: Confidence Interval; Source simulated data: rosu-pfizer-ddi-hv; rosu-pfizer-ddi-hv-15x-lower-ki

In vivo

- **Study HS-10296-103: Study of Drug-Drug Interaction with Itraconazole**

Aumolertinib is mainly metabolised by CYP3A4 enzymes. When combined a single dose of aumolertinib with itraconazole, a strong CYP3A4 and P-gp inhibitor, aumolertinib AUC and Cmax geometric mean ratio increased about 273% (90% CI was 245-304%) and 56% (90% CI was 44.5-69%), HAS-719 AUC and Cmax geometric mean ratio decreased by about 69% (90% CI was 59.6-77%) and 87% (90% CI was 86-88%).

- **Study HS-10296-104: Study of Drug-Drug Interaction with Rifampicin**

When combined a single dose of aumolertinib with rifampicin, a strong CYP3A4 inducer, aumolertinib AUC and Cmax geometric mean ratio decreased by 92.2% (90% CI was 91.4-93%) and 79.3% (90% CI was 76.8-81.4%). HAS-719 AUC and Cmax geometric mean ratio decreased by about 72.6% (90% CI was 70.3-74.7%) and 9.5% (90% CI was 1.1-17.3%).

- **Study HS-10296-107: Study of Drug-Drug Interaction with Fexofenadine**

Based on an *in vitro* study aumolertinib is a P-gp inhibitor. In a clinical drug-drug interaction study, aumolertinib increased the Cmax and AUC of fexofenadine (sensitive P-gp substrate) by 86% (90% CI 50.3-129.5%) and 67% (90% CI 46-91.6%), respectively.

- **Study HS-10296-109: Study of Drug-Drug Interaction with midazolam**

A dedicated clinical DDI study (HS-10296-109) was conducted in patients with advanced non–small cell lung cancer (NSCLC) to evaluate the effect of aumolertinib on the pharmacokinetics of midazolam, a sensitive CYP3A substrate. A total of 20 patients received aumolertinib 110 mg once daily for 28 days to reach steady state. Midazolam 2 mg was administered orally as a single dose during a run-in period (Day –1) and again on Cycle 2 Day 1 after aumolertinib steady state had been achieved. Plasma concentrations of aumolertinib observed in this study were within the anticipated therapeutic range.

Table 23 Effect of Aumolertinib on Midazolam PK (Cycle 2 Day 1 vs Run-in)

Analyte	Parameter	Midazolam Alone (GeoMean, %CV)	Midazolam + Aumolertinib (GeoMean, %CV)	GMR (90% CI)	% Change
Midazolam	Cmax (ng/mL)	18.8 (63.3)	15.6 (37.3)	0.83 (0.72–0.95)	–17%
	AUC_0–t (h·ng/mL)	54.1 (63.5)	39.5 (46.1)	0.73 (0.64–0.84)	–27%
	AUC_0–inf (h·ng/mL)	56.9 (65.4)	41.3 (46.6)	0.73 (0.64–0.83)	–27%

All PK parameters for midazolam were derived from 20 evaluable subjects in the PK analysis set. Geometric least-squares means and geometric mean ratios (GMR 90 % CIs) are from the statistical comparison of log-transformed data. Median Tmax was 0.5 h (range 0.25–1.5 h) in both periods.

2.6.2.2. Pharmacodynamics

Mechanism of action

Aumolertinib is a third generation EGFR TKI, similarly to osimertinib which is currently the only one approved. Its mechanism of action consists of the irreversible inhibition of mutant EGFR, including Ex19del and L858R, leading to the inhibition of cancer cell proliferation, with reduced inhibitory kinase activity against wild type (WT) EGFR compared with earlier-generation EGFR TKIs. The *in vitro* assays demonstrated a reduced potency of aumolertinib and its major metabolite HAS-719 against WT EGFR compared to gefitinib and afatinib with a higher IC_{50}. In addition, aumolertinib displayed an inhibition of EGFR T790M resistance mutation, a new target of the third-generation EGFR-TKI.

Primary and Secondary pharmacology

Concentration-QTc analyses

Potential QTc prolongation was investigated by c-QTc modelling using PK-ECG data from the patients with central over-readings of ECG in the escalation and expansion Part 1 and 2 of Study HS-10296-12-01. Table 24 below shows the outcome of two model-based c-QTC analyses (linear model, Emax model).

ECG and PK data were available from a total of 49 subjects: 16 subjects in the dose-escalation phase (6 subjects treated with 110 mg, 5 subjects with 220 mg, and 5 subjects with 260 mg of aumolertinib), and 33 subjects in the dose-expansion phase (17 subjects treated with 110 mg, and 16 subjects treated with 220 mg of aumolertinib).

Table 24: Predicted ΔQTcF from two model-based cardiac safety analyses (Study HS-10296-01)

Dose (mg QD)	HAS-719 (model C, linear) in cardiac safety report Version 1: ΔQTcF, ms (90% CI)	Parent (model B, Emax) in cardiac safety report Version 2: ΔQTcF, ms (90% CI)
110 mg (therapeutic)	8.0 (6.17 – 9.82)	9.06 (7.11 – 11.01)
220 mg	14.2 (10.9 – 17.4)	10.63 (8.27, 13.5)
260 mg	21.1 (15.4 – 26.8)	13.0 (8.9, 17.2)

All confidence intervals are two-sided 90% CIs, per ICH E14/M14.

From the data provided, the frequency of QTc prolongation seem to increase with dose and the effect is considered clinically relevant. The categorical QTc analysis of Study HS-10296-12-01, including data from all study parts is shown in Table 25 below. In the extension Part 3 where 244 subjects received aumolertinib 110 mg for 21-days, 90% experienced a ΔQTcF ≥10 ms.

Table 25: Categorical QTc analysis (Study HS-10296-01)

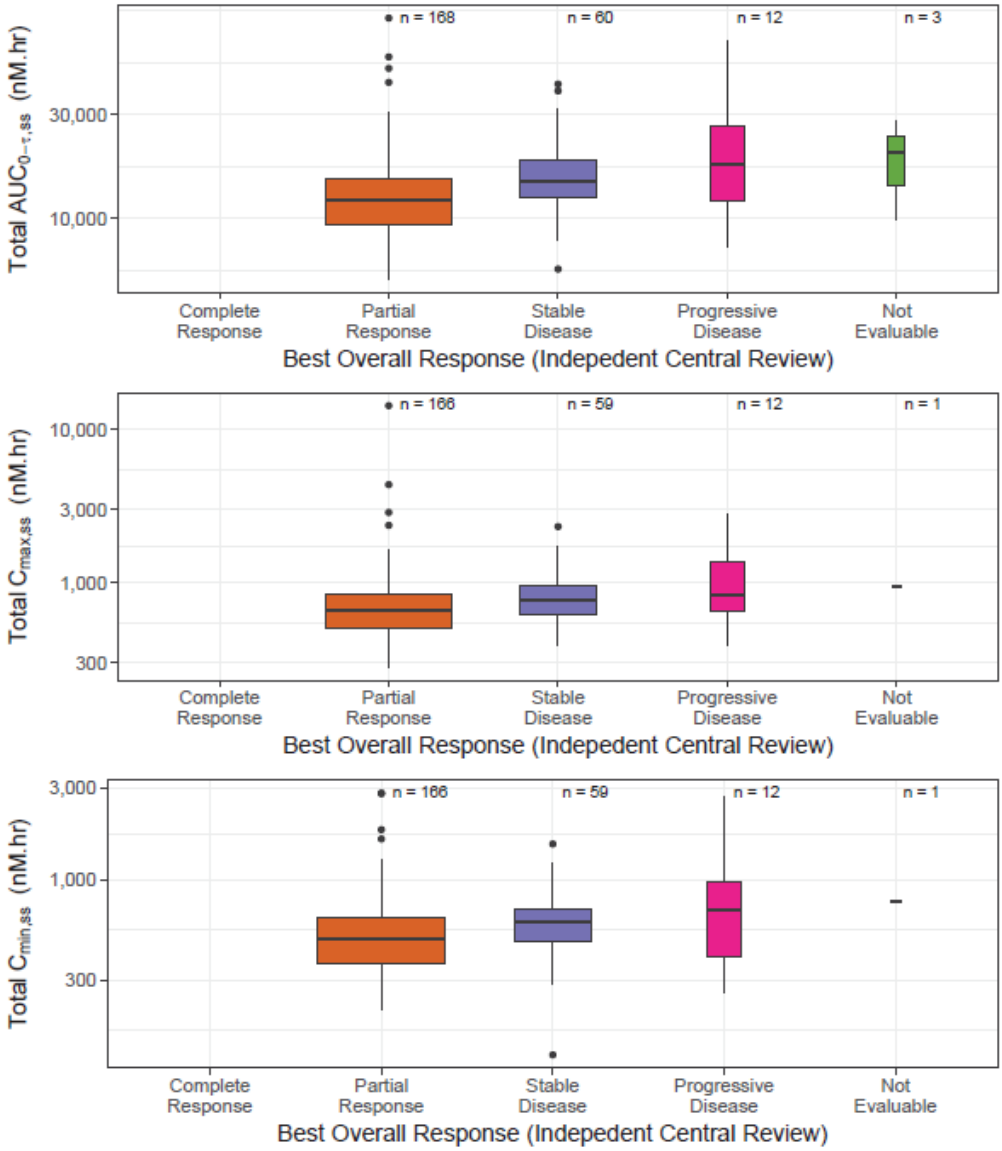
Cohort	QTcF max. increase from baseline (msec)	55 mg (N=6) n (%)	110 mg (N=6) n (%)	220 mg (N=8) n (%)	260 mg (N=6) n (%)
Escalation	<10	2 (33.3)	0	0	2 (33.3)
	≥10 – 30	1 (16.7)	4 (66.7)	5 (62.5)	0
	>30 – 60	3 (50.0)	2 (33.3)	3 (37.5)	4 (66.7)
	>60	0	0	0	0
Expansion		**55 mg (N=30) n (%)**	**110 mg (N=33) n (%)**	**220 mg (N=31) n (%)**	
	<10	3 (10.0)	3 (9.1)	4 (12.9)	-
	≥10 – 30	20 (66.7)	18 (54.5)	15 (48.4)	-
	>30 – 60	5 (16.7)	9 (27.3)	11 (35.5)	-
	>60	1 (3.3)	2 (6.1)	1 (3.2)	-
Extension			**110 mg (N=244) n (%)**		
	<10	-	25 (10.2)	-	-
	≥10 – 30	-	137 (56.1)	-	-
	>30 – 60	-	74 (30.3)	-	-
	>60	-	8 (3.3)	-	-

No pharmacodynamics study was submitted.

Exposure-response (E-R) analysis for efficacy

The E-R dataset was developed from subjects with NSCLC in the Phase 1/2 Study HS-10296-12-01. A total of 362 subjects were included with safety data from HS-10296-12-01 (Safety Analysis Set). Of these 362 subjects, there were 19 subjects who were T790M-negative, leaving 343 subjects in the Investigator-assessed efficacy population. Of these 343 subjects, 243 had efficacy results from ICR assessment—all of whom were in the Phase 2 extension part of Study HS-10296-12-01 and were treated with aumolertinib 110 mg. Exposure-response analysis included updated efficacy and safety data from a data cut-off date of August 2021. No new PK data was available in the updated data cut.

Figure 6 Boxplots of AUCss,total, Cmax,ss,total, and Cmin,ss,total by Best Overall Response per Independent Central Review



The thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. The blue shaded region is the approximate 95% CI for the median, calculated as $\pm 1.58 \times \mathrm{IQR}/\sqrt{n}$. Box widths are proportional to the square-roots of the number of observations in the groups.

Parameters for the final logistic regression model are displayed in Table 26. The final logistic regression exposure-response model for overall response (PR vs SD + PD + NE) as assessed by the Independent Central Review showed a significant relationship between log $AUC_{ss,total}$ and the probability of response,

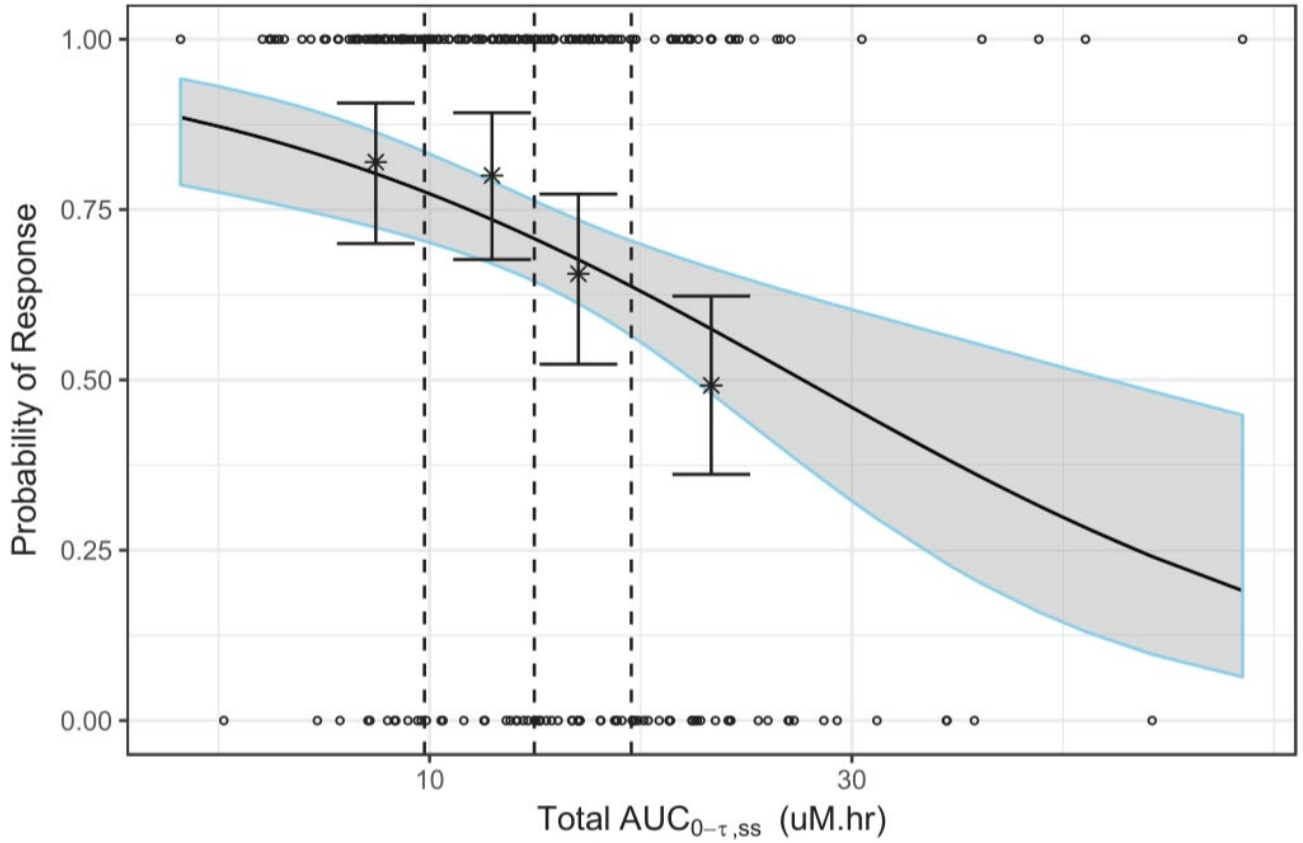
with a corresponding OR of 0.283 (95% CI 0.142 – 0.561, p-value = <0.001, Figure 7). No covariate effects were identified during the model development. Evaluation of the final overall response logistic regression ICR model demonstrated that the model provided an adequate description of the observed data (Figure 7).

Table 26 Final Overall Response Logistic Regression Model(Independent Central Review)

Parameter	Estimate(95%CI)	P value
Intercept	12.865(6.300–19.430)	<0.001
$logAUC_{ss,total}$	0.283(0.142–0.561)	<0.001

Intercept reported as log-odds, other parameters represented as odds ratios.

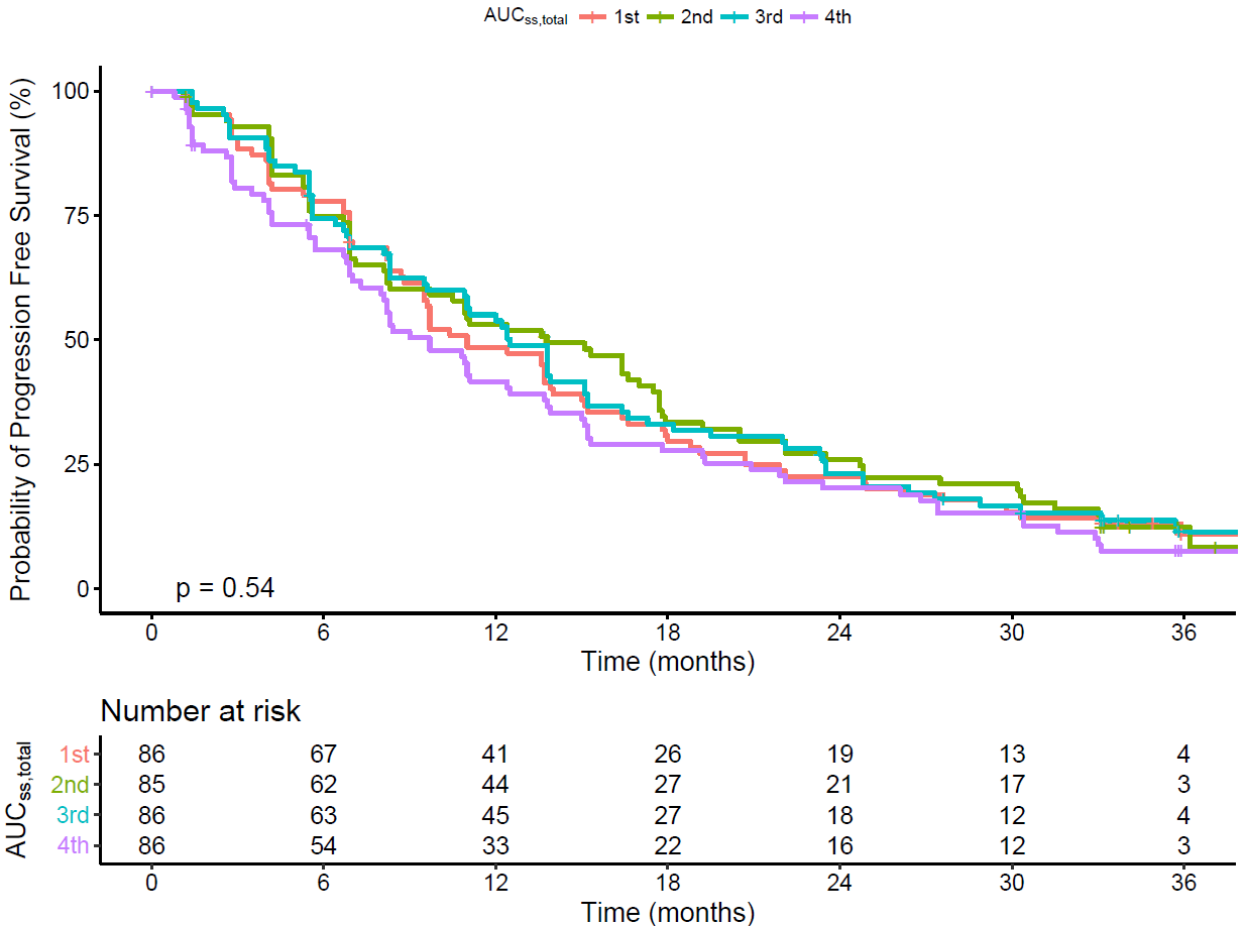
Figure 7 Diagnostic Plot: Final Overall Response Logistic Regression Model (Independent Central Review)



Total $AUC_{0-\tau,ss}$=aumolertinib + HAS-19. Black solid lines (grey shaded areas) model predicted (95%CI) from logistic regression model, stars = observed proportions within each quartile, error bars = 95% CI in observed probabilities.

Progression-free survival

Figure 8: Progression-free Survival by Quartiles of $AUC_{ss,total}$ (Investigator Review)



Legend: Solid lines represent Kaplan-Meier curves, and p-value is derived from a log-rank test. Plot truncated at 36 months.
$AUC_{ss,total}$ = area under the plasma concentration-time curve at steady state for aumolertinib + HAS-719.

Best overall response

The majority of subjects (61.5%) achieved a BOR of PR. There was no clear relationship evident in the graphical analysis between aumolertinib, HAS-719, or total exposure (aumolertinib and HAS-719) and BOR.

Disease control rate

A trend was observed towards a greater DCR as dose increased, with rates of 85.7%, 93.8% and 97.1% for 55 mg, 110 mg, and 220 mg QD, respectively. Overall, DCR was high (> 93%) with no relationship evident by aumolertinib or HAS-719 exposure.

Based on the recommended 110 mg QD dose regimen, an inverse relationship was observed between total exposure (aumolertinib and HAS-719) and probability of response, with the highest exposure

quartile resulting in the lowest probability of response and overall survival. The cause of the inverse relationship has not been determined.

Although there was no relationship present between total exposure and PFS or DoR (Investigator review), there was an observed numerical trend towards improved DoR (Investigator review) as dose increased. Consistent with the observed dose-response profile of aumolertinib in Study HS- 10296-12-01, maximal responses appear to be associated with the 55 mg and 110 mg QD groups, indicating no additional efficacy at exposures above the 110 mg QD dose.

Exposure-response simulation

E-R simulations were conducted to explore the expected E-R relationship for aumolertinib in a non-Asian population with NSCLC. A database of 1000 virtual patients was created by sampling with replacement from the patients enrolled in study HS-10296-12-01. The E-R simulations based on virtual patients did not predict differences in efficacy response at dosages 55mg QD and 110mg QD between Asian and non-Asian population.

PFS (ICR)

Table 27: Probability of Progression Free Survival (ICR)

			Probability of PFS (ICR)		
Dose	Race	Time (months)	5th Percentile	50th Percentile	95th Percentile
55 mg QD	Asian	6	0.644	0.829	0.906
55 mg QD	Non-Asian	6	0.647	0.829	0.907
55 mg QD	Asian	12	0.299	0.598	0.763
55 mg QD	Non-Asian	12	0.303	0.599	0.764
55 mg QD	Asian	18	0.114	0.396	0.615
55 mg QD	Non-Asian	18	0.116	0.397	0.616
55 mg QD	Asian	24	0.037	0.245	0.477
55 mg QD	Non-Asian	24	0.038	0.246	0.479
110 mg QD	Asian	6	0.577	0.791	0.885
110 mg QD	Non-Asian	6	0.583	0.792	0.885
110 mg QD	Asian	12	0.222	0.527	0.716
110 mg QD	Non-Asian	12	0.228	0.528	0.717
110 mg QD	Asian	18	0.066	0.315	0.548
110 mg QD	Non-Asian	18	0.069	0.317	0.548
110 mg QD	Asian	24	0.016	0.173	0.401
110 mg QD	Non-Asian	24	0.017	0.174	0.401

Objective response (ICR)

Table 28: Exposure-response Simulations: Overall Response (ICR)

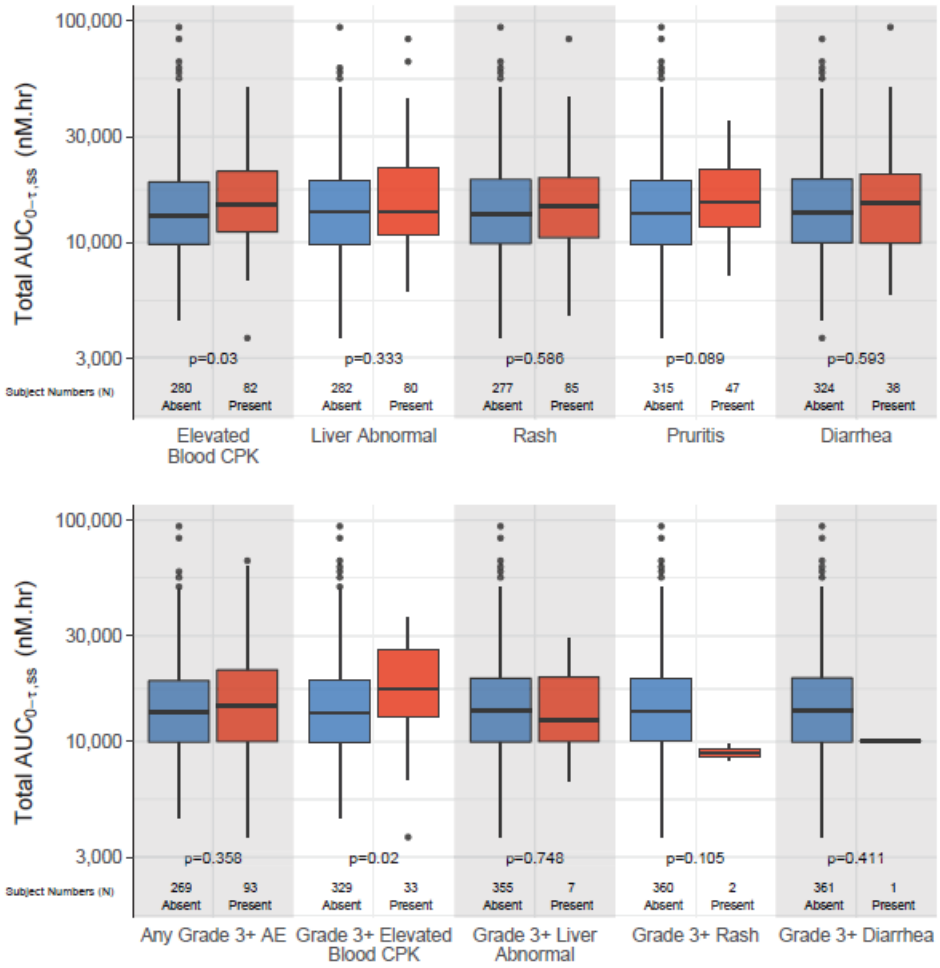
		Probability of Response		
Dose	Race	5th Percentile	50th Percentile	95th Percentile
55 mg QD	Asian	0.690	0.847	0.927
55 mg QD	Non-Asian	0.693	0.849	0.931
110 mg QD	Asian	0.481	0.698	0.842
110 mg QD	Non-Asian	0.484	0.701	0.850

Exposure-response (E-R) analysis for safety

A boxplot of AUCss,total by AEs of interest is presented in Figure 9.

The graphical analysis showed a relationship between increased exposure (only displayed for AUCss,total) and the risk of elevated blood CPK AEs.

Figure 9 Boxplots of $AUC_{ss,total}$ by AEs



The solid horizontal lines and box heights represent the median, and 25th to 75th percentiles, respectively. Dots are the outlier data (≥ 1.5*IQR). Number above each box specifies the number of subjects per group. P-value from Wilcoxon rank sum test.

When adjusted for significant baseline covariates, the final logistic regression E-R model for elevated blood CPK (any grade) failed to show a significant relationship between AUCss,total and the probability of an event (p-value = 0.192). Baseline ECOG score and baseline brain metastases were identified as significant covariate in the final model. Parameters for the final model are displayed in Table 29.

Table 29 Final Elevated Blood CPK (Any Grade) Logistic Regression Model

Parameter	Estimate (95% CI)	p value
Intercept	-3.744 (-8.333 – 0.846)	0.110
log $AUC_{ss,total}$	1.371 (0.853 – 2.202)	0.192
Baseline ECOG Score of 0 vs. 1/2	0.432 (0.237 – 0.786)	0.006
Baseline Brain Metastates (yes vs. no)	0.428 (0.243 – 0.755)	0.003

Intercept reported as log-odds, other parameters represented as odds ratios.

2.6.3. Discussion on clinical pharmacology

In Study HS-10296-108, LC-MS/MS was used for quantification of aumolertinib and metabolites HAS-719, M2, M511a, M440, and M30 plasma concentrations. All methods applied were validated.

The population PK model for aumolertinib and HAS-719 identified the following:

- Significant covariates were fed status on KTR, weight on CLmet/Fm, and subject population (healthy subjects versus subjects with NSCLC) on CLpar/F and CLmet/Fm.
- Non-significant covariates were weight on aumolertinib, ethnicity, sex, age, renal function (as measured by CLCR), markers of liver function (AST, ALT, ALB, TBIL, NCI-ODWG hepatic impairment category), tablet formulation (minor grade change) and concomitant drugs (CYP3A4 inhibitors, CYP3A4 inducers and proton pump inhibitors).

Effect of weight was investigated across 37-106 kg (95% CI 45-80) in patients and in healthy subjects at 60 kg. According to the Forest plots (Figure 3), weight had no effect on aumolertinib exposure in patients, but had large impact on HAS-719. In the Pop PK model, weight was included as a significant covariate of HAS-719 CL. Since HAS-719 is < 30% of total exposure, the effect of weight on HAS-719 is not considered clinically relevant.

For time dependency, considering the estimated elimination t1/2 of aumolertinib of 31 to 35 hours, steady-state conditions would be expected by Day 8 of dosing. The boxplot of aumolertinib trough concentrations (Figure 5) demonstrates no significant changes in aumolertinib trough concentrations between Cycle 1 Day 8 and Cycle 2 Day 1 of dosing, indicating no time dependency in the PK. Additionally, the scatterplot of trough HAS-719 concentrations shows a minor increase occurring between Cycle 1 Day 8 and Cycle 1 Day 15 (~ 15%). The latter finding is expected in consideration of the long t1/2 of HAS-719, with steady state not expected before Day 13. There was no appreciable difference between the mean HAS-719 trough concentrations on Cycle 1 Day 15 (100.3 ng/mL) and Cycle 2 Day 1 (99.7 ng/mL).

Absorption

In general, the pharmacokinetics of Aumolertinib and its main metabolite HAS-719 have been sufficiently described.

Four (4) healthy male subjects were enrolled in the mass-balance study HS-10296-105. After oral administration, 90.18% of the total dose was detected in urine and faeces, while 8.61% of aumolertinib was unchanged, thus it can be estimated that 81.57%, or 82%, of the dose was absorbed.

In fed state, the AUC of aumolertinib was increased by about 20%; and the Cmax of the metabolite HAS-719 was reduced by about 20%. This is not expected to have clinical impact.

Distribution

Volume of distribution (Vd/F) was 554 L after single dose of 110 mg (Study HS-10296-12-01). In the Pop PK model, Vc/F was estimated to be 875 L and Vp/F to 79.8 L for aumolertinib. The V/F for HAS-719 was estimated to 31 L in the Pop PK model. These values appear to be inconsistent with the results from the mass-balance study where a mean Vd/F was determined to 1267 L for aumolertinib and to 5965 L for HAS-719 (Study HS-10296-105, n=4). In conclusion, there is inconsistent results regarding the distribution of aumolertinib.

In vitro aumolertinib and HAS-719 are highly bound to human plasma proteins and bind to both albumin and AAG. The B/P ratio was close to 0.8 across 0.1-1 µM aumolertinib, independent of gender and subject population (HV/NSCLC patient). Aumolertinib and HAS-719 are highly bound to both plasma proteins, albumin and AAG, across 0.1 – 1 µM.

A low distribution of aumolertinib to whole blood cells was observed in the mass-balance study (study HS-10296-105). This stands in contrast to the blood/plasma ratio of aumolertinib in rats which is approximately 1.5, indicating that aumolertinib partitions to red blood cells.

Elimination

Excretion is mainly as metabolites in faeces, urinary excretion is a minor excretion pathway.

In plasma, aumolertinib accounts for 70%, after a single 110 mg dose to 4 healthy subjects in the mass balance study.

Measured CL/F was 13.57 L/h for aumolertinib after a single dose of 110 mg. Estimated CL/F values based on the population PK model of 17.4 L/h for aumolertinib and 45.8 L/h for HAS-719, respectively, also appear to be inconsistent with the results from the mass-balance study. The mean terminal half-lives of aumolertinib and HAS-719 were approximately 31 and 55 hours, respectively

The mass balance study indicated aumolertinib is primarily excreted in faeces (85%), while renal excretion is a minor elimination pathway (5.4%). The mean recovery of radioactivity in the mass-balance study was 90% and is considered acceptable.

Data on metabolites in samples of plasma, urine and faeces identified by LC-RAM/HRMS were provided and abundance was based on radioactivity collected in plasma (0-48 h), urine (0-96 h), and faeces (0-240 h). Only plasma concentration profiles of aumolertinib and HAS-719 was measured.

Several metabolites were detected in human plasma with radioactivity abundances collected within the first 48 hours equal to or higher than HAS-719. This is HS-10296-M30 (M30), M440 and HS-10296-M2 (M2). In clinical PK study HS-10296-108, 18 patients of European origin provided PK samples following single-dose and multiple-dose administration of 110 mg aumolertinib (21-day cycle). Exposure of aumolertinib and circulating metabolites HAS-719, M2, M511a, M440, and M30 were determined at C1D1 and C2D1 and showed HAS-719 and M2 exceeded 10% of parent exposure and of total exposure measured. M2 was detected in rats and dogs but the clinical exposure of M2 is not covered by non-clinical studies. In-vitro, M2 was pharmacological active against EGFR with an inhibitory activity in EGFR cell lines 11 to 37 times weaker than aumolertinib. In principle, further non-clinical safety testing should be conducted with M2. However, given the amount of data already generated in clinical trials in humans and the established safety profile in humans, no further non-clinical safety testing is requested.

The [^{14}C] study data from mass-balance study HS-10296-105 are comparable to the data from Study HS-10296-108 regarding the *qualitative* metabolite profile for aumolertinib.

The observed prolonged total-radioactivity profile compared to the profile of "cold" aumolertinib in Study HS-10296-105, could be explained by covalent binding of aumolertinib-derived material to plasma proteins (demonstrated in human serum albumin incubations with aumolertinib or HAS-719 by intact protein detection mass spectrometry). This explanation aligns with aumolertinib being highly bound to plasma proteins (≥99.55% in vitro).

Dose proportionality and time dependencies

Study HS-10296-1201 showed dose proportionality for C_{max} and AUC_{0-t} at single dose, but under-proportionality for $C_{ss,max}$ and AUC_{ss} (after repeated doses).

Target population

Subject population (NSCLC subjects versus healthy subjects) was identified as a significant covariate on aumolertinib PK. Aumolertinib clearance and volume of distribution are approximately 2-fold higher in healthy subjects compared to subjects with NSCLC with half-life remaining similar. However, the estimated increases in CL/F and Vc did not result in clinically meaningful differences (approximately 25%-29%) in aumolertinib exposure in healthy subjects and subjects with NSCLC.

Comparing C2D1 exposure (AUCtau and Cmax) in Chinese patients (Study HS-10296-12-01, n=237) to patients of European origin (Study HS-10296-108, n=18), slightly higher exposure was observed in Europeans. This is not considered clinically relevant. Thus, the safety and efficacy data collected in Chinese population may be translated to European population.

Special populations

Renal impairment

Data from the clinical studies indicate that renal clearance of aumolertinib is negligible. Consequently, it is not anticipated that aumolertinib PK will be altered by reduced renal function. No data are available in severe renal impairment. This is reflected in section 4.2 and 5.2 of the SmPC with a suggestion to exercise caution in patients with severe or end-stage renal impairment.

Hepatic impairment

The exposure of aumolertinib and HAS-719 was lower in subjects with moderate hepatic impairment in Study HS-10296-106 compared to the control group with normal liver function. Study EQ143-102 was a study in subjects with severe hepatic impairment (Child-Pugh Class C). Both total and protein-free (fu) aumolertinib and HAS-719 were measured. In this study subjects with severe hepatic impairment had notable lower total exposure than subjects with normal liver function, but the unbound exposure seemed comparable. The observed reduction in total aumolertinib exposure in subjects with moderate and severe hepatic impairment was explained by an increased fraction unbound (fu) due to reduced plasma protein binding in these subjects. Fu seemed independent of liver function and therefore no dose adjustments are required in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (see SmPC 4.2). Of note, in-vitro plasma protein binding of aumolertinib is non-linear and fu decreases with increasing drug concentration (Report EQR-R2057). Section 5.2 of the SmPC reflects that no clinically relevant changes in the exposure of unbound aumolertinib were observed.

Pharmacokinetic drug-drug interactions

In vitro: see section2.5.6. discussion on non-clinical aspects

In silico:

The submitted PBPK model is considered high regulatory impact since it was used to predict the drug-drug interaction between aumolertinib and moderate CYP3A4 inhibitors and inducers to support dose selection with concomitant use of moderate CYP3A4 modulators, and to predict the drug-drug interaction liability of aumolertinib as a perpetrator of P-gp and BCRP replacing a clinical study.

The simulated AUC∞ and Cmax ratios for aumolertinib with and without the co-administration of moderate CYP3A4 inhibitors were approximately 2.32 to 2.41- and 1.36 to 1.39-fold, respectively. The simulated AUC∞ and Cmax ratios for aumolertinib with and without the co-administration of moderate CYP3A4 inducer (efavirenz) were 0.35- and 0.68-fold, respectively.

Regarding the transporter inhibition, the analysis indicates that aumolertinib is likely to be a P-gp inhibitor in vivo, as the simulated GMRs of AUC∞ and Cmax for dabigatran (sensitive P-gp substrate) with and without co-administration of aumolertinib were between 1.2- and 2.1-fold, after accounting for the uncertainty in the in vitro Ki values. Aumolertinib is not likely to be a BCRP inhibitor in vivo, as the simulated GMRs of AUC∞ and Cmax for rosuvastatin (sensitive BCRP substrate) with and without co-administration of aumolertinib were < 1.3-fold under simulated steady-state conditions for aumolertinib.

Overall, the principles behind the PBPK model for aumolertinib and HAS-719 are considered acceptable. The results showed that, based on the in vitro Ki value, there is no DDI between

aumolertinib and rosuvastatin. However, under the worst-case scenario, i.e., with a 15-fold reduction in the in vitro estimated Ki value (0.33 µM), the results showed a potential inhibition of aumolertinib on rosuvastatin since the AUC and Cmax GMR are 1.34 and 1.61 respectively, which exceeded the 1.25 threshold. new in vitro study using HEK293-derived BCRP-membrane vesicles demonstrated an IC_{50} value of 1.35 µM, which is substantially lower than the value observed in Caco-2 cells (4.94 µM). This discrepancy suggests a higher potential for BCRP-mediated DDIs than previously estimated, meaning the risk of clinically relevant interactions cannot be excluded.

Additionally, the PBPK model simulations are deemed insufficiently robust to definitively rule out transporter-mediated inhibition. Given the uncertainty in predicting the clinical impact, a dedicated clinical DDI study is recommended to fully characterize the interaction potential between aumolertinib and BCRP substrates **(REC)**. In the absence of clinical data, a precautionary recommendation to avoid co-administration of aumolertinib with known sensitive BCRP substrates was included in section 4.5 of the SmPC. If such co-administration is unavoidable, close clinical monitoring for increased exposure or adverse effects of the BCRP substrate is recommended.

In vivo:

Based on simulations utilizing PBPK modelling to predict exposure to aumolertinib and HAS-719 in the presence of potent CYP3A4 inhibitors, as well as simulations using E-R modelling, the results suggest that reducing the aumolertinib dose from 110 mg to 55 mg when strong CYP3A4 inhibitors are used concurrently is appropriate. This conclusion is drawn from the finding that the GMR of AUC and Cmax for aumolertinib (110mg) alone compared to aumolertinib (55mg) with itraconazole, were both below 1.25. The dose reduction when co-administering with a potent CYP3A4 inhibitor was added in section 4.2 and 4.4 with cross-reference to section 4.5.

No dose adjustment is recommended in case of concomitant administration with a strong CYP3A4 inducer as a PBPK simulation conducted to assess an increase in aumolertinib dosage from 110 mg to 220 mg in the presence of strong CYP3A4 inducers indicated that such dose increase while concurrently using strong CYP3A4 inducers will lead to aumolertinib exposure levels lower than those observed with aumolertinib 110 mg alone, with no concomitant interacting medication. The geometric mean ratio (GMR) of the AUC and Cmax of aumolertinib (220 mg) in the presence of rifampicin, a potent CYP3A4 inducer, compared to aumolertinib (110 mg) alone, was largely <0.8. This suggests that such a combination may result in a reduced efficacy of aumolertinib. The co-administration with moderate or strong CYP3A4 inducers is not recommended in section 4.5 of the SmPC.

Based on an in vitro study aumolertinib is P-gp inhibitor. In a clinical drug-drug interaction study, aumolertinib increased the Cmax and AUC of fexofenadine (sensitive P-gp substrate) by 86% (90% CI 50.3-129.5%) and 67% (90% CI 46-91.6%), respectively. Caution should be used when administering aumolertinib with medicinal products that are sensitive P-gp substrates with narrow therapeutic window (e.g., digoxin, dabigatran) and it is recommended to closely monitor for signs of altered tolerability resulting from increased exposure to the concomitant drug during treatment with aumolertinib (see SmPC 4.5).

The results of the in vitro CYP450 TDI and induction assays have demonstrated that aumolertinib is both an inducer and an irreversible inhibitor of CYP3A4.

Considering the dual feature of aumolertinib, both a CYP3A4 time-dependant inhibitor and inducer, the experiences with drugs having the same profile have shown that the net effect with midazolam can differ with another substrate, notably having multiple enzyme pathways.

Based on the clinical DDI study with midazolam (CYP3A4 prob substrate), where aumolertinib decreased the exposure of midazolam (a sensitive CYP3A substrate) by approximately 27%,

aumolertinib is considered a weak inducer of CYP3A and may decrease concentrations of drugs that are CYP3A substrates.

Therefore, a statement was added in section 4.5 of the SmPC recommending to avoid concomitant use with sensitive CYP3A substrates for which small changes in exposure may lead to loss of efficacy (e.g., some hormonal contraceptives, certain oncology or anti-infective agents) or with CYP3A substrates with a narrow therapeutic index (e.g., tacrolimus, cyclosporine, sirolimus, fentanyl). If concomitant use cannot be avoided, monitor clinical response and consider dose adjustment of the CYP3A substrate, in accordance with its prescribing information.

A recommendation for women of childbearing potential to avoid pregnancy during treatment and for 4 weeks after discontinuation was added in section 4.6 of the SmPC. Considering the potential interaction with hormonal contraceptives, Patients using hormonal contraceptives (e.g., pills, patches, or rings) must switch to highly effective non-hormonal methods or add a e.g., condoms) during therapy and for 4 weeks afterward.

Pharmacodynamics

Aumolertinib is an EGFR TKI with an irreversible inhibition of mutant EGFR, including Ex19del and L858R, leading to the inhibition of cancer cell proliferation, and reduced inhibitory kinase activity against WT EGFR. The in vitro assays demonstrated a reduced potency of aumolertinib and its major metabolite HAS-719 against WT EGFR compared to gefitinib and afatinib with a higher IC_{50}. Aumolertinib showed a potent inhibition of the EGFR TKI-sensitizing Ex19del and L858R with IC_{50} of 0.88 nM and 1.50 nM, respectively; IC_{50} values were however slightly higher than those for gefitinib and afatinib.

In addition, aumolertinib displayed an inhibition of EGFR T790M resistance mutation. The in vitro assays' results showed a more potent inhibition of T790M/Del 19, and T790M/L858R mutations with aumolertinib compared to gefitinib and afatinib. HAS-719 also showed in vitro inhibition of T790M, T790M/Del 19, and T790M/L858R and WT EGFR kinase with a slightly less potent inhibitory activity than aumolertinib.

Exposure-response (E-R) analyses were performed for efficacy and safety based on data from subjects with NSCLC in the Phase 1/2 Study HS-10296-12-01. Based on the recommended 110 mg QD dose regimen, an inverse relationship was observed between total exposure (aumolertinib and HAS-719) and probability of response, with the highest exposure quartile resulting in the lowest probability of response. As for safety, no relationship between exposure to aumolertinib + HAS-719 and risk of AEs was demonstrated.

Regarding cardiac safety, the potential of aumolertinib to prolong QT interval was identified from the hERG study and dog study. The outcome of two model-based c-QTC analyses, showed that aumolertinib exhibits increasing QTc prolongation with dose and the effect is considered clinically relevant. At the therapeutic dose 110 mg, the mean model predicted ΔQTcF was <10 ms and the upper 90% CI 11.01 ms. A negative study as defined by the ICH E14 criteria is an upper one-sided 95% CI (equal to two-sided 90% CIs) of QTc prolongation effect <10 ms. A categorical QTc analysis of Study HS-10296-12-01, including data from all study parts, indicates that treatment with aumolertinib 110 mg may cause QTc prolongation. In the extension Part 3 where 244 subjects received aumolertinib 110 mg for 21-days, 90% experienced a ΔQTcF ≥10 ms. Part 3 data was omitted from the model-based analyses since the on-site ECG-data did not undergo central over-reading. Please refer to the Safety section for further information on this topic.

QTc prolongation leading to torsade de pointes and cardiac arrest is listed as an important identified risk in the RMP. The use of aumolertinib is contraindicated in patients with congenital long QT syndrome, familial history of sudden cardiac death or polymorphic ventricular arrhythmia or with a

QT/QTc interval > 500 msec, regardless of the correction method (see section 4.3 of the SmPC). An electrocardiogram (ECG) must be performed prior to treatment initiation, at least once during the first 3 weeks of therapy, and periodically thereafter as clinically indicated. QTc interval abnormalities should be managed promptly, related warnings and dose adaptations were included in section 4.2 and 4.4 of the SmPC.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of aumolertinib and main metabolite, HAS-719, have been adequately described. The CHMP recommended further investigation of drug-drug interactions to be conducted post approval.

2.6.5. Clinical efficacy

Table 30: Overview of Studies Contributing to the Efficacy and Safety Evaluation of Aumolertinib

Study ID	Phase	Study Design	Study Population	Treatment Regimen [a], Dose [a] and Duration	Number of Centres Location	Number of Subjects	Age and Sex	Study Status
Pivotal Studies in Subjects With NSCLC								
HS-10296-12-01	Phase 1/2	Open-label, multicenter study in 3 sequential parts: • Part 1 (Phase 1, dose escalation) • Part 2 (Phase 1, dose expansion in subjects with T790M mutation) • Part 3 (Phase 2, dose extension in subjects with	Subjects with locally advanced or metastatic NSCLC who have progressed after treatment with EGFR TKIs	Aumolertinib Part 1: 55, 110, 220, or 260 mg QD Part 2: 55, 110, or 220 mg QD Part 3: 110 mg QD Treatment in all 3 parts until disease progression (or other reason for discontinuing)	47 total: China 29; Taiwan 8; US 10	Total 364 subjects, including: • 26 in Part 1 (6 on 55 mg, 6 on 110 mg, 8 on 220 mg, 6 on 260 mg) • 94 in Part 2 (30 on 55 mg, 33 on 110 mg, 31 on 220 mg) • 244 in Part 3 (all	Part 1: Mean 59.5 (range 42 - 80) years 8 M, 18 F Part 2: Mean 61.0 (range 35 - 89) years 35 M, 59 F Part 3: Mean 60.8 (range	Study closeout initiated as of 25 March 2022 (primary analysis complete, using 05 January 2019 data cutoff; updated data cut-off date; 01 August 2021)

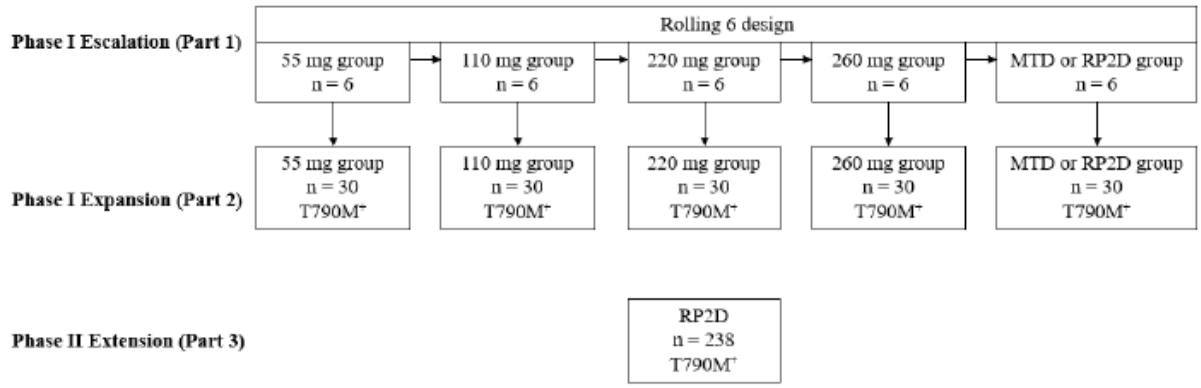
Study ID	Phase	Study Design	Study Population	Treatment Regimen [a], Dose [a] and Duration	Number of Centres Location	Number of Subjects	Age and Sex	Study Status
		T790M mutation)				received 110 mg)	27 - 87) years 102 M, 142 F	
HS-10296-03-01	Phase 3	Randomized, double-blind, controlled, multicenter study	Subjects with locally advanced or metastatic NSCLC with EGFR-sensitive mutations who have not received any systemic treatment	Aumolertinib 110 mg QD + gefitinib placebo tablets QD, versus Gefitinib 250 mg QD + aumolertinib placebo tablets QD Until progressive disease or other criteria for discontinuation	53 China	429: 214 aumolertinib versus 215 gefitinib (48 subjects randomized to gefitinib subsequently crossed over to aumolertinib following confirmed progression + a T790M mutation)	Mean 58.1 (range 32 - 78) years 80 M, 134 F	Ongoing (primary analysis complete, using 15 January 2021 data cutoff; updated data cutoff date: 06 August 2021)

2.6.5.1. Dose response study(ies)

Selection of the aumolertinib 110 mg QD dosing regimen for the pivotal studies was based on initial evaluations of data from the dose escalation, dose expansion, and dose extension parts of Study HS-10296-12-01 of aumolertinib doses (55, 110, 220 and 260 mg QD) in the second-line treatment setting.

Study HS-10296-12-01: Phase 1/2, open-label, multicenter, single-arm clinical study to evaluate the safety, tolerability, PK, and efficacy of oral QD administration of aumolertinib in subjects with locally advanced or metastatic NSCLC who have progressed after previous treatment with EGFR TKIs.

Figure 10 Study design of Study HS-10296-12-01



In Part 1, pre-screening for the T790M mutation was not required for subjects with an EGFR sensitive mutation. In Parts 2 and 3, subjects were required to be positive for the T790M mutation confirmed by a central laboratory before enrollment.
EGFR, epidermal growth factor receptor; RP2D, recommended Phase 2 dose; T790M, presence of a mutation in exon 20 of the EGFR gene, involving the substitution of threonine (T) with a methionine (M) at position 790; T790M+, T790M mutation-positive.

In Part 1, four doses were evaluated, 55, 110, 220, and 260 mg QD. Due to the increased frequency of adverse reactions in the high dose groups (220 and particularly the 260 mg QD group) and the favourable preliminary antitumor efficacy observed in the 55- and 110 mg dose groups (ORRs of 50% and 67.7%, respectively), the SRC decided to halt dose escalation at 260 mg QD without formally establishing the MTD. DLT were reported at 220 mg (n=1) and 260 mg (n=1). Thus, the 260 mg dose was not pursued further and aumolertinib doses of 55 mg, 110 mg, and 220 mg were selected for further evaluation in the dose expansion part of the study for identification of the RP2D.

In Part 2, the 55 and 110 mg QD doses of aumolertinib showed a high tumour treatment response (ORR of 60.0% and 54.5%, respectively) in the target population. A trend in higher DCR was observed in the 110 mg QD dose group as compared to the 55 mg QD dose group (97.0% versus 83.3%). Therefore, 110 mg QD was selected for evaluation in the dose extension portion of the study. Higher doses were not pursued because efficacy was consistently high with the 110 mg QD dose in the dose escalation and dose expansion portions of the study (ORRs of 66.7% and 54.5%, respectively), and higher exposures associated with doses of 220 and 260 mg did not achieve additional clinical benefit. Furthermore, a dose-dependent increase in Grade ≥ 3 AEs and CPK elevation was observed, with a higher risk at 220 and 260 mg QD doses. The incidence of serious adverse reactions and AEs leading to dose adjustment or study withdrawal occurred primarily at the 220 mg dose.

2.6.5.2. Main studies

There are **2 pivotal studies** for the currently sought indication application; 1 for 1st line treatment and 1 for patients with T790M mutation (predominantly resistance mutation to 1st and 2nd generation EGFR TKI, 2nd line).

Data cuts for the pivotal studies presented

Study HS-10296-03-01:

- Primary analysis data cutoff: **15 January 2021**

- Data cutoff for updated analyses (including CNS efficacy analyses): **06 August 2021**

- Data cutoff for updated OS analyses: **30 September 2022**

Study HS-10296-03-01 is a Phase 3, randomized, controlled, double-blind, multicenter study conducted in **China only**. The study was designed to evaluate the safety and efficacy of aumolertinib versus gefitinib as first line treatment in subjects with locally advanced or metastatic NSCLC harbouring EGFR mutations. The primary analysis is complete, with long-term safety and OS data collection continuing.

The **primary efficacy endpoint** was **PFS** as assessed by the Investigator.

Study HS-10296-12-01:

- Primary analysis data cutoff: **05 January 2019**

- Data cutoff for updated analyses (including CNS efficacy analyses): **01 August 2021**

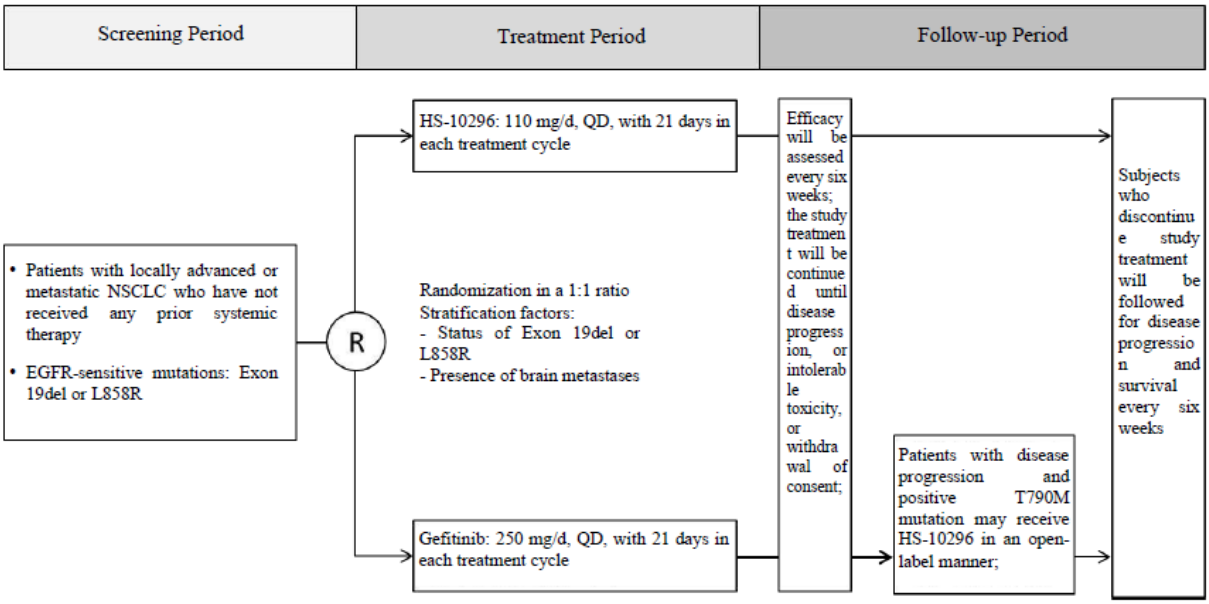
Study HS-10296-12-01 is a Phase 1/2, open-label, multicenter study conducted in **China, Taiwan, and the US** (however, only 7 patients were included in the US, neither of them in part 3). The study was designed to examine the efficacy and safety of aumolertinib in patients with NSCLC and locally advanced or metastatic disease who progressed following prior therapy with EGFR TKIs. The primary study analysis is complete. As of 25 March 2022, all study sites had been provided with an end-of-trial notification; all sites have completed final study visits.

The **primary efficacy endpoint** - **confirmed ORR** evaluated by ICR—was analysed in the pivotal Phase 2 portion (Part 3) of the study.

2.6.5.3. HS-10296-03-01 - AENEAS

Study HS-10296-03-01 is a Randomized, Controlled, Double-Blind, Multi-center, Phase III Study to Assess the Efficacy and Safety of HS-10296 Versus Gefitinib as First-Line Treatment in Patients With EGFR Mutation [Positive], Locally Advanced or Metastatic NSCLC.

Figure 11 : HS-10296-03-01 study design



Study initiation date: 30 November 2018.

Date **last patient completed**: N/A (**ongoing** as of 15 January 2021 data cutoff date).

Recruitment: 54 centres in China

One treatment cycle is 21 days of continuous study drug intake.

Subjects continued treatment until disease progression, unacceptable risk to the patient's health or voluntary withdrawal.

Subjects were followed-up every 6 weeks to obtain data on tumour status, anticancer treatments, and survival.

Imaging data consisted of CT and/or MRI scans, electronic photographs of lesions, and any other relevant imaging data, all of which were anonymized, digitized, and stored using an electronic image display system.

Subjects who discontinued study treatment due to other reasons than disease progression were to continue RECIST v1.1 assessment until disease progression.

Open-label aumolertinib crossover treatment: Subjects who were randomized to the gefitinib group and exhibited disease progression during blinded treatment with gefitinib were eligible to receive crossover open-label treatment with aumolertinib (110 mg po QD), provided that the following conditions were met:

- Disease progression according to RECIST v1.1 under blinded treatment with gefitinib

- Signing of ICF for crossover open-label aumolertinib treatment

- T790M mutation confirmed by the central laboratory (tumour biopsy collected after disease progression)

- No other anticancer treatment planned apart from aumolertinib

Methods

Study Participants

Main inclusion criteria

- Aged ≥ 18 years.
- Histologically or cytologically confirmed locally advanced or metastatic NSCLC (including patients with relapsed disease after prior surgical treatment or patients with newly diagnosed disease at stage IIIB/IV. The disease stage was determined according to TNM staging criteria).
- Patients who have not received any systemic therapy since they were diagnosed with locally advanced or metastatic NSCLC. Patients who have received local treatment may participate in the study if lesions within the local treatment area are non-target lesions.
- Tumour tissue samples or blood samples collected after the diagnosis of locally advanced or metastatic NSCLC were confirmed to harbour EGFR-sensitive mutations (including exon 19 deletion or L858R mutation, either alone or in combination with other EGFR site mutations) as tested by the central laboratory. It was recommended to submit tumour tissue samples if tumour tissue is accessible; blood samples should be submitted if tumour tissue was not accessible or tissue biopsy was unacceptable to the patient.
- Patients with an ECOG PS score of 0 or 1, with no worsening in the previous 2 weeks, and with a minimum expected survival of 12 weeks.
- Patients who have at least 1 tumour lesion that had not received prior local treatment such as irradiation, or had not been performed with tissue biopsy at screening and can be accurately measured at baseline, with the longest diameter ≥ 10 mm at baseline (short axis ≥ 15 mm will be required if the lesions are lymph nodes). The selected measuring methods should be suitable for accurate and repeated measurements, such as computerized tomography (CT) or magnetic resonance scan (MRI). If there was only 1 measurable lesion that has not received prior local treatment such as irradiation, it was acceptable as a target lesion, and a baseline evaluation of the tumour lesion was to be performed at least 14 days after diagnostic biopsy.

Main exclusion criteria

- Patients who had received any of the following treatments:
    - Prior treatment with any EGFR TKI;
    - Have undergone any major surgery within 4 weeks prior to the first dose of study drug;
    - More than 30% bone marrow have received irradiation or the patient have received extensive radiotherapy within 4 weeks prior to the first dose of study drug;
    - Any use of potent CYP3A4 inhibitors, inducers or drugs with a narrow therapeutic window of sensitive substrates of CYP3A4 within 7 days prior to the first dose of the investigational product.
- Patients with any complications or other malignancies requiring treatment or major surgery within 2 years after the first dose of study treatment.

- Patients with unresolved > grade 1 toxicities from prior therapy (e.g., adjuvant chemotherapy) at the start of study treatment, except those who had alopecia and grade 2 neurotoxicity due to prior chemotherapy.
- Patients with spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 2 weeks prior to the first dose of study treatment.
- Patients who had any serious or poorly controlled systemic diseases, such as poorly controlled hypertension, active bleeding-prone constitution, or active infection, as judged by the investigator. Screening for chronic diseases was not required.
- Patients who had any of the following cardiac examination results:
    - QT interval is corrected (QTcF) by the Fridericia formula and the mean corrected QT interval (QTc) is > 470 msec from 3 ECGs at rest;
    - Results of ECGs at rest reveal clinically significant abnormalities in rhythm, conduction or ECG morphology (e.g., complete left bundle branch block, third degree atrioventricular block, second-degree atrioventricular block, and PR interval > 250 msec);
    - Any factors that may increase the risk of QTc prolongation or arrhythmic events, such as heart failure, hypokalaemia, congenital long QT syndrome, a family history of long QT syndrome, or unexplained sudden death in an immediate family member under 40 years of age or any concomitant medications that may prolong the QT interval;
    - LVEF ≤ 40%。
- Patients who had history of interstitial lung disease, history of drug-induced interstitial lung disease, history of radiation pneumonitis requiring steroid treatment, or any evidence of clinically active interstitial lung disease.
- Patients who had inadequate bone marrow reserve or organ function as demonstrated by the following laboratory test limits:
    - Absolute neutrophil count < 1.5 × 109/L;
    - Platelet count < 100 × 109/L;
    - Haemoglobin < 90 g/L (< 9 g/dL);
    - Alanine aminotransferase > 2.5 × the upper limit of normal (ULN) if there is no definite liver metastasis; alanine aminotransferase > 5 × ULN if liver metastases present;
    - Aspartate aminotransferase > 2.5 × ULN if there is no definite liver metastasis; aspartate aminotransferase > 5 × ULN if liver metastases present;
    - Total bilirubin > 1.5 × ULN if there are no definite liver metastases; total bilirubin > 3 × ULN if Gilbert's syndrome (unbound hyperbilirubinemia) or liver metastases present;
    - Creatinine > 1.5 × ULN and creatinine clearance < 50 mL/min (calculated by Cockcroft-Gault equation); confirmation of creatinine clearance is required only if creatinine is > 1.5 × ULN.
- With any serious or uncontrolled ocular lesions, which may increase the safety risk to the patients as judged by the physician.

Treatments

Table 31: Study Interventions

	Aumolertinib Arm	Gefitinib Arm
Dose	110 mg/day	250 mg/day
Drug	Aumolertinib active drug (55 mg/tablet, 2 tablets); gefitinib dummy tablets (1 tablet)	Gefitinib active drug (250 mg/tablet, 1 tablet); aumolertinib dummy tablets (2 tablets)
Method of Administration	QD, PO	QD, PO

PO, orally; QD, once daily.

During the 28-day follow-up period after permanent discontinuation of aumolertinib, all concomitant medications, including anti-tumour therapy, will be recorded in the eCRF, and only anti-tumour therapy will be recorded thereafter.

Objectives

Primary Objective

• To compare PFS in subjects with locally advanced or metastatic NSCLC with confirmed EGFR-sensitizing mutations treated with aumolertinib or gefitinib as first-line treatment.

Secondary Objectives

• To compare the antitumor efficacy of aumolertinib versus gefitinib in terms of OS, ORR, DoR, DCR, and DepOR.

• To compare the safety of aumolertinib and gefitinib treatment.

Outcomes/endpoints

Table 32 Definitions of Primary and Secondary Efficacy Endpoints in Study HS-10296-03-01

Efficacy Endpoint	Definition
Primary	
PFS	Tumour response based on RECIST v1.1 (including CR, PR, SD, PD). Defined as time from start of randomization until objective tumour progression (as evaluated by the Investigator) or death from any cause (whichever was first).
Secondary	
ORR	Percentage of subjects who had at least 1 CR or PR before progression.
DCR	Proportion of subjects with a best overall response of CR, PR, or SD. SD was defined as an interval of at least 35 days prior to disease progression, following the evaluation of SD.
DoR	The interval between the first date on which response was achieved and the date of disease progression or death.

DepOR	The change in the sum of the length of the longest diameter of the target lesions, as defined by RECIST v1.1. The percentage change in tumour size of measurable lesions at baseline was calculated based on the percentage changes in the total diameters of target lesions compared to those measured at baseline. The optimal value of DepOR was generated from all efficacy evaluations before progression or before the start of subsequent antitumor treatment.
OS	The time from start of randomization to the date of death from any cause.

CR = complete response; CSR = clinical study report; DCR = disease control rate; DepOR = depth of response; DoR = duration of response; OS = overall survival; PD = progressive disease; PFS = progression-free

Tumour response, according to RECIST v1.1, was used for the determination of the primary endpoint (i.e., PFS based on Investigator-assessment) and secondary endpoints (i.e., ORR, DCR, DoR, DepOR, and OS). All subjects underwent tumour imaging during screening/at baseline. During the treatment period, tumour assessments (according to RECIST v1.1) were performed every 2 cycles (i.e., every 6 weeks) up to treatment cycle 21. From Cycle 23 onwards, these assessments were performed every 12 weeks. Imaging data were assessed by an ICR consisting of 3 qualified imaging experts and consisted of CT and/or MRI scans, electronic photographs of lesions, and any other relevant imaging data, all of which were anonymized, digitized, and stored using an electronic image display system.

Sample size

In this randomized, active-controlled, double-blind, Phase 3 superiority trial, the following assumptions were made for determination of sample size:

- The PFS HR is 0.67 for aumolertinib versus gefitinib,
- The data follow an exponential distribution,
- The statistical model satisfies the proportional hazards assumption,
- Median PFS improves from 10 months to 15 months,
- The enrolment ratio is 1:1,
- The enrolment time is 8 months,
- The longest observation time after the enrolment of the first subject is 23 months.
- α is 0.05 (two-sided),
- Statistical power is 90%.

Based on these assumptions, 410 subjects needed to be enrolled to detect a difference between aumolertinib and gefitinib at a 2-sided significance level of 0.05 with 90% power.

The protocol and statistical analysis plan describe a targeted number of events of 262 events.

Randomisation and blinding (masking)

Subjects were stratified according to EGFR mutation status (exon 19 deletion versus L858R) and brain metastasis (present versus absent). Randomization was conducted in a 1:1 ratio to aumolertinib (110 mg QD) plus active control or gefitinib (250 mg QD) plus active control.

From the start of randomization until disease progression as assessed by the investigator per RECIST 1.1, the information of the actual treatments was to remain blinded to the subjects, the investigator, data analysts, the Sponsor, and all medical personnel involved in the treatment or clinical assessments.

Statistical methods

Analysis populations

The FAS included all subjects who were enrolled, randomized, and received at least 1 dose of study treatment.

The PPS (a subset of the FAS), included all subjects who satisfied the trial protocol entry criteria, had good compliance, and did not have serious protocol deviations that significantly affected the efficacy evaluation.

Multiplicity adjustment procedure

The log-rank primary test was a two-tailed test with a level of significance of 0.05. There was no multiplicity adjustment procedure for type I error control of secondary endpoints.

Primary analysis

The primary efficacy endpoint of this study was PFS as evaluated by the investigator. The primary analysis was based on the FAS.

Table 33: Rules for determining the date of progression when there is disease progression

	Description of situation	Outcome (occurrence of event or censoring)	Date of occurrence of PFS event or end date
Progression confirmed during treatment	New lesions	Progression	Date of imaging examination during which new lesions were first found (if the criterion for progression is new lesions)
	Non-target lesions	Progression	Date of last imaging examination during which progression of non-target lesions was first found
	Target lesions	Progression	Date of last imaging examination during which progression of target lesions was first confirmed
When two or more are present, the corresponding dates are determined based on the above principles and compared. Finally, the earliest examination date is taken as the date of disease progression			

Table 34: Main and Secondary Censoring Rules for the Analysis of PFS in Study HS-10296-03-01

Situation	Time	Outcome
Main Censoring Rules		
No baseline [a] or post-baseline imaging evaluation results	Date of randomization	Censored
No progression or death before data cutoff	Date of the last valid imaging examination before data cutoff	Censored
Treatment terminated or new systemic tumour therapy started before non-imaging disease progression	Date of the last valid imaging examination before the termination of treatment or the start of new systemic antitumor therapy	Censored
Disease progression or death before data cutoff (including occurrence during a missing visit or unplanned visit)	Examination date of first imaging disease progression or date of death	Progression or death
Progression or death occurred before data cutoff but two or more consecutive visits are missing or evaluation could not be performed before progression or death	Date of last valid imaging examination before progression or death	Censored
Secondary Censoring Rules		
No baseline [a] or post-baseline imaging evaluation results	Date of randomization	Censored
No progression before data cutoff	Date of the last valid imaging examination before data cutoff	Censored
Progression or death before data cutoff	Examination date of first imaging disease progression or date of death	Progression or death

[a] "No baseline" was defined as no baseline examination records, or missing baseline target lesion examinations.
CSR = clinical study report; PFS = progression-free survival.

The log-rank test stratified by EGFR mutation type and brain metastasis status was used to compare the PFS distributions of the HS-10296 group and the gefitinib group to determine whether there are statistical differences. This test is a two-tailed test with a level of significance of 0.05. The results were given as test p values.

The stratified Cox proportional hazards model was used to estimate the PFS hazard ratio (HR) of the two treatment groups and the 95% confidence intervals corresponding to the estimates were given.

Sensitivity analyses

The following sensitivity analyses were performed on the primary efficacy endpoint:

Table 35: Prespecified Sensitivity Analyses Performed on PFS in Study HS-10296-03-01

Analysis	Type
Sensitivity Analysis 1	Based on the results as evaluated by the Investigator, the main event censoring rules were used to analyse the PPS.
Sensitivity Analysis 2	Based on the results of blind evaluation by the ICR, the main event censoring rules were used for analysis in the FAS.

Analysis	Type
Sensitivity Analysis 3	Based on the results as evaluated by the Investigator, the secondary event censoring rules were used for analysis in the FAS. These censoring rules included events (progression or death) after the end of treatment or subsequent anticancer therapy.
Sensitivity Analysis 4	Based on the results as evaluated by the Investigator, considering the presence of primary resistance to EGFR TKIs in subjects with NSCLC and sensitive EGFR mutations, the early progression data may not have satisfied the statistical assumptions of proportional hazards. The main event censoring rules were adopted to analyse the data of subjects with primary drug resistance removed from the primary efficacy endpoint (progression within 3 months) in the FAS.
Sensitivity Analysis 5	Based on the results as evaluated by the Investigator and using the main event censoring rules, subjects with evaluation results of "NE" before disease progression because of the COVID-19 epidemic in the primary efficacy endpoint evaluation were censored to the date on which the evaluation result was "NE" before an event occurred for analysis in the FAS.
Sensitivity Analysis 6	Based on the results as evaluated by the Investigator, considering that the evaluation cycle was changed 15 months after subject enrolment from once every 2 cycles (6 weeks) to once every 4 cycles (12 weeks), analysis was performed in the FAS after using the main event censoring rules to subtract 6 weeks (42 days) from the primary efficacy endpoints of subjects with disease progression after 15 months.

CSR = clinical study report; COVID-19 = coronavirus disease 2019; EGFR = epidermal growth factor receptor; FAS = Full Analysis Set; ICR = independent central review; NSCLC = non-small cell lung cancer; PPS = Per Protocol Set; TKI = tyrosine kinase inhibitor.

Subgroup analyses

Table 36: Subgroups for PFS analysis

Subgroup	Definition
Sex	• Male • Female
Age grouping	• <65 years old • ≥ 65 years old
Baseline brain metastasis status	• Present • None
History of smoking	• Yes • None
EGFR gene mutation type	• Ex19del • L858R
Baseline ECOG PS score	• 0 • 1

Secondary analyses

DoR was defined as the time from the first date on which response is met to the date of disease progression or death from other causes. The response termination date was consistent with the date used for the PFS endpoint. The start date of response time was defined as the most recent date of the first visit that meets the PR or CR criteria. If a subject did not progress after response, the duration of response would be the PFS cut-off time.

As for PFS, DoR and OS were summarized using the Kaplan-Meier method. The log-rank test stratified by EGFR mutation type and brain metastasis status was used for comparing survival time distribution of the aumolertinib and gefitinib groups to determine statistical differences.

The stratified Cox proportional hazards model was used to estimate the OS HR and corresponding 95% CIs of the 2 treatment groups.

For ORR and DCR, the point estimate and 95% Clopper-Pearson CI of each treatment group was estimated. A logistic regression model stratified by EGFR mutation and brain metastasis status was used to compare the proportion of the 2 treatment groups.

For DepOR, the best percentage of tumour response was summarized by treatment group. An ANCOVA model was used to compare the best percentage of tumour response between the 2 treatment groups. Covariates included EGFR mutation type, brain metastasis status, the sum of the diameters of all evaluable target lesions at baseline, and the time interval from the baseline scan date to the date of randomization (days). Waterfall plots with the best percentage of tumour response by treatment group were provided.

Changes to statistical methods and planned analyses

A change in sample size was implemented in version 2 (15 May 2019) of the study protocol, as compared to version 1 (6 August 2018). The total sample size was increased from 350 patients

providing 191 PFS events (version 1) to 410 patients providing 262 events. The rationale given by the Applicant is to increase the power for the primary PFS analysis, from 80% to 90%.

Additional cut-off date

The primary study analysis used a data cutoff date of 15 January 2021.

An updated cut-off date of 6 August 201 led to an addendum CSR, with updated efficacy and safety summaries, as well as post-hoc analyses as described below.

Post-hoc CNS analyses

A post hoc analysis of CNS efficacy based on ICR assessment was performed to assess the CNS efficacy of aumolertinib versus gefitinib in a subset of subjects with baseline brain metastases. This analysis, which was based on the updated data cut-off date of 06 August 2021, was not pre-specified in the study SAP.

The following analysis sets were defined for the post hoc CNS efficacy analysis:

- The cFAS (N = 106), which consisted of all randomized subjects in the FAS who had at least 1 CNS lesion (measurable or immeasurable) identified on their screening/baseline scan that was sent for independent assessment and confirmed by IRC.
- The cEFR (N = 60), a subset of subjects in the cFAS who had at least 1 measurable CNS lesion at baseline identified and confirmed by IRC.

CNS efficacy was based on the data from CNS scans assessed by ICR per RECIST v1.1. CNS efficacy endpoints including PFS, ORR, and DoR followed the same definitions as described in SAP version 1.1, but were based on disease assessment of the CNS scans. The response data per overall RECIST v1.1 assessment was not considered in the CNS efficacy analysis.

Additional post-hoc analyses

The following efficacy analyses were also performed post hoc for Study HS-10296-03-01, using a data cutoff date of 06 August 2021:

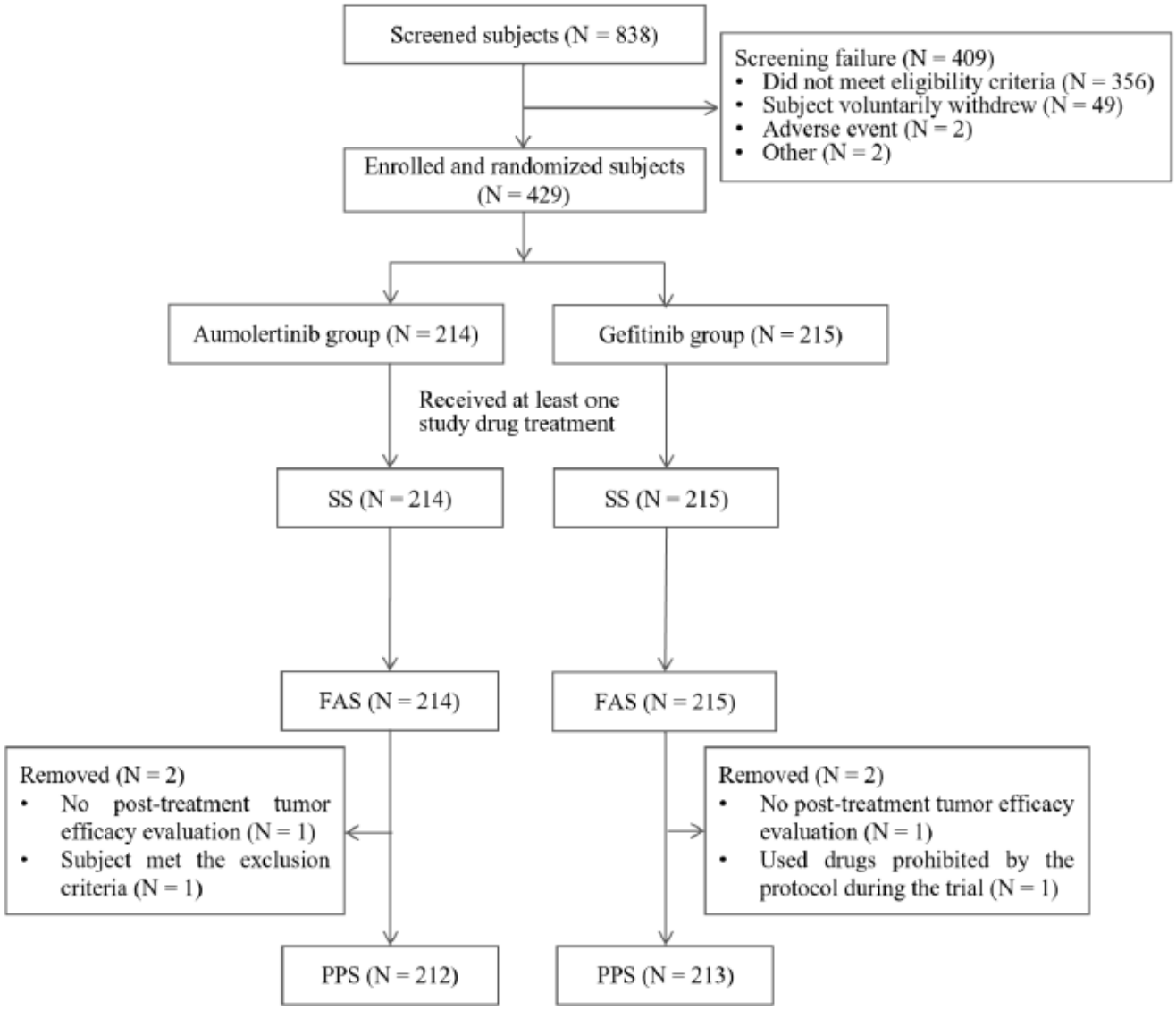
- PFS2, defined as the time from randomization to the first disease progression event subsequent to that used for the primary PFS analysis, or date of death from any cause, during the first subsequent anticancer therapy (including crossover treatment)
- TFST, defined as the time from randomization to the start date of the first subsequent anticancer therapy (including crossover treatment) or the date of death from any cause, whichever occurred first
- Inverse Probability of Censoring Weighting (IPCW), 2-stage Accelerated Failure Time (AFT), and Rank Preserving Structural Failure Time (RPSFT) to account for subjects who crossed over to aumolertinib treatment

An alternative sensitivity analysis of PFS, conducted for the updated study analysis (06 August 2021 data cutoff date) used Restricted Mean Survival Time (RMST).

Results

Participant flow

Figure 12 Disposition of Subjects (DCO: 15 Jan 2021)



FAS, Full Analysis Set; PPS, Per Protocol Set; SS, Safety Set.

Table 37: Disposition of Subjects (Full Analysis Set)

	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)	Total (N = 429) n (%)
Subjects randomized	214	215	429
Subjects who received at least one dose of randomized study treatment	214 (100.0)	215 (100.0)	429 (100.0)
Subjects still on randomized study treatment at data cutoff[a]	93 (43.5)	34 (15.8)	127 (29.6)
Subjects who had discontinued the study treatment at data cutoff	121 (56.5)	181 (84.2)	302 (70.4)
Imaging progression	73 (34.1)	114 (53.0)	187 (43.6)
Progression after compassionate treatment	21 (9.8)	36 (16.7)	57 (13.3)
Voluntary withdrawal by the subject	13 (6.1)	15 (7.0)	28 (6.5)
Adverse event	10 (4.7)	13 (6.0)	23 (5.4)
Decision by the Investigator	2 (0.9)	2 (0.9)	4 (0.9)
Others	2 (0.9)	1 (0.5)	3 (0.7)
Subjects ongoing in the study at data cutoff	152 (71.0)	139 (64.7)	291 (67.8)
Subjects who had discontinued from the study at data cutoff	62 (29.0)	76 (35.3)	138 (32.2)
Death	54 (25.2)	69 (32.1)	123 (28.7)
Withdrawal of informed consent form	4 (1.9)	4 (1.9)	8 (1.9)
Subject lost to follow-up	4 (1.9)	3 (1.4)	7 (1.6)
Subjects who had received crossover treatment at least once	--	41 (19.1)	41 (9.6)
Subjects receiving crossover treatment before the data cutoff	--	41 (19.1)	41 (9.6)
Treatment termination	--	20 (9.3)	20 (4.7)
Imaging progression	--	15 (7.0)	15 (3.5)
Decision by the Investigator	--	2 (0.9)	2 (0.5)
Others	--	2 (0.9)	2 (0.5)
Voluntary withdrawal by the subject	--	1 (0.5)	1 (0.2)

[a] The category of still receiving treatment before the data cutoff includes subjects continuing to receive treatment after objective disease progression (ie, compassionate treatment).
Data cutoff date was 15 January 2021.

Recruitment

First patient enrolled: 30 November 2018

Primary analysis data cutoff: 15 January 2021

Updated and additional analyses (new analyses of efficacy—including post hoc analyses of CNS efficacy performed in subjects with brain metastases—and safety) data cutoff: 06 August 2021

As of DCO of 15 Jan 2021, the median follow-up time in the aumolertinib arm was **20.50 months** (95% CI: 18.00 – 20.63 months) while that of the gefitinib arm was **20.70 months** (95% CI: 19.32 – 20.76 months)

This study was conducted at 54 centres in China.

Conduct of the study

Protocol amendments

The first version of the Protocol was Version 1 (dated 06 August 2018). It was amended 2 times (Version 2 dated 15 May 2019 and Version 3 dated 10 Dec 2019).

The main changes were the sample size with an increase from 350 patients providing 191 PFS events to 410 patients providing 262 events (V1 to V2), addition of optional collection of blood samples for genetic testing (V1 to V2), tumour assessment per RECIST 1.1criteria is required prior to crossover treatment, and must be performed rather than recommended (V1 to V2), addition of two new criteria to be met for receiving the open-label HS-10296 (V1 to V2), treatment the response assessment procedure by RECIST 1.1 changed from every 6 weeks to every 12 weeks after Month 15 after the condition tend to be stabilized (V2 to V3), requirements redefined for dose modification: after dose reduction, it cannot be adjusted back to the higher dose level (V2 to V3).

Based on the clinical study report (CSR), the definition of OS was changed from time between first study drug intake and death from any cause to time between randomization and death from any cause.

Table 38 Key Changes to Study from Protocol Version 01 to Version 02

Category Section	**Version 01 (Dated 06 Aug 2018[a])**	**Version 02 (Dated 15 May 2019[b])**	**Reason for Amendment**
Sample Size 2.0 Number of Subjects; 6.1 Study Design	The study plans to enroll 350 subjects	The study plans to enroll 410 subjects	In order to improve the robustness of clinical trial results, the statistical power was increased from 80% to 90% to allow more events to be observed and more subjects to be treated.
Sample Size 2.0 Sample Size Calculation; 5.3 Sample Size	The enrollment time is 6 months and the maximum observation period after the first subject is enrolled is 21 months. When α is 0.05 on both sides and the power is 80%, the statistical difference between the groups can be detected through 191 events, an enrollment of about 350 subjects is required.	The enrollment time is 8 months and the maximum observation period after the first subject is enrolled is 23 months. When α is 0.05 on both sides and the power is 90%, the statistical difference between the groups can be detected through 262 events, an enrollment of about 410 subjects is required.	

Category Section	Version 01 (Dated 06 Aug 2018[a])	Version 02 (Dated 15 May 2019[b])	Reason for Amendment
Exclusion Criteria 7.2 Exclusion Criterion 7b	The resting ECG indicates the presence of abnormalities in various clinically rhythms, conduction, or ECG morphology.	The resting ECG indicates the presence of abnormalities in various clinically important rhythms, conduction, or ECG morphology.	ECG criteria was changed to specify clinically important rhythm abnormalities as an exclusion criteria, not any rhythm abnormality.
Study Management and Monitoring 11.5 Study Management and Monitoring	The establishment of Independent Data Management Committee (IDMC).	Section deleted	Cumulative safety data showed a good safety profile and no unexpected adverse reactions. IB was updated. Sponsor determined that an IDMC was no longer necessary and the Investigator would manage and monitor subjects.

Note: New text is denoted by underline.

[a] Date of adoption: 06 Aug 2018.

[b] Date of adoption: 15 May 2019.

ECG = electrocardiogram; IDMC = Independent Data Management Committee.

Table 39: Key Changes from Protocol Version 02 to Version 03

Category Section	Version 02[a] (dated 15 May 2019)	Version 03[b] (dated 10 Dec 2019)	Reason for Amendment
Assessment Cycle 6.1 Study Design	Treatment Period (Updated Assessment Process): The continuous dosing of 21 days is a treatment cycle. Efficacy assessment is performed according to RECIST 1.1 criteria every 6 weeks after the start of treatment.	Treatment Period (Updated Assessment Process): The continuous dosing of 21 days is a treatment cycle. Efficacy assessment is performed according to RECIST 1.1 criteria every 6 weeks (once every 2 cycles until C21; the first 15 months) or 12 weeks (once every 4 cycles, starting from C23; after the 15th month) after the start of treatment.	After 15 months on study, the scans were collected every 12 weeks. This was done to minimize cumulative radiation exposure for subjects. After 22 cycles, it was felt patients were likely stable and per standard of care scan intervals could be spaced out.
	Follow-up Period: Subjects who have not progressed when the treatment is terminated will continue to be followed up once every 6 weeks.	Follow-up Period: Subjects who have not progressed when the treatment is terminated will continue to be followed up once every 6 weeks (C1-C21) or 12 weeks (C23 and after).	

Category Section	Version 02[a] (dated 15 May 2019)	Version 03[b] (dated 10 Dec 2019)	Reason for Amendment
Treatment Beyond Progression 6.1 Study Design	Treatment Period: As long as the Investigator judges that the subject can continue to benefit from the treatment, even if the subject meets disease progression as defined in RECIST 1.1, the subject can still continue to receive the treatment.	Treatment Period: As long as the Investigator judges that the subject can continue to benefit from the treatment, even if the subject meets disease progression as defined in RECIST 1.1, the subject can still continue to receive the treatment. It is recommended to make a judgment based on tumour treatment response in a blind state; according to current clinical practice, it is difficult to judge blindly whether the continued treatment will provide benefit, so the judgment can be made after unblinding; once the treatment is judged to have no clinical benefit and terminated, the treatment cannot be restarted.	This change was made to minimize potential for bias in the decision for subjects to continue on treatment.
Treatment Beyond Progression 9.2.2.6 Survival Follow-up	Not Applicable	If progression follow-up for cross-treatment is not completed according to the study procedures, and the date of disease progression is missing, the dates of documented refusal to progression follow-up for crossover treatment/acceptance of survival follow-up will be used as the starting point.	To refine the start time of the cross-treatment survival follow-up.

Note: New text is denoted by underline.

[a] Date of adoption: 15 May 2019.

[b] Date of adoption: 11 Dec 2019.

Cx = Cycle x; ECOG PS = Eastern Cooperative Oncology Group Performance Status; RECIST = Response Evaluation Criteria in Solid Tumors.

Protocol deviations

Of the 429 subjects, 144 (33.6%) subjects had a total of 186 major protocol deviations, including 79 (36.9%) subjects in the aumolertinib arm and 65 (30.2%) in the gefitinib arm. Amongst these protocol deviations are deviations caused by the COVID-19 pandemic which were mostly related to missing study visit procedures. No subjects were excluded from the primary analysis due to protocol deviations.

Table 40: Summary of All Major Protocol Deviations

Classification	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
At least one serious protocol deviation occurred	79 (36.9)	65 (30.2)
Visit plan	49 (22.9)	39 (18.1)
Overall missing visits during medication	47 (22.0)	36 (16.7)
All missing subsequent follow-up/survival visit information (excluding withdrawal of informed consent, death, termination of the study, and loss to follow-up)	3 (1.4)	2 (0.9)
Visits outside of the permitted time window	0	1 (0.5)
Concomitant medication	11 (5.1)	11 (5.1)
Subject used medications prohibited by the protocol during the trial (use because of AEs is not considered a protocol violation)	11 (5.1)	11 (5.1)
Study procedure standards	11 (5.1)	11 (5.1)
The study drug was continued despite meeting criteria for study drug discontinuation	8 (3.7)	9 (4.2)
Other study procedures were either not performed or not performed in accordance with the protocol	3 (1.4)	2 (0.9)
Inclusion and exclusion criteria	9 (4.2)	8 (3.7)
Subject met the exclusion criteria	5 (2.3)	6 (2.8)
Subject did not meet the inclusion criteria	4 (1.9)	2 (0.9)
Safety reports	4 (1.9)	3 (1.4)
Late reporting or underreporting of SAE	4 (1.9)	3 (1.4)
Missing laboratory tests/other procedures	3 (1.4)	3 (1.4)
Missing target lesion imaging evaluations	2 (0.9)	2 (0.9)
Missing non-target lesion imaging evaluations	0	1 (0.5)
Missing pregnancy testing (if applicable)	1 (0.5)	0
Study drug	3 (1.4)	2 (0.9)
Subject received the wrong study drug based on the IWRS	0	2 (0.9)
Drug compliance outside of a range of 80%-120%	3 (1.4)	0
Randomization and blinding	4 (1.9)	1 (0.5)
Subject was not correctly enrolled in accordance with the randomization procedure stipulated by the protocol	4 (1.9)	1 (0.5)
Informed consent	1 (0.5)	0
The signed version of the informed consent form was incorrect	1 (0.5)	0

AE, adverse event; IWRS, interactive Web response system; SAE, serious adverse event.

Baseline data

- *Baseline Demographics*

Table 41: Baseline Demographic Characteristics (FAS)

	HS-10296 (N = 214) n (%)	**Gefitinib (N = 215) n (%)**	**Total (N = 429) n (%)**
Age (years)			
n	214	215	429
Mean (SD)	58.1 (9.59)	60.6 (9.72)	59.3 (9.72)
Median	59.0	62.0	60.0
Min, Max	32, 78	25, 81	25, 81
Age group (years) (n, %)			
< 65	155 (72.4)	139 (64.7)	294 (68.5)
≥ 65	59 (27.6)	76 (35.3)	135 (31.5)
Height (cm)			
n	214	215	429
Mean (SD)	161.29 (8.182)	161.37 (7.457)	161.33 (7.818)
Median	160.00	160.00	160.00
Min, Max	135.0, 185.0	140.0, 182.0	135.0, 185.0
Weight (kg)[a]			
n	214	215	429
Mean (SD)	60.33 (10.676)	59.45 (9.575)	59.89 (10.137)
Median	59.00	59.00	59.00
Min, Max	36.0, 92.0	34.5, 89.0	34.5, 92.0
BMI (kg/m^2) [a, b]			
n	214	215	429
Mean (SD)	23.12 (3.306)	22.77 (2.959)	22.94 (3.138)
Median	22.70	22.80	22.80
Min, Max	16.0, 37.9	14.7, 32.8	14.7, 37.9
Gender (n, %)			
Male	80 (37.4)	80 (37.2)	160 (37.3)
Female	134 (62.6)	135 (62.8)	269 (62.7)
Race (n, %)			
Asian	214 (100)	215 (100)	429 (100)

	HS-10296 (N = 214) n (%)	**Gefitinib (N = 215) n (%)**	**Total (N = 429) n (%)**
Ethnicity (n, %)			
Han	207 (96.7)	206 (95.8)	413 (96.3)
Other [c]	7 (3.3)	9 (4.2)	16 (3.7)
Smoking history (n, %)			
Yes	58 (27.1)	71 (33.0)	129 (30.1)
No	156 (72.9)	144 (67.0)	300 (69.9)

a Baseline is defined as the last non-missing observation before the first dose of study treatment.
b Body Mass Index is derived by baseline weight in kg divided by baseline height in meters squared.
c Including 4 Manchu; 2 Mongolian; 2 Hui; 1 Yao; 1 Xibe; 1 Daur; 1 Tujia; 1 Dong; 1 Tujia minority; 1 Gao shan; and 1 Miao.
BMI = body mass index; FAS = full analysis set; max = maximum; min = minimum.

- *Disease Characteristics*

Table 42: Baseline Disease Characteristics (FAS)

Characteristic	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
EGFR Gene Mutation Type		
Ex19del	140 (65.4)	141 (65.6)
L858R	74 (34.6)	74 (34.4)
EGFR T790M Mutation		
Positive	2 (0.9)	3 (1.4)
Negative	212 (99.1)	212 (98.6)
Other EGFR Mutations		
Positive	0	1 (0.5)
Negative	214 (100)	214 (99.5)
Initial stage at Diagnosis		
IA	0	1 (0.5)
IB	2 (0.9)	0
IIA	1 (0.5)	0
IIB	1 (0.5)	3 (1.4)
IIIA	2 (0.9)	1 (0.5)
IIIB	11 (5.1)	16 (7.4)
IV	197 (92.1)	194 (90.2)
Pathological Type		
Adenocarcinoma	210 (98.1)	211 (98.1)
Squamous cell carcinoma	0	1 (0.5)
Large cell carcinoma	0	1 (0.5)
Other	4 (1.9)	2 (0.9)
Recurrence Status		
Yes	6 (2.8)	5 (2.3)
No	208 (97.2)	210 (97.7)
Tumor Staging at Baseline		
IIIB	12 (5.6)	17 (7.9)
IV	202 (94.4)	198 (92.1)
Brain Metastasis		
Yes	56 (26.2)	59 (27.4)
No	158 (73.8)	156 (72.6)
ECOG PS		
0	54 (25.2)	53 (24.7)
1	159 (74.3)	162 (75.3)
Missing	1 (0.5)	0

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; L858R, point mutation in which leucine at amino acid 858 is replaced by arginine; PS, performance status;T790M, mutation that substitutes a threonine with a methionine at position 790 of exon 20.

Table 43: Summary of Metastatic Disease Sites (FAS)

Metastatic Disease Sites	HS-10296 (N = 214) n (%)	Gefitinib (N = 215) n (%)	Total (N = 429) n (%)
Subjects with metastasis sites	**214 (100.0)**	**214 (99.5)**	**428 (99.8)**
Lymph Node	177 (82.7)	168 (78.1)	345 (80.4)
Lung	140 (65.4)	145 (67.4)	285 (66.4)
Bone	117 (54.7)	115 (53.5)	232 (54.1)
Thoracic Cavity	97 (45.3)	92 (42.8)	189 (44.1)
Brain	56 (26.2)	59 (27.4)	115 (26.8)
Pleura	31 (14.5)	37 (17.2)	68 (15.9)
Liver	25 (11.7)	29 (13.5)	54 (12.6)
Pericardial Cavity	25 (11.7)	23 (10.7)	48 (11.2)
Adrenal Gland	28 (13.1)	18 (8.4)	46 (10.7)
Others	6 (2.8)	6 (2.8)	12 (2.8)
Mediastinum	2 (0.9)	6 (2.8)	8 (1.9)
Kidney	4 (1.9)	1 (0.5)	5 (1.2)
Soft Tissue	4 (1.9)	1 (0.5)	5 (1.2)
Spleen	4 (1.9)	1 (0.5)	5 (1.2)
Peritoneum	2 (0.9)	1 (0.5)	3 (0.7)
Neck	1 (0.5)	1 (0.5)	2 (0.5)
Pancreas	2 (0.9)	0	2 (0.5)
Abdominal Cavity	1 (0.5)	0	1 (0.2)
Chest	0	1 (0.5)	1 (0.2)
Pelvis	1 (0.5)	0	1 (0.2)

FAS = full analysis set.

The median age (cFAS) was 58.0 years in aumolertinib and 61.0 years in gefitinib with 21.6% and 34.5% of subjects ≥65 years in aumolertinib and gefitinib groups, respectively. Female subjects were 62.7% in aumolertinib and 63.6% in gefitinib. The rate of non-smoking history subjects was 70.6% in aumolertinib and 67.3% in gefitinib. EGFR gene mutation type Ex19del was reported in 58.8% of subjects from aumolertinib group and 63.6% in gefitinib.

- *NSCLC-related surgical history*

Of the 429 subjects included in the FAS, 17 subjects had a history of tumour resection. Of these, 11 subjects had relapsed NSCLC with a history of resection, while 6 subjects were diagnosed with NSCLC for the first time and underwent resection before or after the date of first diagnosis (palliative surgery).

- *Prior anti-cancer therapies*

Table 44: Prior Anticancer Therapies by Therapy Category and Type (FAS)

Therapy	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
Number of subjects with at least one prior anticancer therapy	38 (17.8)	26 (12.1)
Traditional Chinese Medicine for cancer	22 (10.3)	9 (4.2)
Local treatment (Radiotherapy)	13 (6.1)	12 (5.6)
Local therapy (Perfusion)	2 (0.9)	5 (2.3)
Adjuvant therapy (Chemotherapy)	3 (1.4)	1 (0.5)

FAS, Full Analysis Set.

- *Concomitant treatment*

Of the 429 subjects, 16 (7.9%) in the aumolertinib arm and 7 (3.3%) in the gefitinib arm received antitumor radiotherapy.

Of the 429 subjects, 9 (4.2%) in the aumolertinib arm and 6 (2.8%) in the gefitinib arm received antitumor drug treatments other than the study drug. Of the 9 subjects in the aumolertinib arm: 8 received antitumor traditional Chinese medicine and 1 received osimertinib and gefitinib (Subject 31014). Based on the information in the original medical record, the start time was confirmed to be "used after terminating the study treatment because of disease progression" and this had no significant impact on the evaluation of the efficacy results. Of the 6 subjects in the gefitinib arm, 2 received antitumor traditional Chinese medicine, 1 received chemotherapy after disease progression, 1 received anti-angiogenic drugs after disease progression, and 2 received other third-generation EGFR TKIs (osimertinib).

Table 45: Summary of Subsequent Anticancer Therapy (FAS)

	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
Still on Study Treatment	93 (43.5)	34 (15.8)
No Subsequent Therapy	45 (21.0)	49 (22.8)
Received Subsequent Therapy	76 (35.5)	132 (61.4)
Number of Patients who Received a First Subsequent Therapy	**76 (35.5)**	**132 (61.4)**
3G EGFR TKI	6 (2.8)	59 (27.4)
Aumolertinib [a]	0	43 (20.0)
Osimertinib	6 (2.8)	16 (7.4)
Non-Platinum Chemotherapy	36 (16.8)	23 (10.7)

	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
Platinum Chemotherapy	36 (16.8)	21 (9.8)
1/2G EGFR TKI	18 (8.4)	34 (15.8)
Afatinib	3 (1.4)	1 (0.5)
Erlotinib	0	1 (0.5)
Gefitinib	8 (3.7)	15 (7.0)
Icotinib	1 (0.5)	8 (3.7)
Unknown	6 (2.8)	9 (4.2)
Anti-vegf	20 (9.3)	12 (5.6)
Traditional Chinese Medicine	8 (3.7)	8 (3.7)
PD1/PD-L1	7 (3.3)	4 (1.9)
Radiotherapy	4 (1.9)	7 (3.3)
Other Targeted Therapy	3 (1.4)	2 (0.9)
Others	1 (0.5)	0
Number of Patients who Received a Second Subsequent Therapy	**44 (20.6)**	**61 (28.4)**
Non-Platinum Chemotherapy	17 (7.9)	23 (10.7)
Platinum Chemotherapy	13 (6.1)	17 (7.9)
Anti-vegf	13 (6.1)	15 (7.0)
1/2G EGFR TKI	11 (5.1)	8 (3.7)
Afatinib	3 (1.4)	1 (0.5)
Erlotinib	1 (0.5)	0
Gefitinib	3 (1.4)	0
Icotinib	0	2 (0.9)
Other	0	1 (0.5)
Unknown	4 (1.9)	4 (1.9)
Traditional Chinese Medicine	9 (4.2)	5 (2.3)
Radiotherapy	2 (0.9)	10 (4.7)
3G EGFR TKI	0	9 (4.2)
Aumolertinib	0	2 (0.9)
Osimertinib	0	7 (3.3)
PD1/PD-L1	4 (1.9)	4 (1.9)
Other Targeted Therapy	2 (0.9)	2 (0.9)
Others	1 (0.5)	2 (0.9)
Number of Patients who Received a Third or More Subsequent Therapy	**31 (14.5)**	**31 (14.4)**
Non-Platinum Chemotherapy	26 (12.1)	14 (6.5)
Anti-vegf	22 (10.3)	15 (7.0)

	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
Platinum Chemotherapy	16 (7.5)	12 (5.6)
1/2G EGFR TKI	12 (5.6)	7 (3.3)
Afatinib	3 (1.4)	1 (0.5)
Erlotinib	1 (0.5)	0
Gefitinib	1 (0.5)	0
Icotinib	3 (1.4)	0
Other	1 (0.5)	1 (0.5)
Unknown	3 (1.4)	5 (2.3)
PD1/PD-L1	10 (4.7)	4 (1.9)
Radiotherapy	5 (2.3)	5 (2.3)
Traditional Chinese Medicine	3 (1.4)	7 (3.3)
Others	3 (1.4)	4 (1.9)
3G EGFR TKI	1 (0.5)	5 (2.3)
Aumolertinib	0	1 (0.5)
Osimertinib	1 (0.5)	4 (1.9)
Other Targeted Therapy	2 (0.9)	4 (1.9)

[a] Includes crossover treatment. Note that 41 subjects received aumolertinib as part of the crossover and 2 subjects received aumolertinib outside of protocol.
1/2/3 G = first/second/third generation; EGFR = epidermal growth factor receptor; FAS = full analysis set; PD1 = programmed cell death protein 1; PD-L1 = programmed cell death 1 ligand 1; TKI = tyrosine kinase inhibitor; vegf = vascular endothelial growth factor.
DCO date: 06 Aug 2021

- *Underlying conditions*

Table 46 Common Underlying Conditions with Incidence ≥ 20% (FAS)

System Organ Class	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
Any past medical history	185 (86.4)	187 (87.0)
Vascular disorders	65 (30.4)	66 (30.7)
Hepatobiliary system diseases	57 (26.6)	64 (29.8)
Infection and infectious diseases	62 (29.0)	51 (23.7)
Gastrointestinal diseases	35 (16.4)	47 (21.9)
Respiratory, thoracic and mediastinal disorders	55 (25.7)	46 (21.4)
Kidney and urinary system diseases	39 (18.2)	43 (20.0)
Eye organ diseases	39 (18.2)	43 (20.0)
Nervous system disorders	21 (9.8)	43 (20.0)
Metabolic and nutritional diseases	51 (23.8)	37 (17.2)

FAS, Full Analysis Set.

Numbers analysed

Table 47: Distribution of Subjects in Each Analysis Set

Category	Aumolertinib (N=214) n (%)	Gefitinib (N=215) n (%)
FAS	214 (100.0)	215 (100.0)
PPS	212 (99.1)	213 (99.1)
SS	214 (100.0)	215 (100.0)

FAS, Full Analysis Set; PPS, Per Protocol Set; SS, Safety Set.

Outcomes and estimation

- ***Primary endpoint: PFS***

- Primary analysis (DCO date: 15 Jan 2021): PFS by Investigator

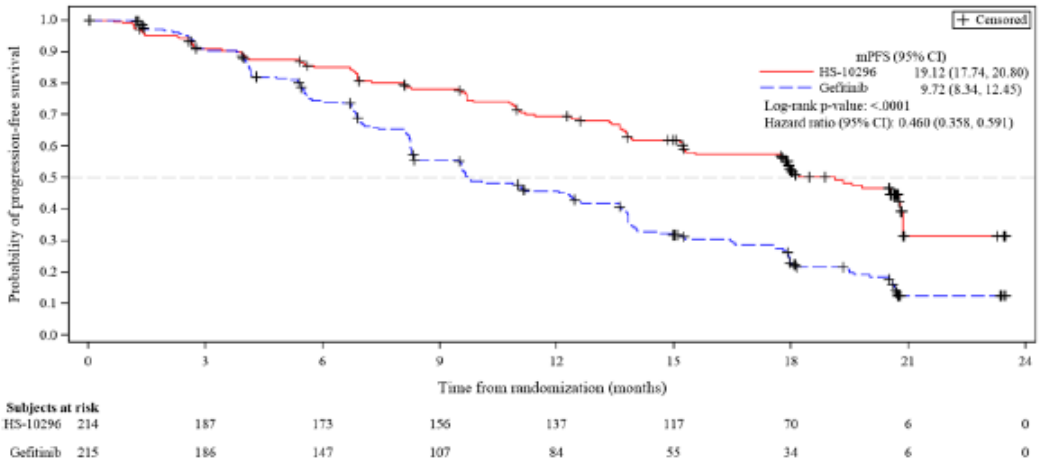
The median follow-up time in the aumolertinib arm was 20.50 months (95% CI: 18.00 – 20.63 months) while that of the gefitinib arm was 20.70 months (95% CI: 19.32 – 20.76 months).

Table 48: Primary Endpoint: Investigator-assessed PFS

Parameter	**Aumolertinib (N = 214)**	**Gefitinib (N = 215)**
Number of subjects with events, n (%)	106 (49.5)	160 (74.4)
Number of subjects censored, n (%)	108 (50.5)	55 (25.6)
No post-baseline tumour assessment and no death within two scheduled visits after randomization	2 (0.9)	1 (0.5)
Treatment termination or subsequent anticancer therapy started prior to PD or death	5 (2.3)	14 (6.5)
PD or death immediately after missing two consecutive visits	6 (2.8)	1 (0.5)
No PD or death at the time of analysis	95 (44.4)	39 (18.1)
Estimated time to progressive disease or death (months)[a]		
25th percentile (95% CI)[b]	9.69 (6.93, 12.35)	5.72 (5.13, 6.90)
Median (95% CI)[b]	19.12 (17.74, 20.80)	9.72 (8.34, 12.45)
75th percentile (95% CI)[b]	NA (20.86, NA)	17.94 (15.18, 20.01)
6-month PFS (95% CI)[b]	85.05 (79.42, 89.24)	74.02 (67.42, 79.50)
12-month PFS (95% CI)[b]	69.56 (62.72, 75.39)	45.65 (38.57, 52.45)
18-month PFS (95% CI)[b]	52.59 (45.25, 59.41)	22.93 (17.03, 29.37)
24-month PFS (95% CI)[b]	NA	NA
p-value [c]	< 0.0001	
HR (95% CI)[d]	0.460 (0.358, 0.591)	

[a] PFS was defined as the time from randomization to the occurrence of objective tumour progression or death, whichever occurred first. PFS in months was calculated as (first event date/censored date – date of randomization + 1) / 30.4375. Censoring rules were specified as per the HS-10296-03-01 SAP Version 1.1.
[b] Estimated using the Kaplan-Meier method.
[c] p-value was calculated using the log-rank method, stratified according to EGFR mutation type and brain metastasis status.
[d] Hazard ratio was estimated using the stratified Cox proportional hazards model. The stratification factors used are the same as noted above.
CI = confidence interval; CSR = clinical study report; EGFR = epidermal growth factor receptor; FAS = Full Analysis Set; PFS = progression-free survival; NA = not available; SAP = statistical analysis plan.
Data cutoff date (primary analysis): 15 January 2021.

Figure 13 Kaplan-Meier Curve for PFS in Study HS-10296-03-01 (FAS)



CI, confidence interval; mPFS, median progression-free survival.

Sensitivity analyses of PFS

See Table 35: Prespecified Sensitivity Analyses Performed on PFS in Study HS-10296-03-01 for the definitions of sensitivity analyses.

Table 49: Summary of Primary PFS Outcomes and PFS Sensitivity Analyses in Study HS-10296-03-01

Analysis	Aumolertinib Median PFS [a] (months) (95% CI [b])	Gefitinib Median PFS [a] (months) (95% CI [b])	HR [c] (95% CI)
Primary Analysis	19.12 (17.74, 20.80)	9.72 (8.34, 12.45)	0.460 (0.358, 0.591)
Sensitivity Analysis 1	19.12 (17.74, 20.80)	9.72 (8.31, 12.45)	0.454 (0.353, 0.585)
Sensitivity Analysis 2	17.94 (15.18, 20.50)	9.72 (9.53, 11.14)	0.490 (0.383, 0.628)
Sensitivity Analysis 3	17.97 (15.31, 20.53)	9.66 (8.28, 12.22)	0.475 (0.374, 0.603)
Sensitivity Analysis 4	20.53 (18.00, 20.86)	12.06 (9.59, 13.80)	0.402 (0.306, 0.529)
Sensitivity Analysis 5	19.12 (17.77, 20.80)	9.72 (8.34, 12.45)	0.456 (0.355, 0.586)
Sensitivity Analysis 6	18.17 (16.39, NA)	9.72 (8.34, 12.45)	0.451 (0.351, 0.581)

[a] PFS was defined as the time from randomization to the occurrence of objective tumour progression or death, whichever occurred first. PFS in months was calculated as (first event date/censored date – date of randomization + 1) / 30.4375. Censoring rules were specified as per the HS-10296-03-01 SAP Version 1.1.
[b] Estimated using Kaplan-Meier method.
[c] Calculated using the stratified Cox proportional hazard model.
CI = confidence interval; CSR = clinical study report; HR = hazard ratio; PFS = progression-free survival.
Data cutoff date (primary analysis): 15 January 2021.

- Updated analysis (DCO date: 06 August 2021): PFS by Investigator

The median follow-up time was 26.2 months in the aumolertinib group and 26.3 months in the gefitinib group.

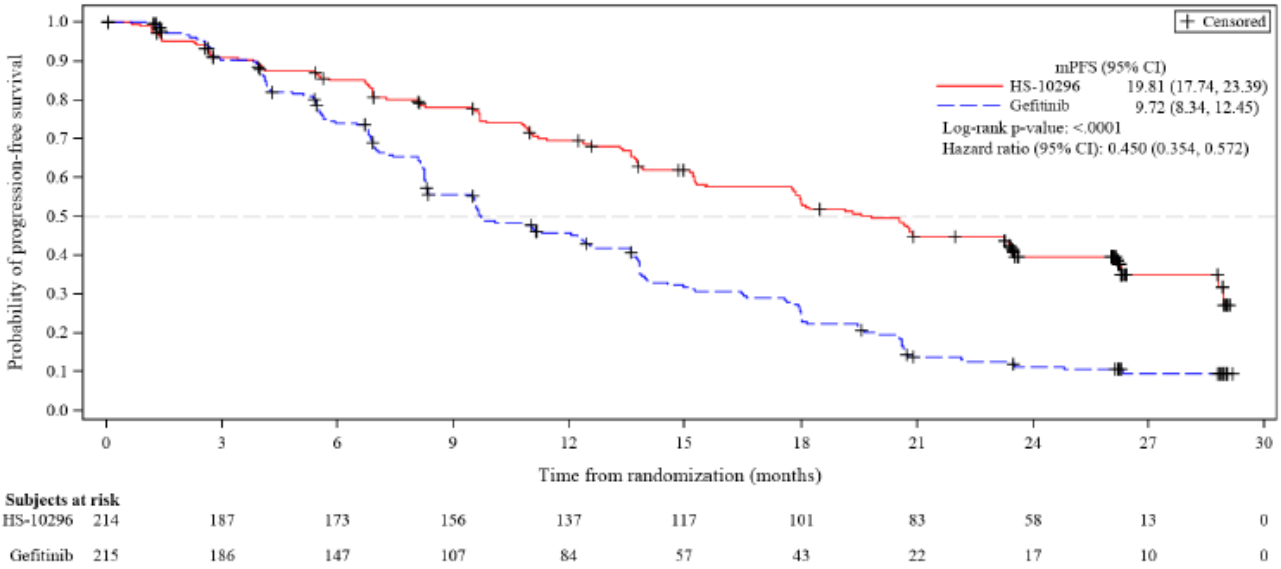
Table 50: Primary Endpoint: Analysis of Investigator-assessed Progression-free Survival (Full Analysis Set)

	Aumolertinib (N = 214) n (%)	Gefitinib (N = 215) n (%)
Number of subjects [a] (n, %)		
Subjects with events	124 (57.9)	171 (79.5)
PD	120 (56.1)	167 (77.7)
Death	4 (1.9)	4 (1.9)
Subjects censored	90 (42.1)	44 (20.5)

	Aumolertinib (N = 214) n (%)	**Gefitinib (N = 215) n (%)**
No post-baseline tumour assessment and no death within two scheduled visits after randomization	2 (0.9)	1 (0.5)
Treatment termination or subsequent anti-cancer therapy started prior to PD or death	7 (3.3)	17 (7.9)
PD or death immediately after missing two consecutive visits	6 (2.8)	1 (0.5)
No PD or death at the time of analysis	75 (35.0)	25 (11.6)
Estimated time to PD or death (months)[a]		
25th Percentile (95% CI)[b]	9.69 (6.93, 12.35)	5.72 (5.13, 6.90)
Median (95% CI)[b]	19.81 (17.74, 23.39)	9.72 (8.34, 12.45)
75th Percentile (95% CI)[b]	NA (28.81, NA)	17.97 (15.18, 20.50)
PFS rate (95% CI)[b]		
6 months	85.05 (79.42, 89.24)	74.02 (67.42, 79.50)
12 months	69.56 (62.72, 75.39)	45.65 (38.57, 52.45)
18 months	53.37 (46.16, 60.05)	23.99 (18.12, 30.33)
24 months	39.57 (32.59, 46.46)	11.21 (7.08, 16.39)
HR (95% CI)[c]	0.450 (0.354, 0.572)	
p-value [d]	< 0.0001	
Median follow-up time (95% CI)[e]	26.18 (26.05, 26.25)	26.28 (26.12, 28.94)

a PFS was defined as the time from randomization to the occurrence of objective tumour progression or death, whichever occurred first. PFS in months was calculated as (first event date / censored date – date of randomization + 1) / 30.4375. Censoring rules specified per the SAP
b Estimated using Kaplan-Meier method.
c Calculated using the stratified Cox proportional hazard model.
d Calculated using the log-rank test stratified by EGFR mutation type (Ex19del versus L858R) and brain metastasis status (present versus absent).
e Estimated using reverse Kaplan-Meier method.
CI = confidence interval; EGFR = epidermal growth factor receptor; Ex19del = exon 19 deletion; L858R = leucine to arginine substitution at position 858 in exon 21 of the EGFR; NA = not available; PD = progressive disease;
PFS = progression-free survival.
Data cutoff date was 06 August 2021.

Figure 14 Primary Endpoint: Investigator-assessed Progression-free Survival – Kaplan-Meier Curve (Full Analysis Set)



Note: PFS was defined as the time from randomization to the occurrence of objective tumour progression or death, whichever occurred first. Censoring rules specified per the SAP
CI = confidence interval; HS-10296 = aumolertinib; mPFS = median progression-free survival.
Data cutoff date was 06 August 2021.

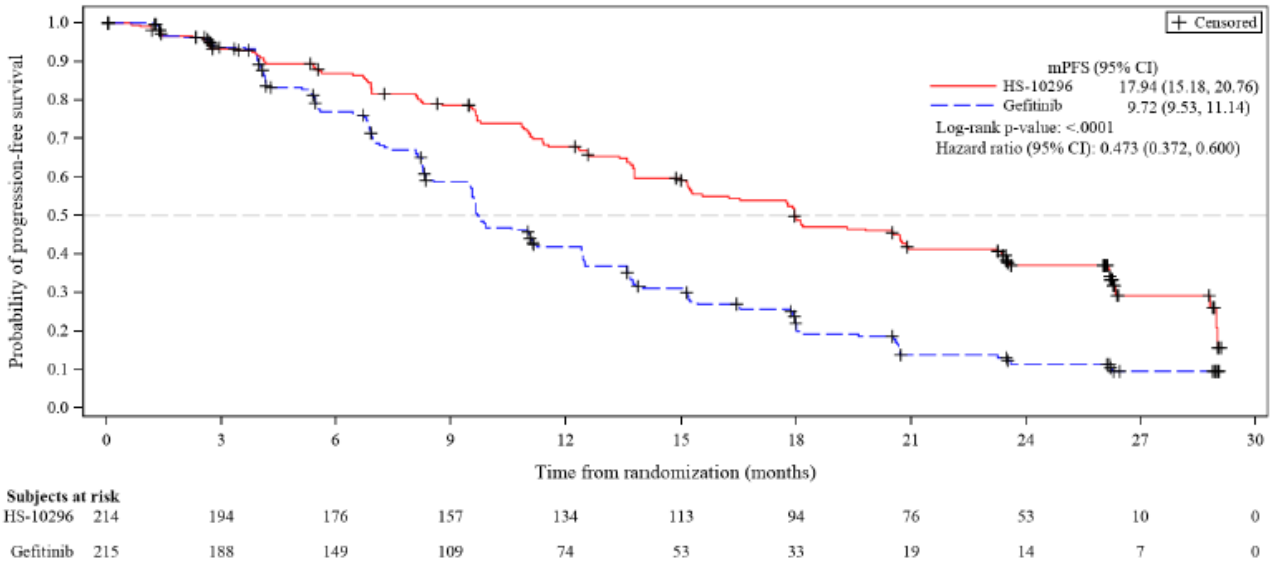
PFS by ICR (FAS)

Table 51 Sensitivity Analysis of PFS (Months) by Independent Review Committee (IRC) Full Analysis Set

	HS-10296 (N=214) n (%)	Gefitinib (N=215) n (%)
Number of subjects [1] (n, %)		
Subjects with events	132 (61.7)	163 (75.8)
Progressive Disease (PD)	127 (59.3)	161 (74.9)
Death	5 (2.3)	2 (0.9)
Subjects censored	82 (38.3)	52 (24.2)
No baseline tumor assessment	0	0
No post-baseline tumor assessment and no death within two scheduled visits after randomization	3 (1.4)	1 (0.5)
Treatment termination or subsequent anti-cancer therapy started prior to PD or death	13 (6.1)	21 (9.8)
PD or death immediately after missing two consecutive visits	0	2 (0.9)
No PD or death at the time of analysis	66 (30.8)	28 (13.0)
Estimated time to PD or death (months) [1]		
25th Percentile (95% CI) [2]	9.69 (8.08, 11.40)	6.80 (5.42, 7.00)
Median (95% CI) [2]	17.94 (15.18, 20.76)	9.72 (9.53, 11.14)
75th Percentile (95% CI) [2]	28.98 (26.28, NA)	17.91 (14.03, 19.61)
Progression free survival rate (95% CI) [2]		
6 months	86.96 (81.56, 90.87)	77.04 (70.56, 82.28)
12 months	67.90 (60.97, 73.86)	41.89 (34.81, 48.79)
18 months	49.74 (42.57, 56.49)	21.88 (16.09, 28.25)
24 months	37.03 (30.18, 43.88)	11.44 (7.03, 17.03)
p-value [3]	<.0001	
Hazard ratio (95% CI) [4]	0.473 (0.372, 0.600)	
Median follow-up time (95% CI) [5]	26.18 (26.02, 26.22)	26.18 (23.49, 28.88)

[1] Progressive-Free survival is defined as the time from randomization to the occurrence of objective tumor progression or death, whichever comes first. PFS in months is calculated as (first event date / censored date – date of randomization + 1) / 30.4375. Censoring rules are specified per SAP.
[2] Estimated using Kaplan-Meier method.
[3] Calculated using the log-rank test stratified by EGFR mutation type (Ex19del vs. L858R) and brain metastasis status (present vs. absent).
[4] Calculated using the stratified Cox proportional hazard model.
[5] Estimated using reverse Kaplan-Meier method.
PD = Progressive disease, PFS = Progression-free survival, SAP = Statistical analysis plan.

Figure 15 Kaplan-Meier Plot of Progression-Free Survival (Months) by Independent Review Committee (IRC) Full Analysis Set



Progressive-Free survival is defined as the time from randomization to the occurrence of objective tumor progression or death, whichever comes first. Censoring rules specified per SAP.

- ***Secondary endpoint: OS***
    - Primary analysis: DCO date of 15 Jan 2021

At **data cutoff date (15 January 2021)**, a total of 123 subjects from the FAS had died (28.7%), including 54 subjects (25.2%) in the aumolertinib arm and 69 subjects (32.1%) in the gefitinib arm. The median OS of both arms was not yet reached (HR = 0.820, 95% CI: 0.573, 1.173). In total, 41 subjects have switched to treatment with aumolertinib after disease progression during gefitinib treatment.

Figure 16 Kaplan-Meier Curve of Overall Survival (FAS)

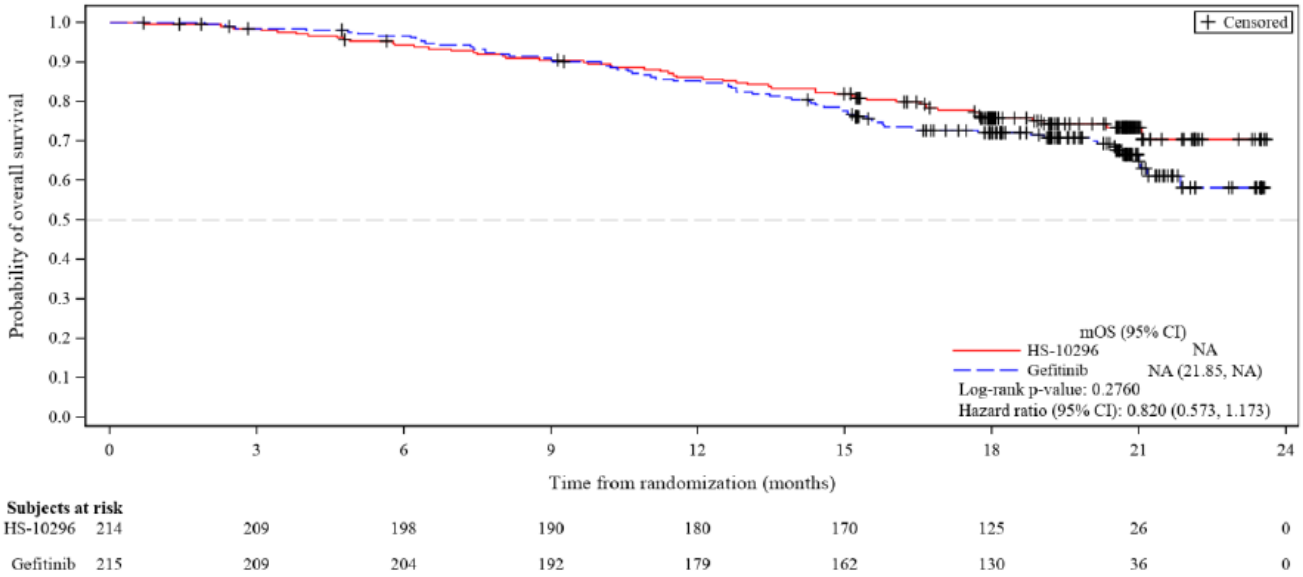


Table 52: OS in Study HS-10296-03-01 (FAS)

	Aumolertinib (N = 214)	**Gefitinib (N = 215)**
Number of death events, n (%)[a]	54 (25.2)	69 (32.1)
Number censored, n (%)	160 (74.8)	146 (67.9)
OS (months)[a]		
25th percentile (95% CI)[b]	19.06 (15.21, NA)	15.54 (13.90, 20.44)
Median (95% CI)[b]	NA (NA, NA)	NA (21.85, NA)
75th percentile (95% CI)[b]	NA (NA, NA)	NA (NA, NA)
12-month OS rate (95% CI)[b]	86.21 (80.77, 90.21)	85.30 (79.76, 89.43)
p-value [c]	0.2760	
HR (95% CI)[d]	0.820 (0.573, 1.173)	

[a] OS was defined as the time from randomization to the date of the death from any cause. OS in months was calculated as (event date / censored date – date of randomization +1) / 30.4375.
[b] Estimated using the Kaplan-Meier method.
[c] Calculated using the log-rank test stratified by EGFR mutation type and brain metastasis status.
[d] HR estimated with the stratified Cox proportional hazards model. The stratification factors used are the same as noted above.
CI = confidence interval; CSR = clinical study report; EGFR = epidermal growth factor receptor; FAS = Full Analysis Set; HR = hazard ratio; NA = not available; OS = overall survival.

Data cutoff date (primary analysis): 15 January 2021.

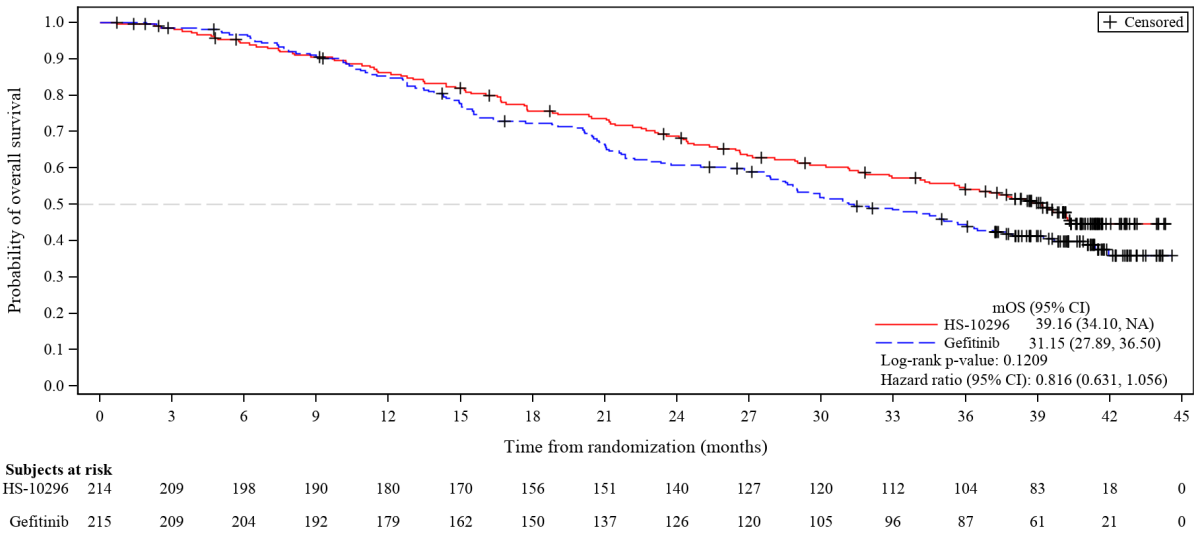
Updated OS data with DCO date of 30 Sep 2022:

Table 53: Analysis of OS (Months) (FAS) (DCO 30 Sep 2022)

	Aumolertinib (N = 214)	Gefitinib (N = 215)
Number of subjects [a], n (%)		
Subjects with death events	109 (50.9)	126 (58.6)
Overall survival, months [a]		
Median (95% CI)[b]	39.16 (34.10, NA)	31.15 (27.89, 36.50)
Hazard ratio (95% CI)[d]	0.816 (0.631, 1.056)	
p-value [c]	0.1209	
Overall survival, months [a]		
25th Percentile (95% CI)[b]	19.06 (15.21, 23.56)	15.54 (13.90, 20.44)
75th Percentile (95% CI)[b]	NA	NA
Overall survival rate (95% CI)[b]		
12 months	86.21 (80.77, 90.21)	85.30 (79.76, 89.43)
24 months	68.78 (61.99, 74.60)	60.80 (53.83, 67.05)
Median follow-up time (95% CI)[e]	40.77 (40.31, 41.20)	40.87 (40.11, 41.30)

[a] OS is defined as the time from randomization to the date of the death of any cause. OS in months is calculated as (event date / censored date – date of randomization + 1) / 30.4375.
[b] Estimated using Kaplan-Meier method.
[c] Calculated using the log-rank test stratified by EGFR mutation type (Ex19del vs L858R) and brain metastasis status (present vs absent).
[d] Calculated using the stratified Cox proportional hazard model.
[e] Estimated using reverse Kaplan-Meier method.
CI = confidence interval; DCO = data cutoff; EGFR = epidermal growth factor receptor; FAS = full analysis set; NA = not applicable; OS = overall survival.

Figure 17: Kaplan-Meier Curve of OS (FAS) (DCO 30 Sep 2022)



Note: OS is defined as the time from randomization to the date of the death of any cause.
CI = confidence interval; DCO = data cutoff; FAS = full analysis set; mOS = median overall survival;

NA = not applicable; OS = overall survival.

- ***Secondary endpoint: ORR***

Table 54: ORR and DCR based on Investigator assessment (FAS), DCO 15 Jan 2021

Parameter	Aumolertinib (N = 214)	Gefitinib (N = 215)
Best tumour response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	157 (73.4)	154 (71.6)
SD	41 (19.2)	53 (24.7)
PD	12 (5.6)	6 (2.8)
NE	3 (1.4)	1 (0.5)
ORR (95% CI)[a]	73.8 (67.4, 79.6)	72.1 (65.6, 78.0)
p-value [b]	0.6939	
Odds ratio (95% CI)[c]	1.092 (0.704, 1.693)	
DCR (95% CI)[a]	93.0 (88.7, 96.0)	96.7 (93.4, 98.7)
p-value [b]	0.0814	
Odds ratio (95% CI)[c]	0.448 (0.178, 1.128)	

[a] The exact 95% CI was calculated using the Clopper-Pearson method.
[b] Calculated based on the stratified (stratified by EGFR mutation type [ex19del versus L858R] and brain metastasis status [present versus absent]) Cochran-Mantel-Haenszel test.
[c] The analysis was performed using a logistic regression stratified by EGFR mutation type (ex19del versus L858R) and brain metastasis status (present versus absent). CI and p-values were calculated using the Wald Chi-square test. An odds ratio > 1 favours aumolertinib.
CI = confidence interval; CR = complete response; CSR = clinical study report; DCR = disease control rate; EGFR = epidermal growth factor receptor; ex19del = exon 19 deletion; FAS = Full Analysis Set; L858R = substitution of a leucine (L) with an arginine (R) at position 858 in exon 21; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Data cutoff date (primary analysis): 15 January 2021.

A total of 315 subjects (160 aumolertinib-treated, 155 gefitinib-treated) in the FAS had experienced an Investigator-assessed objective response as of the 06 August 2021 data cutoff date. The updated analyses (DCO: 06 August 2021) of ORR and DCR were consistent with the primary analyses, i.e. ORR of 74.8% (95%CI 68.4, 80.4) in aumolertinib and 72.1% (95%CI 65.6, 78.0) in gefitinib, including one CR (0,5%) in each arm, 159 (74.3%) PR in the aumolertinib arm and 154 (71,6%) PR in the gefitinib arm, and DCR of 93.0% (95%CI 88.7, 96.0) in aumolertinib and 96.7% (95%CI 93.4, 98.7) in gefitinib.

Table 55: Concordance Analysis: Investigator and IRC Assessment of RECIST Best Overall Response (FAS)

		Best Overall Response by IRC					
	Best Overall Response by Investigator	**CR**	**PR**	**SD**	**PD**	**NE**	**Total**
Aumolertinib (N = 214) n (%)	**CR**	0	1 (0.5)	0	0	0	1 (0.5)
	PR	0	153 (71.5)	4 (1.9)	0	0	157 (73.4)
	SD	0	23 (10.7)	18 (8.4)	0	0	41 (19.2)

		Best Overall Response by IRC					
	Best Overall Response by Investigator	**CR**	**PR**	**SD**	**PD**	**NE**	**Total**
	PD	0	1 (0.5)	3 (1.4)	7 (3.3)	1 (0.5)	12 (5.6)
	NE	0	0	0	0	3 (1.4)	3 (1.4)
	Total	0	178 (83.2)	25 (11.7)	7 (3.3)	4 (1.9)	214
	Investigator and IRC Assessment Matched						181 (84.6)
	Investigator and IRC Assessment Mismatched						33 (15.4)
	Kappa (95% CI)						0.578 (0.455, 0.701)
Gefitinib (N = 215) n (%)	**CR**	0	1 (0.5)	0	0	0	1 (0.5)
	PR	0	142 (66.0)	11 (5.1)	1 (0.5)	0	154 (71.6)
	SD	0	33 (15.3)	18 (8.4)	2 (0.9)	0	53 (24.7)
	PD	0	2 (0.9)	0	4 (1.9)	0	6 (2.8)
	NE	0	0	0	0	1 (0.5)	1 (0.5)
	Total	0	178 (82.8)	29 (13.5)	7 (3.3)	1 (0.5)	215
	Investigator and IRC Assessment Matched						165 (76.7)
	Investigator and IRC Assessment Mismatched						50 (23.3)
	Kappa (95% CI)						0.376 (0.241, 0.511)

CI = confidence interval; CR = complete response; FAS = full analysis set; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

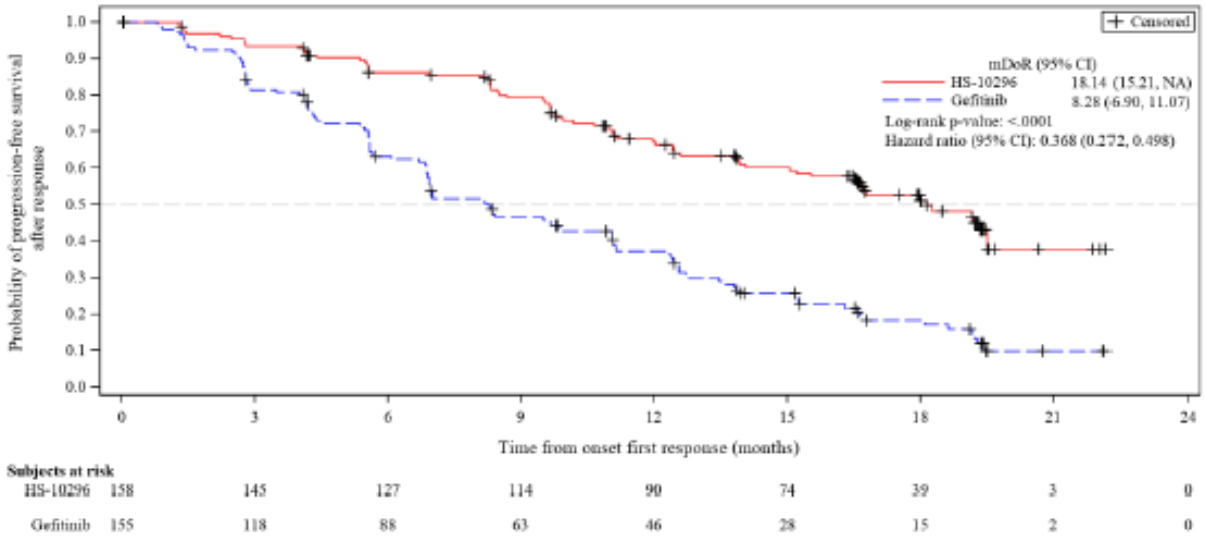
- ***<u>Secondary endpoint: DoR</u>***

Table 56: Duration of Response in the FAS, DCO 15 Jan 2021

Parameter	**Aumolertinib (N = 214)**	**Gefitinib (N = 215)**
Number of subjects with objective response, n (%)	158 (73.8)	155 (72.1)
Number of subjects with subsequent events, n (%)[a]	72 (45.6)	115 (74.2)
Number censored, n (%)[a]	86 (54.4)	40 (25.8)
HR (95% CI)[c]	0.368 (0.272, 0.498)	
DoR (months)		
25th percentile (95% CI)[d]	9.79 (8.31, 11.17)	4.30 (2.86, 5.59)
Median (95% CI)[d]	18.14 (15.21, NA)	8.28 (6.90, 11.07)
75th percentile (95% CI)[d]	NA (19.52, NA)	15.24 (12.55, 18.10)

Note: DoR, as evaluated by the Investigator, was defined as the time from the date of initial response to the date of disease progression or death from any cause. DoR in months was calculated as (first event date/censored date – the initial date that the subject meets PR or CR criteria + 1) / 30.4375. Censoring rules were the same as for the PFS analysis and specified as per the HS-10296-03-01 SAP Version 1.1.
[a] Percentage was based on the number of subjects with objective response.
[c] Calculated using the stratified Cox proportional hazards model.
[d] Calculated using the Kaplan-Meier method.
CI = confidence interval; CR = complete response; CSR = clinical study report; DoR = duration of response; FAS = Full Analysis Set; NA = not available; PFS = progression-free survival; PR = partial response; SAP = statistical analysis plan.
Data cutoff date (primary analysis): 15 January 2021.

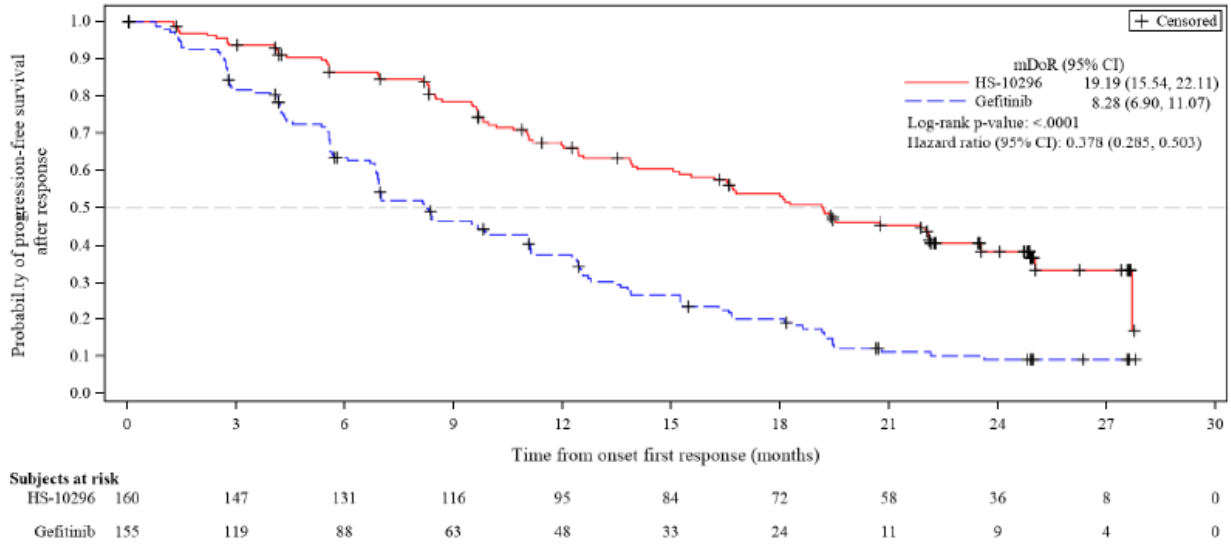
Figure 18: Kaplan-Meier Curve of DoR (FAS)



CI, confidence interval; mDoR, median duration of response.

Data cutoff date (primary analysis): 15 January 2021.

Figure 19: Kaplan-Meier Curve of DoR in Study HS-10296-03-01 (FAS) - Updated Analysis



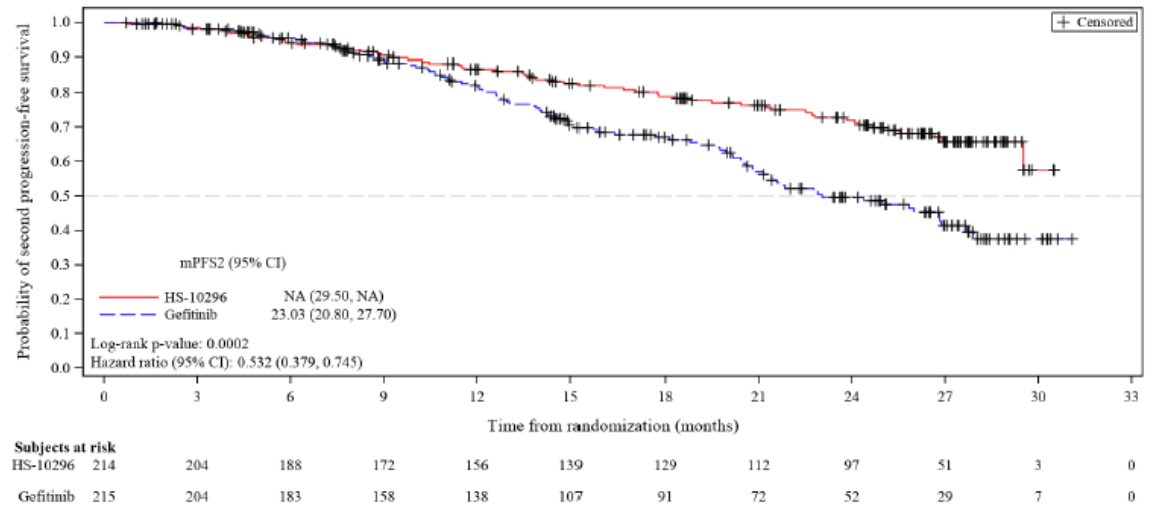
Note: DoR, as evaluated by the Investigator, was defined as the time from the date of initial response to the date of disease progression or death from any cause. DoR in months was calculated as (first event date / censored date – the initial date that the subject meets PR or CR criteria + 1) / 30.4375. Censoring rules were the same as for the PFS analysis and specified as per the HS-10296-03-01 SAP Version 1.1.
CI = confidence interval; CR =complete response; CSR = clinical study report; DoR = duration of response; FAS = Full Analysis Set; HS-10296 = aumolertinib; mDoR = median duration of response; PFS = progression-free survival; PR = partial response; SAP = statistical analysis plan.
Data cutoff date (updated analysis): 06 August 2021.

- ***Additional post-hoc efficacy analysis: PFS2 by Investigator***

PFS2 was defined as the time from randomization to the first disease progression event subsequent to that used for the primary PFS analysis or date of death, during the first subsequent anticancer therapy (including crossover treatment).

In the PFS2 analysis, at the DCO date of 06 August 2021, 57 (26.6%) patients from aumolertinib and 88 (40.9%) patients from gefitinib had second progression events during the first subsequent therapy or died.

Figure 20: Kaplan-Meier Plot of Second Progression Free Survival (PFS2) by Investigator Full Analysis Set



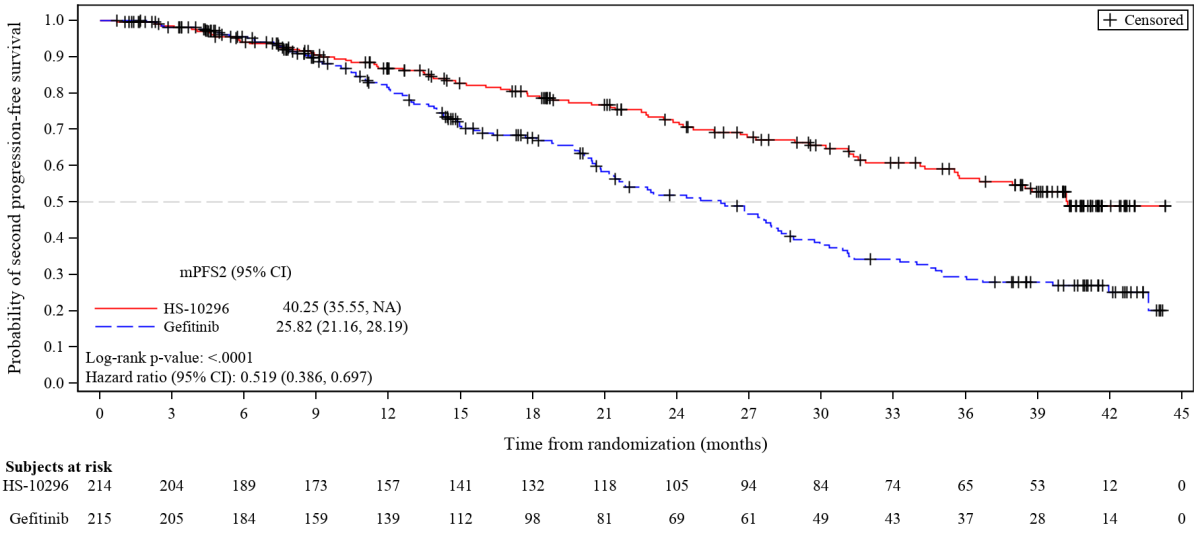
Second Progression Free Survival (PFS2) is defined as the time from randomization to the first disease progression event subsequent to that used for the primary PFS analysis or date of death, during the first subsequent anti-cancer therapy, including crossover treatment. Censoring rules are specified per SAP addendum.

Table 57: Analysis of Second PFS (Months) by Investigator (FAS) (DCO 30 Sep 2022)

	Aumolertinib (N = 214)	Gefitinib (N = 215)
Number of subjects [a], n (%)		
Subjects with events	77 (36.0)	113 (52.6)
Death (by any cause) prior to starting any subsequent anticancer therapy	33 (15.4)	38 (17.7)
Progression or death (by any cause) during the first subsequent anticancer therapy	44 (20.6)	75 (34.9)
Alive and no subsequent anticancer therapy	65 (30.4)	26 (12.1)
No progression or death during the first subsequent anticancer therapy	72 (33.6)	76 (35.3)
Estimated time to PD or death, months [a]		
Median (95% CI)[b]	40.25 (35.55, NA)	25.82 (21.16, 28.19)
Hazard ratio (95% CI)[d]	0.519 (0.386, 0.697)	-
p-value [c]	<.0001	-
Estimated time to PD or death, months [a]		
25th Percentile (95% CI)[b]	22.51 (16.66, 26.64)	14.06 (12.02, 16.36)
75th Percentile (95% CI)[b]	NA	43.60 (34.50, NA)
Second progression-free survival rate (95% CI)[b]		
12 months	86.80 (81.20, 90.82)	81.67 (75.27, 86.56)
24 months	71.99 (64.65, 78.07)	51.88 (43.73, 59.42)

[a] Second PFS (PFS2) is defined as the time from randomization to the first disease progression event subsequent to that used for the primary PFS analysis or date of death, during the first subsequent anticancer therapy, including crossover treatment. PFS2 in months is calculated as (first event date / censored date – date of randomization + 1) / 30.4375. Censoring rules are specified per SAP addendum.
[b] Estimated using Kaplan-Meier method.
[c] Calculated using the log-rank test stratified by EGFR mutation type (Ex19del vs L858R) and brain metastasis status (present vs absent).
[d] Calculated using the stratified Cox proportional hazard model.
CI = confidence interval; DCO = data cutoff; EGFR = epidermal growth factor receptor; FAS = full analysis set; PD = progressive disease; PFS = progression-free survival; PFS2 = second progression-free survival; SAP = statistical analysis plan.

Figure 21: Kaplan-Meier Curve of Second PFS by Investigator (FAS) (DCO 30 Sep 2022)



CI = confidence interval; DCO = data cutoff; FAS = full analysis set; mPFS2 = median second progression-free survival; PFS = progression-free survival.

- ***Additional post-hoc efficacy analysis: TFST by Investigator***

Time to first subsequent (anticancer) therapy—defined as the time from randomization to the start date of the first subsequent anticancer therapy (including crossover treatment), or date of death, whichever is earlier is presented below.

Table 58: Time to First Subsequent (Anticancer) Therapy (Full Analysis Set)

	Aumolertinib (N = 214)	Gefitinib (N = 215)
Number of subjects (%)[a]		
Subjects with events	123 (57.5)	178 (82.8)
Received first subsequent anticancer therapy	98 (45.8)	142 (66.0)
Death	25 (11.7)	36 (16.7)
Estimated time in months to first subsequent anticancer therapy[a]		
25th Percentile (95% CI)[b]	11.24 (8.51, 13.31)	7.72 (6.44, 8.84)
Median (95% CI)[b]	21.52 (18.56, 26.64)	12.85 (11.14, 14.78)
75th Percentile (95% CI)[b]	29.77 (29.47, NA)	19.32 (17.81, 21.55)
First subsequent anticancer therapy-free rate, % (95% CI)[b]		
6 months	89.17 (84.15, 92.66)	83.96 (78.28, 88.26)
12 months	71.95 (65.35, 77.52)	54.08 (47.11, 60.52)
18 months	58.52 (51.54, 64.85)	29.71 (23.67, 35.97)
24 months	46.87 (39.96, 53.47)	17.66 (12.83, 23.13)
Hazard ratio (95% CI)[c]	0.487 (0.385, 0.616)	
p-value[d]	< 0.0001	
Median follow-up time in months (95% CI)[e]	27.30 (26.81, 27.50)	27.76 (26.48, 28.91)

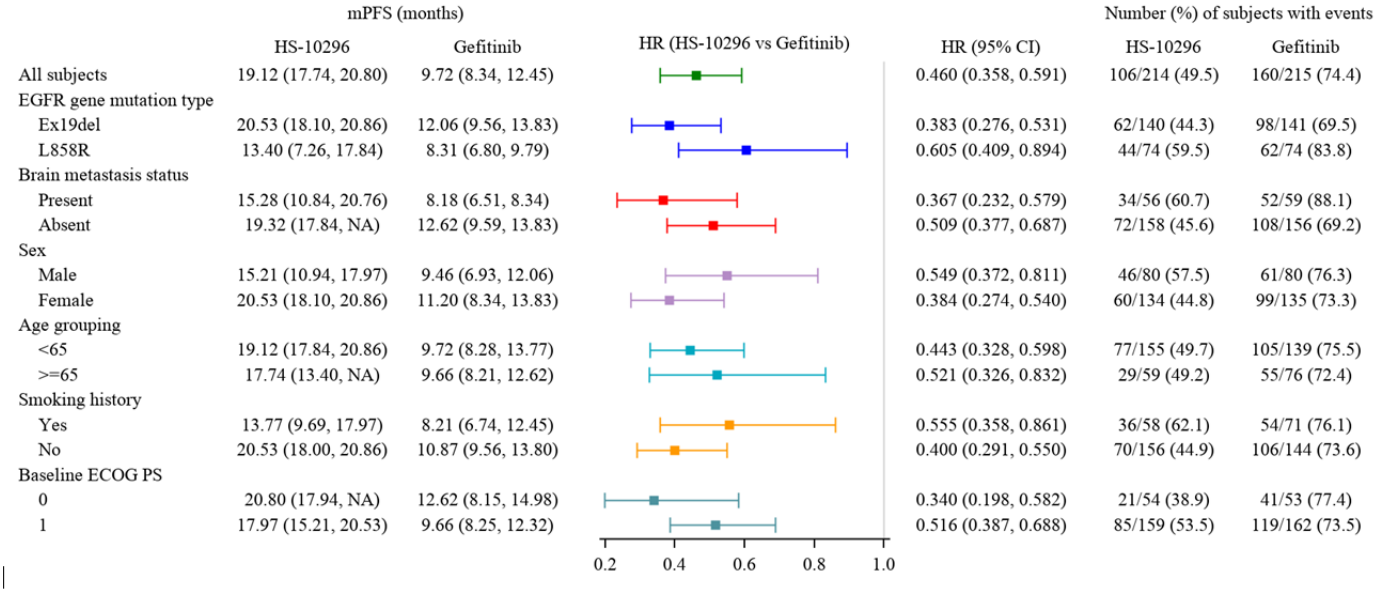
[a] TFST was defined as the time from the date of randomization to the start date of the first subsequent anticancer therapy, including crossover treatment, or date of death, whichever is earlier. TFST in months was calculated as (first event date / censored date − date of randomization + 1) / 30.4375.

As specified in the SAP Addendum (Appendix 16.1.9), any subject not known to have received a first subsequent anticancer therapy, or to have not died at the time of the analysis, was censored at the last contact date.
[b] Estimated using Kaplan-Meier method.
[c] Calculated using the stratified Cox proportional hazard model.
[d] Calculated using the log-rank test stratified by EGFR mutation type (Ex19del versus L858R) and brain metastasis status (present versus absent).
[e] Estimated using reverse Kaplan-Meier method.
CI = confidence interval; EGFR = epidermal growth factor receptor; Ex19del = exon 19 deletion; L858R = leucine to arginine substitution at position 858 of exon 21 of the EGFR; SAP = statistical analysis plan; TFST = time to first subsequent anticancer therapy.
Data cutoff date was 06 August 2021.

Ancillary analyses

Subgroup analyses for PFS

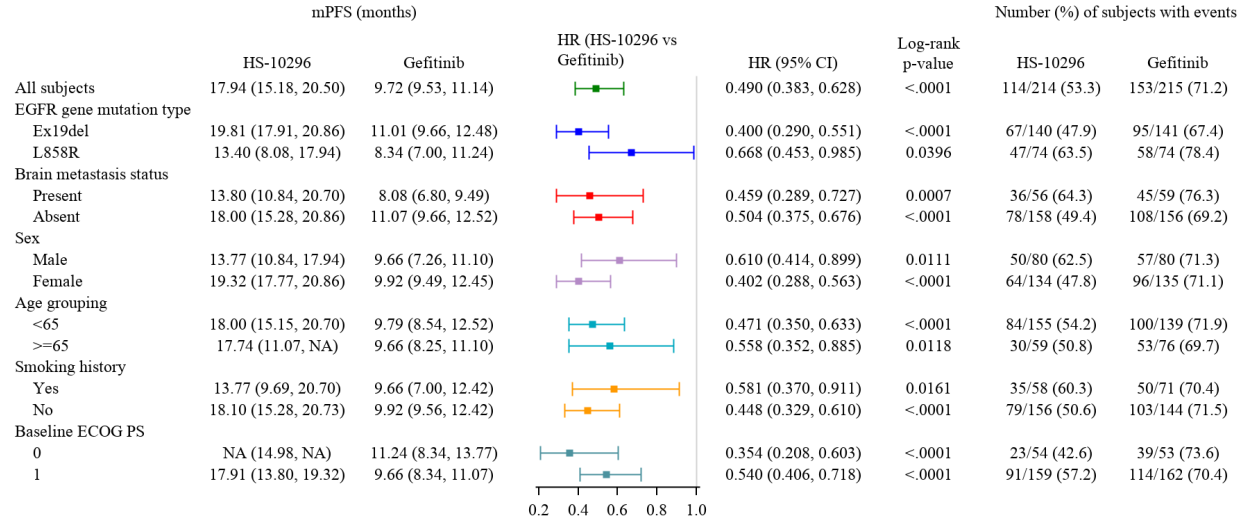
Figure 22: PFS by Subgroup in Study HS-10296-03-01 (FAS)



	mPFS (months)		HR (HS-10296 vs Gefitinib)		Number (%) of subjects with events	
	HS-10296	Gefitinib		HR (95% CI)	HS-10296	Gefitinib
All subjects	19.12 (17.74, 20.80)	9.72 (8.34, 12.45)		0.460 (0.358, 0.591)	106/214 (49.5)	160/215 (74.4)
EGFR gene mutation type						
Ex19del	20.53 (18.10, 20.86)	12.06 (9.56, 13.83)		0.383 (0.276, 0.531)	62/140 (44.3)	98/141 (69.5)
L858R	13.40 (7.26, 17.84)	8.31 (6.80, 9.79)		0.605 (0.409, 0.894)	44/74 (59.5)	62/74 (83.8)
Brain metastasis status						
Present	15.28 (10.84, 20.76)	8.18 (6.51, 8.34)		0.367 (0.232, 0.579)	34/56 (60.7)	52/59 (88.1)
Absent	19.32 (17.84, NA)	12.62 (9.59, 13.83)		0.509 (0.377, 0.687)	72/158 (45.6)	108/156 (69.2)
Sex						
Male	15.21 (10.94, 17.97)	9.46 (6.93, 12.06)		0.549 (0.372, 0.811)	46/80 (57.5)	61/80 (76.3)
Female	20.53 (18.10, 20.86)	11.20 (8.34, 13.83)		0.384 (0.274, 0.540)	60/134 (44.8)	99/135 (73.3)
Age grouping						
<65	19.12 (17.84, 20.86)	9.72 (8.28, 13.77)		0.443 (0.328, 0.598)	77/155 (49.7)	105/139 (75.5)
>=65	17.74 (13.40, NA)	9.66 (8.21, 12.62)		0.521 (0.326, 0.832)	29/59 (49.2)	55/76 (72.4)
Smoking history						
Yes	13.77 (9.69, 17.97)	8.21 (6.74, 12.45)		0.555 (0.358, 0.861)	36/58 (62.1)	54/71 (76.1)
No	20.53 (18.00, 20.86)	10.87 (9.56, 13.80)		0.400 (0.291, 0.550)	70/156 (44.9)	106/144 (73.6)
Baseline ECOG PS						
0	20.80 (17.94, NA)	12.62 (8.15, 14.98)		0.340 (0.198, 0.582)	21/54 (38.9)	41/53 (77.4)
1	17.97 (15.21, 20.53)	9.66 (8.25, 12.32)		0.516 (0.387, 0.688)	85/159 (53.5)	119/162 (73.5)

Note: The analysis was performed using a Cox proportional hazards model including treatment, the subgroup, and the stratification factors including EGFR mutation type (ex19del versus L858R) and brain metastasis status (present versus absent). HR < 1 favours aumolertinib.
CI = confidence interval; CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ex19del = exon 19 deletion; FAS = Full Analysis Set; HR = hazard ratio; HS-10296 = aumolertinib; L858R = substitution of a leucine (L) with an arginine (R) at position 858 in exon 21; mPFS = median progression-free survival; PFS = progression-free survival; PS = performance status.
Data cutoff date (primary analysis): 15 January 2021.

Figure 23: Subgroup Analysis of PFS (Months) by ICR – Forest Plot (FAS) (DCO 15 Jan 2021)



	mPFS (months)		HR (HS-10296 vs Gefitinib)		Log-rank p-value	Number (%) of subjects with events	
	HS-10296	Gefitinib		HR (95% CI)		HS-10296	Gefitinib
All subjects	17.94 (15.18, 20.50)	9.72 (9.53, 11.14)		0.490 (0.383, 0.628)	<.0001	114/214 (53.3)	153/215 (71.2)
EGFR gene mutation type							
Ex19del	19.81 (17.91, 20.86)	11.01 (9.66, 12.48)		0.400 (0.290, 0.551)	<.0001	67/140 (47.9)	95/141 (67.4)
L858R	13.40 (8.08, 17.94)	8.34 (7.00, 11.24)		0.668 (0.453, 0.985)	0.0396	47/74 (63.5)	58/74 (78.4)
Brain metastasis status							
Present	13.80 (10.84, 20.70)	8.08 (6.80, 9.49)		0.459 (0.289, 0.727)	0.0007	36/56 (64.3)	45/59 (76.3)
Absent	18.00 (15.28, 20.86)	11.07 (9.66, 12.52)		0.504 (0.375, 0.676)	<.0001	78/158 (49.4)	108/156 (69.2)
Sex							
Male	13.77 (10.84, 17.94)	9.66 (7.26, 11.10)		0.610 (0.414, 0.899)	0.0111	50/80 (62.5)	57/80 (71.3)
Female	19.32 (17.77, 20.86)	9.92 (9.49, 12.45)		0.402 (0.288, 0.563)	<.0001	64/134 (47.8)	96/135 (71.1)
Age grouping							
<65	18.00 (15.15, 20.70)	9.79 (8.54, 12.52)		0.471 (0.350, 0.633)	<.0001	84/155 (54.2)	100/139 (71.9)
>=65	17.74 (11.07, NA)	9.66 (8.25, 11.10)		0.558 (0.352, 0.885)	0.0118	30/59 (50.8)	53/76 (69.7)
Smoking history							
Yes	13.77 (9.69, 20.70)	9.66 (7.00, 12.42)		0.581 (0.370, 0.911)	0.0161	35/58 (60.3)	50/71 (70.4)
No	18.10 (15.28, 20.73)	9.92 (9.56, 12.42)		0.448 (0.329, 0.610)	<.0001	79/156 (50.6)	103/144 (71.5)
Baseline ECOG PS							
0	NA (14.98, NA)	11.24 (8.34, 13.77)		0.354 (0.208, 0.603)	<.0001	23/54 (42.6)	39/53 (73.6)
1	17.91 (13.80, 19.32)	9.66 (8.34, 11.07)		0.540 (0.406, 0.718)	<.0001	91/159 (57.2)	114/162 (70.4)

Note: The analysis was performed using a Cox proportional hazards model including treatment, the subgroup and the stratification factors including EGFR mutation type (Ex19del vs. L858R) and brain metastasis status (present vs. absent). A hazard ratio < 1 favours HS-10296.
L858R = mutation that substitutes a leucine with an arginine at position 858; DCO = data cutoff; EGFR = epidermal growth factor receptor; Ex19del = Exon 19 deletion; FAS = full analysis set; IRC = independent review committee; PFS = progression-free survival.

CNS additional post-hoc analyses

The evaluation of the central nervous system (CNS) efficacy of aumolertinib versus gefitinib in patients identified to have brain metastases at baseline by independent central review (ICR) was planned as post-hoc analysis in the addendum to the study HS-10296-03-01 SAP. The CNS analyses used the updated DCO date of 01 August 2021.

- **CNS PFS by ICR, cFAS**

Table 59 PFS in the CNS Population in Study HS-10296-03-01

Parameter	Aumolertinib (N = 51) cFAS	Gefitinib (N = 55) cFAS	Aumolertinib (N = 28) cEFR	Gefitinib (N = 32) cEFR
Subjects with events[a], n (%)	20 (39.2)	33 (60.0)	10 (35.7)	21 (65.6)
Median PFS, months[b] (95% CI)[c]	29.01 (12.32, NA)	8.25 (6.90, 9.72)	29.01 (12.32, NA)	8.28 (6.90, 9.53)
Hazard ratio (95% CI)[d]	0.308 (0.170, 0.558)		0.256 (0.114, 0.574)	
p-value[e]	< 0.0001		0.0004	
Median FU time, months (95% CI)[f]	20.90 (19.68, 26.02)	13.80 (8.28, 16.49)	20.73 (13.93, 23.46)	13.80 (11.07, NA)

[a] Assessed by ICR.
[b] PFS was defined as the time from randomization to the occurrence of objective tumor progression or death, whichever occurred first. PFS in months was calculated as (first event date / censored date – date of randomization + 1) / 30.4375. Censoring rules specified per the SAP (Appendix 16.1.9 of the HS-10296-0301 CSR Addendum).
[c] Estimated using Kaplan–Meier method.
[d] Calculated using the stratified Cox proportional hazard model, stratified by EGFR mutation type (Ex19del versus L858R) and brain metastasis status (present versus absent).
[e] Calculated using the log-rank test stratified by EGFR mutation type (Ex19del versus L858R) and brain metastasis status (present versus absent).
[f] Estimated using reverse Kaplan–Meier method.
CI = confidence interval; cEFR = CNS Evaluable for Response Set; cFAS = CNS Full Analysis Set; CNS = central nervous system; EGFR = epidermal growth factor receptor; Ex19del = exon 19 deletion; FU = follow-up; ICR = independent central review; NA = not available; PFS = progression-free survival; SAP = statistical analysis plan.
Data cutoff date was 06 August 2021.

- **CNS ORR, cFAS**

Number of subjects with confirmed CNS response (%): 32 (62.7) in aumolertinib and 27 (49.1) in gefitinib group.

Complete CNS response: 12 (23.5) in aumolertinib and 3 (5.5) in gefitinib group.

Partial CNS response: 20 (39.2) in aumolertinib and 24 (43.6) in gefitinib group.

- **Duration of response in subjects with CNS confirmed objective response, cFAS**

Median DoR (95% CI): 27.70 (NA, NA) months in aumolertinib, 6.93 (5.52, 9.43) months in gefitinib

- **Best Percentage Change from Baseline in CNS Lesion Size, cEFR**

Median: -56.50% in aumolertinib, -50.50% in gefitinib

Table 60 Summary of Subjects Who Received Radiation on the Brain (cFAS and cEFR)

	cFAS		cEFR	
	Aumolertinib (N = 51) n (%)	**Gefitinib (N = 55) n (%)**	**Aumolertinib (N = 28) n (%)**	**Gefitinib (N = 32) n (%)**
Number of subjects who received radiation for brain metastases	10 (19.6)	15 (27.3)	7 (25.0)	11 (34.4)
Prior radiation	4 (7.8)	4 (7.3)	4 (14.3)	4 (12.5)
Concomitant radiation	1 (2.0)	1 (1.8)	0	0
Subsequent radiation	4 (7.8)	12 (21.8)	2 (7.1)	9 (28.1)

cFAS = CNS full analysis set; cEFR = CNS evaluable for response set; CNS = central nervous system.

The range (in days) for subjects who received radiation prior to the start of study treatment was -856 to -31 days for subjects in the aumolertinib arm and -36 to -7 days for subjects in the gefitinib arm (cFAS and cEFR Analysis Sets). The range (in days) for subjects who received radiation after receiving study treatment was 6 to 44 days for subjects in the aumolertinib arm and 4 to 95 days for subjects in the gefitinib arm (cFAS and cEFR Analysis Sets).

Table 61: HS-10296-03-01 Analysis of Central Nervous System (CNS) Confirmed Overall Response Rate (ORR) (Excluding RT ≤3 Months Pre-EFGR TKI)

Parameter	**cFAS**		**cEFR**	
	Aumolertinib (N=48) n (%)	Gefitinib (N=51) n (%)	Aumolertinib (N=25) n (%)	Gefitinib (N=28) n (%)
CNS Confirmed Overall response rate (CR/PR) (95% CI) [1]	60.4 (45.3, 74.2)	47.1 (32.9, 61.5)	84.0 (63.9, 95.5)	75.0 (55.1, 89.3)
Complete Response (CR)	12 (25.0)	3 (5.9)	4 (16.0)	0
Partial Response (PR)	17 (35.4)	21 (41.2)	17 (68.0)	21 (75.0)

[1] The exact 95% confidence interval (CI) is calculated using Clopper-Pearson method.

OS sensitivity analyses adjusting for crossover treatment

OS could have been potentially confounded by the crossover treatment. A subset of subjects in the gefitinib treatment arm could cross over to the aumolertinib treatment arm after progressive disease was confirmed by the Investigator and confirmation of the T790M resistance mutation

Post hoc sensitivity analyses of OS were performed using the Inverse Probability of Censoring Weighting (IPCW), Two-stage Accelerated Failure Time (2-stage AFT), and Rank Preserving Structural Failure Time (RPSFT) methods to account for those subjects who crossed over from gefitinib to receive open-label aumolertinib.

Analyses based on DCO date: 15 Jan 2021

• IPCW method: HR = 0.773 (95% CI: 0.562, 1.062; p = 0.1173)

• 2-stage AFT method: HR = 0.822 (95% CI: 0.604, 1.119; p = 0.2131)

• RPSFT method: HR = 0.771 (95% CI: 0.556, 1.068; p = 0.1164)

Analyses based on DCO 30 Sep 2022

Table 62: Method 1: Inverse Probability of Censoring Weighting [a]

`	Aumolertinib	Gefitinib
N	214	215
Subjects with events, n (%)	109 (50.9)	102 (47.4)
Median duration, months (95% CI)	39.13 (34.07, NA)	29.54 (21.82, 34.46)
Hazard ratio (95% CI)	0.7306 (0.5577, 0.9569)	
p-value (Robust-Score)	0.0242	

[a] Based on SW estimated using Cox model as the WD model. Baseline predictors included in the WD model for the numerator of SW: EGFR Mutation Type, Brain Metastasis; ECOG Performance Status. Baseline and time-varying predictors included in the WD model for the denominator of SW: all baseline predictors in the numerator model and time-dependent ECOG (ECOG Performance Status (0 = ECOG of 0; 1 = ECOG of ≥1) and serious adverse event current (0 = No; 1 = Yes). Stratified Cox model was used for the weighted marginal structural model, in which robust variance estimation used to account for the within-subject correlation caused by the weights.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NA = not applicable; OS = overall survival; SW = stabilized weights; WD = weight determining.

Table 63: Method 2: Two-stage Accelerated Failure Time[a]

	Aumolertinib	Gefitinib
N	214	215
Subjects with events, n (%)	109 (50.9)	126 (58.6)
Median duration, months (95% CI)	39.16 (34.1, NA)	29.71 (26.29, 34.5)
Hazard ratio (95% CI)	0.757 (0.584, 0.98)	
p-value (Log-Rank)	0.0341	

[a] In fitting the two-stage model, the ATF due to switching was estimated from a Weibull AFT model, with adjustment for baseline ECOG Performance Status, EGFR Mutation Type, and Brain Metastasis. Stratified method was used for hazard ratio and p-value.
AFT = Accelerated Failure Time; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NA = not applicable.

Table 64: Method 3: Rank Preserving Structural Failure Time[a]

	Aumolertinib	Gefitinib
N	214	215
Subjects with events, n (%)	109 (50.9)	112 (52.1)
Median duration, months (95% CI)	39.16 (34.1, NA)	31.15 (26.959, 36.012)
Hazard ratio (95% CI)	0.76 (0.576, 1.002)	
p-value (Log-Rank)	0.0510	

[a] Counterfactual survival times were calculated assuming an ever-treated model, with a log-rank test using fixed steps employed for g-estimation. Stratified method was used for hazard ratio and p-value.
CI = confidence interval; NA = not applicable.

2.6.5.4. HS-10296-12-01 (Part 3) (APOLLO)

Pivotal study for the T790M mutation (2nd line) indication - Study HS-10296-12-01

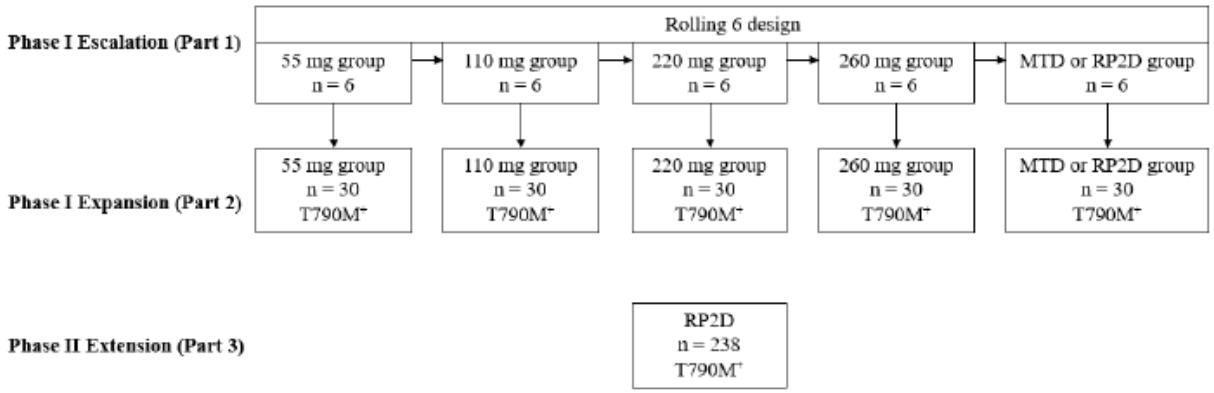
Title:

A Phase I/II, Open-label, Multicenter Clinical Trial to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Oral Once-Daily Administration of HS-10296 in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) That Have Progressed after Previous Treatment with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs)

This single arm study consists of 3 parts: part 1 dose-escalation (phase 1), part 2 dose-expansion (phase 1) and part 3 dose-extension (phase 2) to evaluate the safety, efficacy, and PK characteristics of aumolertinib 110 mg QD.

Only the Part 3 will be described below.

Figure 24 Study design of Study HS-10296-12-01



Methods

Study Participants

A central laboratory was used to confirm EGFR mutation status, including T790M status for subjects in Parts 2 and 3. Mutation status in the study was assessed by the central testing of tumour or blood samples, using the real-time polymerase chain reaction (PCR)-based **cobas®** EGFR Mutation Test v2 (Roche Diagnostics) to identify **mutations in exons 18, 19, 20 and 21** in the EGFR gene.

Main inclusion criteria

- Age at least 18 years.
- Histological or cytological confirmation diagnosis of NSCLC.
- Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI (e.g., gefitinib or erlotinib). In addition, other lines of therapy may have

been given. All patients had to have documented radiological progression on the last treatment administered, prior to enrolling in the study.

- Patients had to fulfil 1 of the following:
    - Must have experienced clinical benefit from EGFR TKI, according to the Jackman1 criteria (followed by systemic objective progression, RECIST or WHO) while on continuous treatment with an EGFR TKI.
    - Patients must also have confirmation of tumour T790M+ mutation status from a biopsy sample taken after disease progression on the most recent treatment regimen with an EGFR TKI.

Prior to entry, a result from the central analysis of the patient's T790M mutation status had to be obtained.

- A WHO performance status equal to 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
- At least 1 lesion that had not previously been irradiated, that had not been chosen for biopsy during the study screening period, and that could be accurately measured at Baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), whichever was suitable for accurately repeated measurements.

Main exclusion criteria

- Treatment with any of the following:
    - An EGFR TKI (e.g., erlotinib, gefitinib, or osimertinib) within 8 days or approximately 5 ×half-life, whichever is longer, of the first dose of study drug.
    - Previous or current treatment with third-generation EGFR TKIs
    - Any cytotoxic chemotherapy, investigational agents, or anticancer drugs for the treatment of advanced NSCLC from a previous treatment regimen or clinical study within 14 days of the first dose of study drug.
    - Medications that are predominantly CYP3A4 strong inhibitors or inducers or sensitive substrates of CYP3A4 with a narrow therapeutic range within 7 days of the first dose of study drug.
    - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug.
    - Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study drug, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Previously untreated NSCLC patients. To be eligible for this study, patients had to have received and progressed on EGFR TKI therapy.
- Any unresolved toxicities from prior therapy > CTCAE Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 prior platinum-therapy-related neuropathy.

- Spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of study treatment.
- Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension or active bleeding diatheses, which, in the Investigator's opinion, makes it undesirable for the patient to participate in the trial OR which would jeopardize compliance with the protocol, such as active infection (e.g., hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]).
- Any of the following cardiac criteria:
    - Mean resting QTc > 470 ms obtained from 3 ECGs, using the screening clinic's ECG machine and Fridericia's formula for QT interval correction (QTcF).
    - Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG (e.g., complete left bundle branch block, third-degree heart block, second degree heart block, PR interval > 250 ms).
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.
    - Left ventricular ejection fraction (LVEF) ≤ 40%.
- Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.
- Inadequate bone marrow reserve or organ function

Treatments

Aumolertinib was orally administered at 110mg once daily. Patients should avoid consumption of food for at least 1 hour prior to and 2 hours post dosing.

Objectives

Primary objective

• To evaluate the safety, tolerability, PK, and efficacy of oral aumolertinib in subjects with locally advanced or metastatic NSCLC who have progressed on prior therapy with EGFR TKIs.

Secondary objectives

• To evaluate the PK of aumolertinib and its metabolite HAS-719 after single-dose and multiple-dose oral administration of aumolertinib at steady state.

• To determine the antitumor efficacy of aumolertinib in terms of ORR, DCR, PFS, and DoR

Outcomes/endpoints

For the extension cohort, an independent central review (ICR) of the RECIST assessments was used for the primary analysis of ORR and other RECIST-based outcomes

- **ORR** was defined as the percentage of patients who have at least 1 confirmed response of CR or PR prior to any evidence of progression, as defined by RECIST 1.1.

- **PFS** was defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patients withdraw from aumolertinib therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis were censored at the time of the date of their last evaluable RECIST assessment. If the patients had no evaluable visits or do not have baseline data, they were to be censored at 0 days unless they die within 2 visits of baseline.
- **DoR** was defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.
- **DCR** was defined as the proportion of patients with a best overall response of CR, PR, or SD.
- **Tumour size** was defined as the sum of the lengths of the longest diameters of the RECIST 1.1 TLs. Percentage change in tumour size was to be determined for patients with measurable disease at Baseline and was derived at each visit by the percentage change in the sum of the diameters of TLs compared with Baseline.
- **Overall survival** was to be assessed based on the date of first dose and survival status at the time of analysis. Overall survival was defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who had not died at the time of the statistical analysis were to be censored at the time that the patient was last known to be alive.

At baseline, all subjects underwent tumour imaging, which included either CT or MRI. During the treatment period, tumour assessment was performed every 6 weeks according to the RECIST v1.1 criteria. These criteria were used to assess the response of each subject and to calculate ORR, DCR, DoR, PFS, and DepOR. Definitions of measurable, unmeasurable, TLs, NTLs, CR, PR, SD, and PD were according to those of RECIST v1.1. Restaging scans were obtained at 6-week intervals during treatment and were evaluated by ICR (for evaluation of the primary endpoint in the Phase 2 extension portion [Part 3]) or by Investigators (Parts 1 and 2).

Sample size

The primary objective for the phase of dose escalation and expansion cohorts in this study was to investigate the safety and tolerability and thereby identify the MTD of aumolertinib to recommend the dose(s) for evaluation in future clinical studies. The number of patients in the cohorts was based on the desire to obtain adequate tolerability, safety, pharmacokinetic, and pharmacodynamic data, while exposing as few patients as possible to aumolertinib and procedures. Tumour response as measured using RECIST 1.1, was to be assessed to provide preliminary antitumor activity in a patient population thought most likely to respond to aumolertinib.

Dose-Escalation Cohorts

For the dose-escalation phase of the study, cohorts of 3 to 6 evaluable patients were required. The total number of patients would depend upon the number of dose escalations necessary.

Dose-Expansion Cohorts

Patients were evaluable for the assessment of response in the expansion cohorts if they were dosed and had a baseline RECIST assessment. In addition, for the purposes of decision-making on the expansion cohorts, a patient's T790M+ status must also have been identified via central testing and match the cohort expansion population under assessment.

The expansion cohorts consisted of patients whose NSCLC has progressed following therapy with an EGFR TKI agent and whose tumour status is T790M+. Data from these cohorts were to provide a preliminary assessment of anti-tumour activity based on ORR (providing an acceptable false-negative risk of concluding that there is no activity if the true response rate is at least 30%).

A conclusion of no evidence of activity would be reached if no objective RECIST responses (confirmed partial response [PR] or complete response [CR]) were observed. If the true response rate was ≥ 30%, the chance of observing no responses in 30 evaluable patients was < 1%.

If anti-tumour activity in the form of responses was observed, 30 evaluable patients in each dose expansion cohort were to provide reasonable confidence of estimating what the true response rate would be in this population as well as in the ≥ second-line T790M+ population with EGFRm+ advanced NSCLC. Confidence intervals (CIs) were to be constructed (using the Clopper-Pearson interval) around the response rates observed in each population to enable decisions about the likely success of future studies in each of the populations, such as:

- 17% ORR (5 of 30 responses); 80% CI [8%, 29%]
- 30% ORR (9 of 30 responses); 80% CI [19%, 43%]
- 50% ORR (15 of 30 responses); 80% CI [37%, 63%]
- 70% ORR (21 of 30 responses); 80% CI [57%, 81%]

In the event that there was little evidence of anti-tumour activity observed within the cohort expansions, individual cohorts could be closed prior to 30 evaluable patients being recruited. This was to avoid exposing patients to a potentially ineffective therapy, providing that the evidence of no antitumor activity was strong enough at that time. If no responses were observed in up to 8 evaluable patients recruited to the first expansion cohort at the 55-mg dose, it could be appropriate to conclude no evidence of activity, because if the true response was ≥ 30%, the chance of observing no responses in 8 evaluable patients was < 6%. If this individual cohort expansion was terminated prior to the full 30 evaluable patients being recruited, other cohorts at the next dose level within the expansion would still be able to initiate recruitment as planned. Any such decision was to be at the discretion of Hansoh. The same role specified above for the first expansion cohort was to be followed for subsequent expansion cohorts prior to the full 30 evaluable patients being recruited.

Paired Biopsy Cohort

Patients were evaluable for the paired biopsy cohort if they have provided at a minimum the pre-study tumour biopsy and 1 tumour biopsy on study treatment. There were no published data available that adequately characterize or describe the variability of the biomarkers of interest in this patient population; thus, the sample size could not be calculated with consideration to statistical power. Data from 12 evaluable patients were considered to be adequate to allow a preliminary investigation of the objectives of this study.

Phase 2 Extension Cohort

The primary endpoint of the extension phase was ORR. A sample size of 238 evaluable patients achieves 90% power to detect a difference (P1 – P0) of 0.1 using a 2-sided binomial test with a significance level of 0.05 to test the following hypotheses:

H0: $P \leq 0.3$ ($P0 = 0.3$)

H1: $P > 0.3$ ($P1 = 0.4$)

In addition, with 238 evaluable patients, the precision of the estimation of ORR 0.4 in the overall study population would be ±6.4% (e.g., ORR 40%, 95% CI 33.7%, 46.5%). Thus, the lower bound of the 95% CI for ORR 40% is 33.7%, which is greater than 30%.

In addition, the number of 238 evaluable patients was considered to be adequate to assess the safety and tolerability of aumolertinib.

Randomisation and blinding (masking)

This is an open-label single-arm trial.

Statistical methods

Analysis populations

Efficacy analyses were performed on the FAS, which included patients with a baseline RECIST assessment who received at least one dose of aumolertinib (The assessment was based on ICR for extension cohort, investigator for escalation and expansion cohorts).

Multiplicity adjustment procedure

There was no multiplicity adjustment procedure for type I error control across primary and secondary endpoints.

Primary / secondary analyses

In Parts 1 and 2, the secondary efficacy analyses of ORR, DCR, PFS, and DOR (assessed by ICR) were used for the preliminary evaluation of the antitumor activity of aumolertinib and did not involve hypothesis testing.

For ORR and DCR, the point estimate and 95% Clopper-Pearson CIs were reported.

PFS and OS (Part 3 only) were summarized using the Kaplan-Meier method with 25th, 50^{th} (median), and 75th percentiles and associated 2-sided 95% CIs. DoR was summarized using the Kaplan-Meier method with the 50th (median) percentile and an associated 2-sided 95% CI.

For DepOR (Part 3 only), the best percentage change from baseline and the percentage change from baseline of the total diameter of TLs at Week 6 were summarized and plotted on waterfalls, if appropriate.

No adjustments were made for covariates. Missing data was not imputed.

Sensitivity analyses

In Part 3, sensitivity analyses of ORR, DCR, PFS, and DepOR, as assessed by the Investigator, were evaluated in the same manner as the primary and secondary analyses.

Subgroup analyses

The main efficacy outcome of ORR by ICR, was also analysed in Part 3 according to the following subgroups: gender, age (< 65 years and ≥ 65 years), presence of brain metastases at baseline, smoking status, EGFR mutation type (exon 19 deletion or L858R), and baseline ECOG PS (0 or 1).

Changes in planned analyses

DoR was changed from a secondary endpoint to an exploratory endpoint in version 6 (7 June 2017) of the study protocol.

There is a single version of the SAP, dated 6 March 2019. The CSR mentions there were no changes made to the planned analyses.

Additional cut-off date

The primary study analysis used a data cut-off date of 5 January 2019.

An updated cut-off date of 1 August 2021 led to an addendum CSR, with updated efficacy and safety summaries, as well as post-hoc analyses as described below.

Post-hoc analyses

Post hoc analyses were performed for Part 3 of the study to assess the efficacy of aumolertinib in a subset of subjects with brain metastases. These analyses were not prespecified in the study SAP and were presented within this CSR Addendum.

The following Analysis Sets were defined for the post hoc efficacy analyses:

• The CNS Full Analysis Set (cFAS) is a subset of the FAS including subjects have identified with at least 1 CNS lesion at baseline as assessed by ICR, whether measurable or not.

• The CNS Evaluable for Response set (cEFR) is a subset of the cFAS including subjects identified with at least 1 measurable CNS lesion at baseline as assessed by CNS ICR.

Subject disposition, analysis populations, demography, and baseline characteristics were summarized for the cFAS.

CNS efficacy is based on the data from CNS scans assessed by ICR per RECIST v1.1. The response data per overall RECIST assessment is not considered in the CNS efficacy analysis. CNS efficacy endpoints including ORR, DCR, TTR, PFS, DoR, OS and depth of response (DepOR) were defined as the same as the corresponding study efficacy endpoint but using the CNS ICR data.

Results

Participant flow

Of 496 subjects screened at 37 centres in China and Taiwan, 244 subjects were enrolled and received 110 mg QD (Table 65).

Table 65: Subject disposition in Part 3 – DCO date of 05 January 2019

Disposition	110 mg (N = 244) n (%)
Screened	496
Enrolled	244 (100.0)
Received Study Treatment	244 (100.0)
Ongoing Study Treatment at DCO	182 (74.6)
Discontinued Study Treatment	62 (25.4)
Subject's Decision	3 (1.2)
Adverse Events	6 (2.5)
Disease Progression	50 (20.5)
Lost to Follow-up	1 (0.4)
Poor Compliance	1 (0.4)

Data cutoff date was 05 January 2019.
DCO, data cutoff date.

Table 66: Subject disposition in Part 3 – DCO date of 01 August 2021

Disposition	110 mg (N = 244) n (%)
Screened	496
Enrolled	244 (100.0)
Received Study Treatment	244 (100.0)
Ongoing Study Treatment at DCO	30 (12.3)
Discontinued Treatment	214 (87.7)
Subject's Decision	13 (5.3)
Adverse Events	11 (4.5)
Disease Progression	187 (76.6)
Lost to Follow-up	1 (0.4)
Poor Compliance	1 (0.4)
Additional Treatment	1 (0.4)

Data cutoff date was 01 August 2021.

Table 67: Summary of Median Follow-up Time (Months) at the Initial and Updated DCO Dates for Subjects in Part 3

	110 mg (N = 244)
Initial DCO Date [a]	
Mean (SD)	4.7 (1.65)
Median	**4.7**
Min, Max	0.2, 7.7

	110 mg (N = 244)
Updated DCO Date [b]	
Mean (SD)	14.3 (11.06)
Median	**11.1**
Min, Max	0.2, 38.6

[a] Initial cutoff date was 05 Jan 2019. [b] Updated cutoff date was 01 Aug 2021.
DCO = data cutoff; max = maximum; min = minimum; SD = standard deviation.

Recruitment

Study initiation date: 08 May 2017

Primary analysis data cutoff: 05 January 2019

Updated and additional analyses data cutoff (including addition of post hoc efficacy analyses for subjects with brain metastases): 01 August 2021

This international multicenter study was conducted at 47 centres in the following countries: China (29 sites), Taiwan (8 sites), and the US (10 sites).

Conduct of the study

The first version of the protocol used in the United States was Version 4 (dated 08 December 2016). The first version of the protocol used in Taiwan was Version 5 (dated 05 April 2017). The first version of the protocol used in China was Version 7 (dated 29 August 2017). The last version was Version 7.3 (17 December 2019).

The Applicant considers the following changes major amendments made to the protocol for Part 3 (dose-extension) of the study:

- Primary endpoint revision from duration of response to confirmed ORR as analyses for time-to-event endpoints are not interpretable in a single-arm trial (Section 5.2.1 of Protocol Amendment Version 3 [dated 18 Apr 2016])
- Sample size increase to 238 evaluable subjects based on primary endpoint revision (Section 5.2.2 of Protocol Amendment Version 3 [dated 18 Apr 2016])
- For subjects showing clinical benefit, restarting study treatment when an AE resolved to Common Terminology Criteria of Adverse Events (CTCAE) Grade ≤ 2 within 21 days of onset (Section 6.8.2 of Protocol Amendment Version 2 [dated 08 Apr 2016])
- Established 110 mg of aumolertinib as the recommended dose for Part 3 of the study (Section 8.1.1 of Protocol Amendment Version 7.2 [dated 29 Aug 2019])

Other protocol amendments primarily relate to changes in the management of individual AEs.

Table 68: Summary of Major Protocol Amendments (for Part 3 only)

Section	Change	Reason
Version 7.3 (dated 17 Dec 2019)[a]		

Section	Change	Reason
Sections 6.2 Administration Regimen; 8.1.1 Dosing Regimen; 9.1.10.2 Follow-up of Disease Progression; 9.4.1.2 Collection of Plasma cfDNA for Exploratory Analysis; 9.5.4 Exploratory Study Samples; 9.6 Anti-tumour Activity [b]; 9.8 Management of Patients' Self-reported Outcomes; Appendix B Study Schedule; Appendix D 4.1 Schedule of Evaluation [c]	**Updated the Assessment Cycle** If HS-10296 is discontinued for reasons other than disease progression, the patient must go on assessments every 6 weeks (C1~C17; first 12 months) or 12 weeks (C21 and thereafter; 12 months later) until disease progression, even if the patient has received other anticancer treatments After the median PFS (12 months), the condition will become stable.	Changing the assessment cycle from once every 6 weeks to once every 12 weeks will reduce the patient's radiation exposure during assessment
Version 7.2 (dated 29 Aug 2019)[a]		
7.8 Rescreening Procedures	Added section: Patients who fail screening can be rescreened if the investigator considers it necessary. Rescreening requires the following: • Patients are required to re-sign the informed consent. • Patients whose biopsy samples were collected after disease progression post latest EGFR-TKI treatment are positive for T790M in the central laboratory test are not required to be retested for T790M • Patients previously negative for T790M may have the test repeated • Laboratory and imaging tests are not required to be repeated if performed within the window period at rescreening, but	Clarify the process for rescreening of patients

Section	Change	Reason
	required if outside the window	
8.1.1 Dosing Regimen	Added 110 mg QD to the Phase 2 dose extension phase	Clarify that the dose of phase 2 administration is to be 110 mg QD
Version 7 (dated 29 Aug 2017)		
Synopsis	Changed the estimated total number of patients from approximately 370 to approximately 430	Increase in sample size and number of sites as synopsis included expansion cohorts for both the 55 and 110 mg dose groups.
	Changed the duration of study from 24 to 36 months	
	Changed the estimated total number of sites from 10 to 20	
9.4.1.1 Collection of Tumour Biopsy Samples	Deleted "optional" from the Paired Biopsy Cohort Screening visit	Paired biopsy is mandatory at the Screening Visit
Version 6 (dated 07 Jun 2017)		
5.2.1 Definition of Study Endpoints	DoR changed from the Primary endpoint to an Exploratory endpoint	To address health authority's comment that analyses for time-to-event endpoints are not interpretable in a single arm trial
7.2 Exclusion Criterion	Added the following exclusion for the expansion and extension cohorts: Previous or current treatment with third-generation EGFR-TKI is not allowed	Updated per health authority's recommendation that the criterion related to third-generation EGFR-TKI be revised
	Added the following exclusion: Medications that are predominantly CYP3A4 strong inhibitors or inducers or sensitive substrates of CYP3A4 with a narrow therapeutic range are not allowed during study and within7 days of the first dose of study drug.	Per health authority's that CYP3A4 strong inhibitors or inducers or sensitive substrates of CYP3A4 be excluded. Also, as per FDA request to exclude patients who have been exposed within seven days of planned first study treatment day to medications that are predominant CYP3A4 strong inhibitors or inducers, or sensitive substrates of CYP3A4

Section	Change	Reason
		with a narrow therapeutic range.
7.4 Concomitant Medications; Appendix G Prohibited Medication	Added a statement to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent substrates/inducers/inhibitors of CYP3A4 and/or CYP2D6 and CYP1A2. A list of prohibited medications has been added as Appendix G which also includes those known to prolong QT interval	As per health authority's request to include a list of medications that will be avoided during protocol therapy including predominant substrates, strong inhibitors or inducers of CYP3A4, CYP2D6, and CYP1A2, or sensitive substrates of CYP3A4 with a narrow therapeutic range.
8.1.1 Treatments Administered	Added text that patients should avoid consumption of food for at least 1 hour prior to and up to 2 hours post dosing with study drug	Added to address health authority's recommendation to include instructions on how the drug will be taken with regard to food (i.e., fasting window)
9.1.7 Electrocardiograms; Appendix B Study Plan (footnote d)	Added extension cohorts to Day 1 C1 assessments. Added predose ECGs to Days 8 and 15 of C2 for all cohorts	As per health authority's request to increase QT monitoring at the anticipated Cmax
10.5.1 Analysis Data Set	Revised the Full Analysis Set to include patients who received at least one dose of study drug	To address health authority's comments that the as-treated population (all patients who received at least 1 dose of study drug) be the primary analysis population
Appendix G Prohibited Medications	Added list of prohibited medications	Provide a list of drugs prohibited for QTc prolongation per principal investigator request. Also includes list of predominant substrates, strong inhibitors or inducers of CYP3A4, CYP2D6, and CYP1A2, or sensitive substrates of CYP3A4 with a narrow therapeutic range as per FDA request
Protocol Version 5 (dated 05 Apr 2017) was the Chinese Translation for China.		

Section	Change	Reason
Version 4 (dated 08 Dec 2016)		
6.4 Definition of Dose-limiting Toxicity	Added cardiac toxicity greater than Grade 3 as a dose-limiting toxicity	Revised based on health authority's recommendations for further safety measures.
7.2 Exclusion Criteria	Added to Criterion #6: Patients with LVEF ≤ 40%	Follow health authority's recommendation to add an exclusion criterion for LVEF
	Criterion #11: Added women who have a positive urine or serum pregnancy text at the Screening Visit are also excluded from the study.	Clarified that women who are pregnant will not be enrolled
	Criterion #16: Added that patients with any severe and uncontrolled ocular diseases (per ophthalmologist's opinion) that may present a specific risk to the patient's safety are excluded	Added an exclusion criterion to exclude patients with ocular disease
7.3 Restrictions	Added that patients must try to avoid concomitant use of medications, herbal supplements, or foods with known potent substrates/inducers/inhibitors of cytochrome P450 3A4, except as clinically indicated for the treatment of AEs; and that patients must have discontinued these drugs for at least 1 month before screening through 3 months after the last dose of study drug	Follow health authority's recommendation to add the restriction of cytochrome P450 3A4 (CYP3A4) potent inducer and inhibitory medications, herbal supplements, and grapefruit. Also per health authority's request to specify plans for more frequent safety monitoring in patients who, while receiving investigational drug treatment, require the use of concomitant medications that are predominant substrates, strong inhibitors, or inducers of CYP3A4, CYP2D6, and CYP1A2 or sensitive substrates of CYP3A4 with a narrow therapeutic range.
9.1.8 Echocardiogram/MUGA Scan	Clarified that echocardiogram or MUGA scan will be conducted	Add per health authority's recommendation

Section	Change	Reason
	in escalation, expansion, and extension cohort patients	
9.4.2 Pharmacogenetics	Added that blood-borne biomarkers (e.g., L858R, 19 exon deletion, T790M) will be investigated for their gene expression, mutation, or deletion to assess response to the study drug and development of NSCLC	Specified the biomarkers to be investigated and added the purpose of the test

[a] The versions were implemented after the primary analysis data cutoff date (05 Jan 2019).
[b] Also applies to patients who stop treatment before progression.
[c] Any other sites at which new disease is suspected should also be imaged at follow-up.
AE = adverse event; C = cycle; CI = confidence interval; C_{max} = maximum concentration; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; EDC = electronic data capture; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitors;; F/U = follow-up; HRCT = high-resolution computed tomography; IVRS = Interactive Voice Response system; LVEF = left ventricular ejection fraction; MTD = maximum tolerated dose; MUGA = multigated acquisition; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; QD = once daily; RP2D = recommended Phase 2 dose; SAE = serious adverse event; SRC = Safety Review Committee;

Twenty-five of the 244 subjects (10.2%) had major protocol deviations, of whom 13 failed to adhere to study procedures/visit schedules (e.g., missing laboratory or RECIST assessments). Seven subjects (2.9%) violated inclusion/exclusion criteria, 2 (0.8%) took prohibited drugs, 1 (1.1%) had DNA testing without providing ICF for this procedure, 1 (1.1%) continued to take aumolertinib for 5 days after treatment discontinuation (one subject died approximately 1 month later from disease progression), and for 1 subject (1.1%) an SAE was reported late. The SAE was a Grade 2 pulmonary embolism, which was considered probably related to aumolertinib by the Investigator and had resolved.

Baseline data

Table 69: Baseline demographics and disease characteristics of patients in FAS of study 12-01, part 3

Parameters		**110 mg (N = 244)**
Age (years)	Mean ± Std Dev	60.8 ± 10.79
	Median	61.0
	Minimum, maximum	27, 87
Sex, n (%)	Male	102 (41.8)
	Female	142 (58.2)
Height (cm)	Mean ± Std Dev	161.55 ± 7.832
	Median	160.60

	Minimum, maximum	144.0, 180.0
Weight (kg)	Mean ± Std Dev	60.44 ± 10.678
	Median	59.20
	Minimum, maximum	39.0, 100.0
BMI (kg/m^2)	Mean ± Std Dev	23.08 ± 3.231
	Median	23.16
	Minimum, maximum	15.2, 33.7
Race, n (%)	Asian	244 (100)
Region, n (%)	Mainland China	189 (77.5)
	China Taiwan	55 (22.5)
History of Smoking, n (%)	Never smoke	178 (73.0)
	Smoking	4 (1.6)
	Quit smoking in the past	62 (25.4)
History of Underlying Disease, n (%)	Yes	215 (88.1)
	None	29 (11.9)
AJCC Staging, n (%)	IA	2 (0.8)
	IB	1 (0.4)
	IIA	1 (0.4)
	IIIB	8 (3.3)
	IV	173 (70.9)
	IVA	30 (12.3)
	IVB	27 (11.1)
	IVC	2 (0.8)
Primary Tumour Site, n (%)	Right lung	140 (57.4)
	Left lung	100 (41.0)
	Both lungs	4 (1.6)
Histological Classification, n (%)	Adenocarcinoma	242 (99.2)
	Squamous cell carcinoma	2 (0.8)
Previous History of Chemotherapy, n (%)	Yes	111 (45.5)
	None	132 (54.1)
	Unknown	1 (0.4)

Previous History of Radiotherapy, n (%)	Yes	64 (26.2)
	None	180 (73.8)
Previous Surgical History, n (%)	Yes	64 (26.2)
	None	179 (73.4)
	Unknown	1 (0.4)
EGFR Gene Mutation, n (%)	Exon 19 deletion	155 (63.5)
	L858R	85 (34.8)
	Other	4 (1.6)
T790M Mutation Status, n (%)	Positive	244 (100)
ECOG PS Score, n (%)	0	85 (34.8)
	1	159 (65.2)
Brain Metastasis, n (%)	Yes	90 (36.9)
	No	154 (63.1)

AJCC = American Joint Committee on Cancer; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; L858R = leucine to arginine substitution at position 858 in exon 21 of the epidermal growth factor receptor; PS = performance status; Std Dev = standard deviation; T790M = threonine to methionine substitution at position 790 in exon 20 of the epidermal growth factor receptor.

Data cutoff date was 01 August 2021

In cFAS, the subjects were aged 32 to 87 years (median 62.0 years) received 110 mg aumolertinib QD. Of these, 45 (51.1%) were female and 43 (48.9%) were male; 58 (65.9%) never smoked, 3 were active smokers (3.4%), and 27 (30.7%) quit smoking. A total of 47 subjects (53.4%) harboured exon 19 deletion, 38 subjects (43.2%) with the L858R mutation, and 3 subjects (3.4%) with other mutations. Twenty-three subjects (26.1%) had an ECOG PS score of 0 and 65 subjects (73.9%) had a score of 1. Eighty-three (94.3%) subjects had brain metastasis.

A total of 220 (90.2%) subjects in Part 3 received prior medications. The most common prior medications used in ≥ 10% of the subjects included: herbal and traditional medicines (93 subjects, 38.1%), analgesics (57 subjects, 23.4%), digestive and metabolic system drugs (52 subjects, 21.3%), various kinds of drugs (drugs difficult to be classified) (52 subjects, 21.3%), cough and cold drugs (51 subjects, 20.9%), nervous system drugs (37 subjects, 15.2%), ophthalmic treatment drugs (33 subjects, 13.5%), bisphosphonates (30 subjects, 12.3%), musculoskeletal system drugs (30 subjects, 12.3%), other systemic antibiotics (28 subjects, 11.5%), other β-lactam antibiotics (27 subjects, 11.1%), and proton pump inhibitors (27 subjects, 11.1%).

Table 70: Summary of Prior Anticancer Therapies (Safety Population – Part 3 [N = 244])

Prior Anticancer Therapies	**Aumolertinib n (%)**
Any Prior Anticancer Therapies	**244 (100.0)**
Any TKIs	**244 (100.0)**
Gefitinib	120 (49.2)
Icotinib	68 (27.9)
Erlotinib	57 (23.4)

Prior Anticancer Therapies	Aumolertinib n (%)
Afatinib	21 (8.6)
Any Chemotherapies	**106 (43.4)**
Pemetrexed	77 (31.6)
Cisplatin	55 (22.5)
Carboplatin	44 (18.0)
Docetaxel	19 (7.8)
Gemcitabine	19 (7.8)
Nedaplatin	13 (5.3)
Paclitaxel	10 (4.1)
Vinorelbine	6 (2.5)
Tegafur	4 (1.6)
Uracil	3 (1.2)
Bevacizumab	2 (0.8)
Lobaplatin	2 (0.8)
Cyclophosphamide	1 (0.4)
Endostatin	1 (0.4)
Fluorouracil	1 (0.4)
Gimeracil	1 (0.4)
Oteracil	1 (0.4)
Peplomycin	1 (0.4)
Tumour Necrosis Factor Inhibitors	1 (0.4)
Unknown	1 (0.4)
Any Other Therapies	**14 (5.7)**
Bevacizumab	6 (2.5)
Endostatin	4 (1.6)
Atezolizumab	1 (0.4)
Cantharis capsule	1 (0.4)
Nivolumab	1 (0.4)
Pembrolizumab	1 (0.4)

TKI = tyrosine kinase inhibitor.

There were 215 (88.1%) subjects in Part 3 that received concomitant medications. The most common concomitant medications used in ≥ 10% of the subjects include: digestive and metabolic system drugs (52 subjects, 21.3%), analgesics (57 subjects, 23.4%), bisphosphonate drugs (30 subjects, 12.3%), cough and cold drugs (51 subjects, 20.9%), musculoskeletal system drugs (30 subjects, 12.3%), nervous system drugs (37 subjects, 15.2%), ophthalmic treatment drugs (33 subjects, 13.5%), other systemic antibiotics (28 subjects, 11.5%), other β-lactam antibiotics (27 subjects, 11.1%), proton pump inhibitors (27 subjects, 11.1%), herbal and traditional medicines (93 subjects, 38.1%), and various kinds of drugs (drugs difficult to be classified) (52 subjects, 21.3%).

Numbers analysed

Table 71: Analysis Set- All Enrolled Subjects

Cohort: Extension

	Mainland China (N=189) n (%)	Taiwan (N=55) n (%)	Total (N=244) n (%)
Safety Set	189 (100.0%)	55 (100.0%)	244 (100.0%)
Full Analysis Set	189 (100.0%)	55 (100.0%)	244 (100.0%)

In each study part, all enrolled subjects were included in both the FAS and SS. The PKAS included

• Part 1: all enrolled subjects;

• Part 2: 85/94 enrolled subjects (55 mg: 86.7%, 110 mg: 100%, 220 mg: 83.9% of the enrolled subjects);

• Part 3: 237/244 (97.1%) enrolled subjects.

Reasons for exclusion from the PKAS were missing plasma concentration measurements or unusually high PK values (HS-10296-12-01 PK Statistical Analysis Report).

244 patients were included, so the FAS is 244 patients and this population (number in denominator) is the one by which all efficacy measures shall be calculated.

Outcomes and estimation

Table 72: Efficacy Results – Updated Analysis in Study HS-120296-12-01 (Part 3)

Efficacy Parameter	ICR (N = 244)	Investigator (N = 244)
ORR		
ORR, n (%) (95% CI)[a]	168 (68.9) (62.6, 74.6)	151 (61.9) (55.5, 68.0)
DCR		
DCR, n (%) (95% CI)[a]	228 (93.4) (89.6, 96.2)	224 (91.8) (87.6, 94.9)
PFS		
Number of events	218 (89.3)	216 (88.5)
Median PFS (months)	12.4	12.4
P25, P75	5.5, 20.7	5.5, 22.1
95% CI[b]	9.7, 15.0	9.7, 13.9
DoR		
Median DoR (months)	15.1	13.8
95% CI[b]	12.9, 16.6	12.5, 15.6
OS		
Median OS (months)	NA	31.50

Efficacy Parameter	ICR (N = 244)	Investigator (N = 244)
95% CI[b]	NA	25.9, 35.7

Note: Tumour response assessments were performed according to RECIST v1.1. All responses were confirmed. Duration of response applies only to subjects who had confirmed complete response (CR) or partial response (PR) as the best response, defined as the time from the date of first response (PR or CR) until the date of progression or death in the absence of disease progression.

[a] Two-sided CI based on Clopper-Pearson test.

[b] Calculated from the Kaplan-Meier plot.

CI = confidence interval; DCR = disease control rate; DoR = duration of response; ICR = independent central review; NA = not available; ORR = objective response rate; P25: 25th percentile; P75: 75th percentile; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
Data cutoff date: 01 August 2021.

- ***Confirmed ORR and DCR***

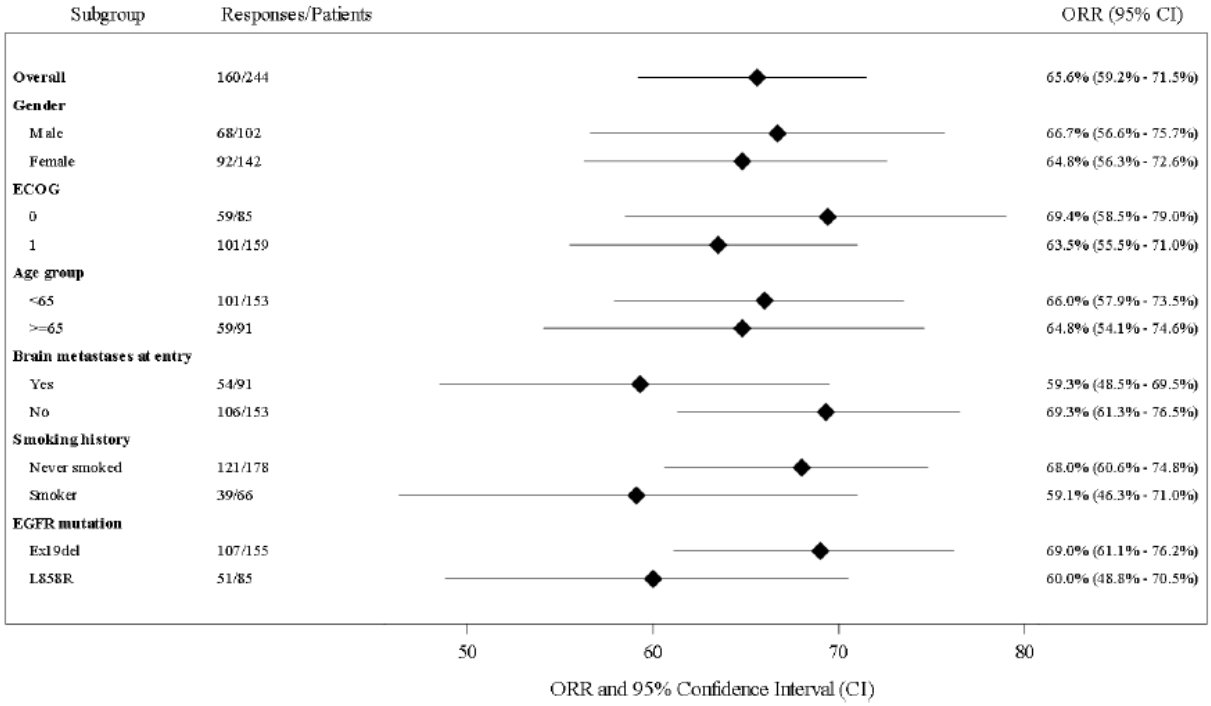
Table 73: ORR and DCR for Part 3 (FAS; ICR and Investigator Assessment)

Parameter	ICR (N = 244) n (%)	Investigator (N = 244) n (%)
Complete response	0	0
Partial response	160 (65.6%)	137 (56.1)
Stable disease	68 (27.9%)	87 (35.7)
Progressive disease	12 (4.9%)	13 (5.3)
Not evaluable	4 (1.6%)	7 (2.9)
ORR (95% CI)[a]	160 (65.6) (59.2, 71.5)	137 (56.1) (49.7, 62.5)
DCR (95% CI)[a]	228 (93.4) (89.6, 96.2)	224 (91.8) (87.6, 94.9)

[a] Two-sided CI based on Clopper-Pearson test.

Note: ORR is defined as the percentage of subjects who have at least 1 confirmed response of CR or PR prior to any evidence of progression. DCR is defined as the proportion of subjects with a best overall response of CR, PR, or SD.
CI = confidence interval; CR = complete response; CSR = clinical study report; DCR = disease control rate; FAS = Full Analysis Set; ICR = independent central review; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Data cutoff date (primary analysis): 05 January 2019.

Figure 25 Efficacy of Aumolertinib: ORR Subgroup Analysis in Part 3 (FAS, ICR Assessment)



CI = confidence interval; CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ex19del = exon 19 deletion; FAS = Full Analysis Set; ICR = independent central review; L858R = substitution of a leucine (L) with an arginine (R) at position 858 in exon 21; ORR = objective response rate.
Data cutoff date (primary analysis): 05 January 2019.

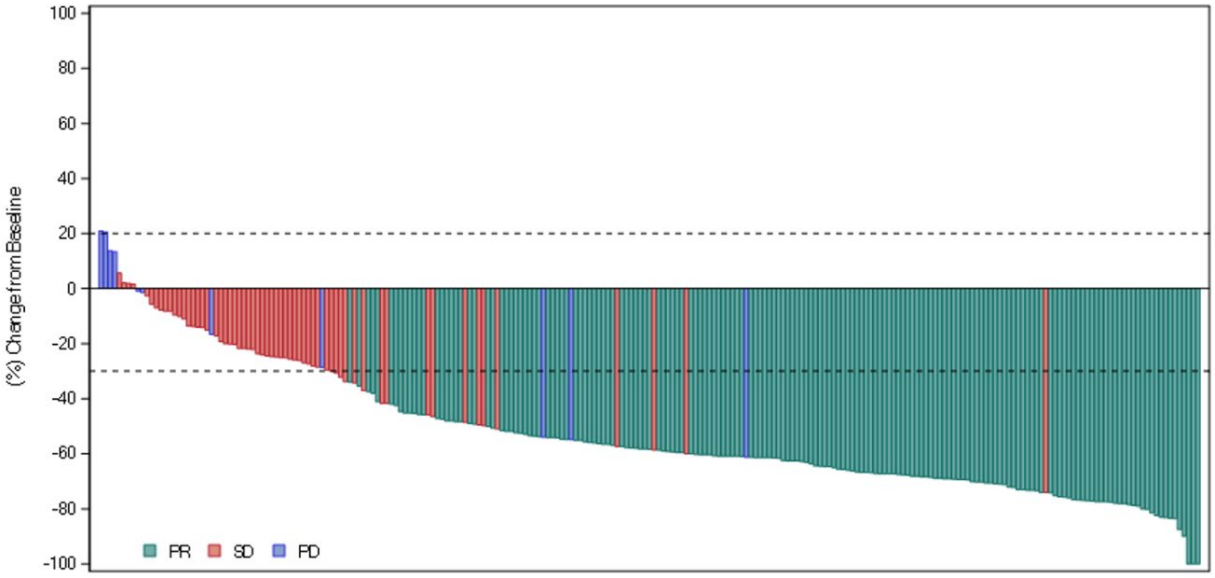
Updated analysis – DCO 01 August 2021

Table 74: Objective Response Rate and Disease Control Rate in Part 3 (Full Analysis Set; ICR and Investigator Assessment)

Parameter	ICR (N = 244) n (%)	Investigator (N = 244) n (%)
Complete response	0	0
Partial response	168 (68.9)	151 (61.9)
Stable disease	60 (24.6)	73 (29.9)
Progressive disease	12 (4.9)	16 (6.6)
Not evaluable	4 (1.6)	4 (1.6)
ORR (95% CI)[a]	168 (68.9) (62.6, 74.6)	151 (61.9) (55.5, 68.0)
DCR (95% CI)[a]	228 (93.4) (89.6, 96.2)	224 (91.8) (87.6, 94.9)

[a] Two-sided CI based on Clopper-Pearson test.
Note: Tumour response assessments were performed according to RECIST v1.1. All responses were confirmed. ORR is defined as the percentage of patients who have at least 1 confirmed response of CR or PR prior to any evidence of progression. DCR is defined as the proportion of patients with a best overall response of CR, PR, or SD.
CI = confidence interval; CR = complete response; CSR = clinical study report; DCR = disease control rate; FAS = Full Analysis Set; ICR = independent central review; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
Data cutoff date (updated analysis): 01 August 2021.

Figure 26: DepOR in Part 3 of Study HS-10296-12-01 – Best Percentage Change From Baseline (FAS) – Updated Analysis



Note: Tumour response assessments were performed according to RECIST v1.1. All responses were confirmed.
CSR = clinical study report; DepOR = depth of response; FAS = Full Analysis Set; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
Data cutoff date (updated analysis): 01 August 2021.

Table 75: Concordance Analysis: Investigator and IRC RECIST Best Overall Response (FAS)

		Best Overall Response by IRC					
	Best Overall Response by Investigator	**CR**	**PR**	**SD**	**PD**	**NE**	**Total**
Aumolertinib (N = 244) n (%)	**CR**	0	0	0	0	0	0
	PR	0	122 (50.0)	14 (5.7)	1 (0.4)	0	137 (56.1)
	SD	0	35 (14.3)	51 (20.9)	1 (0.4)	0	87 (35.7)
	PD	0	1 (0.4)	2 (0.8)	10 (4.1)	0	13 (5.3)
	NE	0	2 (0.8)	1 (0.4)	0	4 (1.6)	7 (2.9)
	Total	0	160 (65.6)	68 (27.9)	12 (4.9)	4 (1.6)	244
	Investigator and IRC Assessment Matched						187 (76.6)
	Investigator and IRC Assessment Mismatched						57 (23.4)
	Kappa (95% CI)						0.559 (0.459, 0.659)

CI = confidence interval; CR = complete response; FAS = full analysis set; IRC = Independent Review Committee; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

- ***DoR***

Table 76: DoR for Part 3 (FAS; ICR Assessment) – DCO 05 January 2019

Parameter	**ICR (N = 160) n (%)**
Subjects with DoR > 3 months	68 (42.5)
Median DoR (months)	NA
95% CI[a]	5.6, NA

[a] Calculated from the Kaplan Meier plot.
Note: DoR applies only to subjects who have CR or PR as the best response, defined as the time from the date of first response (PR or CR) until the date of progression or death in the absence of disease progression.
CI = confidence interval; CR = complete response; CSR = clinical study report; DoR = duration of response; FAS = Full Analysis Set; NA = not applicable; PR = partial response.
Data cutoff date (primary analysis): 05 January 2019.

Updated analysis – DCO 01 August 2021

Table 77: Duration of Response in Part 3 (Full Analysis Set; ICR and Investigator Assessment)

Table 78: DoR in Part 3 of Study HS-10296-12-01 (FAS) – Updated Analysis

Parameter	ICR (N = 168) n (%)	Investigator (N = 151) n (%)
Median DoR (months)	15.1	13.8
95% CI [a]	12.9, 16.6	12.5, 15.6

[a] Calculated from the Kaplan-Meier plot.
Note: DoR applies only to subjects who had confirmed CR or PR as the best response, defined as the time from the date of first response (PR or CR) until the date of progression or death in the absence of disease progression.
CI = confidence interval; CR = complete response; CSR = clinical study report; DoR = duration of response; FAS = Full Analysis Set; PR = partial response.
Data cutoff date (updated analysis): 01 August 2021.

Ancillary analyses

CNS additional post-hoc analyses

The post hoc CNS efficacy analyses performed for Part 3 included the cFAS, which comprised 88 subjects, of whom 73 were evaluable for response (cEFR).

Table 79: CNS Efficacy in Study HS-120296-12-01 (Part 3)

CNS Efficacy Parameter	cFAS (N = 88)	cEFR (N = 73)
Confirmed ORR, n (%) (95% CI)[a]	48 (54.5) (43.6, 65.2)	46 (63.0) (50.9, 74.0)
DCR, n (%) (95% CI)[a]	82 (93.2) (85.7, 97.5)	68 (93.2) (84.7, 97.7)
Median DoR (95% CI)[b], months	12.5 (9.2, 19.5)	12.5 (8.3, 16.4)
Median PFS (95% CI)[b], months	13.6 (10.5, 16.6)	12.5 (9.6, 15.3)
Median OS (95% CI)[b], months	19.1 (16.0, 23.8)	19.1 (16.0, 23.7)

Note: Tumour response assessments were performed according to RECIST v1.1. All responses were confirmed.
Duration of response is only for subjects with confirmed response (n = 48 and n = 46 for cFAS and cEFR, respectively).
[a] Two-sided CI based on Clopper-Pearson test.
[b] Calculated from the Kaplan–Meier curve.
cEFR = CNS Evaluable for Response set; cFAS = CNS Full Analysis Set; CI = confidence interval; CNS = central nervous system; DCR = disease control rate; DoR = duration of response; ORR = objective response rate; PFS = progression-free survival; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumours.
Data cutoff date was 01 August 2021.

The range (in days) for subjects who received radiation prior to the start of study treatment was -1158 to -18 days for subjects in cFAS and cEFR Analysis.

Table 80: Summary of Subjects Who Received Prior and/or Subsequent Radiation on the Brain (cFAS and cEFR)

	cFAS (N = 88) n (%)	**cEFR (N = 73) n (%)**
Number of subjects who received radiation for brain metastases	33 (37.5)	25 (34.2)
Prior radiation	31 (35.2)	23 (31.5)
Subsequent radiation	3 (3.4)	3 (4.1)

cFAS = CNS full analysis set; cEFR = CNS evaluable for response set; CNS = central nervous system.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 81: Summary of efficacy for trial HS-10296-03-01

Title: A Randomized, Controlled, Double-blind, Multicenter, Phase III Study to Assess the Efficacy and Safety of HS-10296 Versus Gefitinib as First-line Treatment in Patients With EGFR Mutation (Positive), Locally Advanced or Metastatic NSCLC		
Study identifiers:	HS-10296-03-01	
Design:	Randomized (1:1), active-controlled, double-blind, multicenter	
	Duration of main (treatment) phase:	From first dose of study treatment until treatment discontinuation due to disease progression (per RECIST v1.1) or other protocol-specified treatment termination criteria were met. Upon treatment discontinuation, subjects proceeded to the follow-up period to complete a 28-day safety follow-up after the last dose, and subsequently underwent survival follow-up once every 6 weeks. Subjects who experienced disease progression while continuing to receive gefitinib under randomized, blinded conditions during the blinded study treatment period could, if meeting the protocol-specified criteria, begin open-label aumolertinib crossover treatment.
	Duration of Run-in phase:	

	Duration of Extension phase:		Not applicable Not applicable; however, there were follow-up and crossover treatment periods in the study, as described above.
Hypotheses:	H_0: PFS HR > 0.67 for aumolertinib versus gefitinib. H_1: PFS HR ≤ 0.67 for aumolertinib versus gefitinib.		
Treatment groups:	Aumolertinib		N = 214 subjects
	Gefitinib		N = 215 subjects
Endpoints and definitions:	Primary endpoint	PFS	Tumour response based on RECIST v1.1 criteria (including CR, PR, SD, PD). Defined as time (in months) from start of randomization until objective tumour progression (as evaluated by the Investigator)
	Secondary endpoint	ORR	Percentage of subjects who had at least 1 CR or PR before progression.
	Secondary endpoint	DoR	Interval between the first date on which response was achieved and the date of disease progression or death (in months).
	Secondary endpoint	OS	Time (in months) from start of randomization to the date of death from any cause.
Database lock:	15 Jan 2021		
Results and Analysis			
Analysis description:	**Primary analysis (DCO 15 Jan 2021, as per SAP V1.1)**		
Analysis population and time point descriptions:	Analysis population: - FAS: All subjects who were enrolled, randomized, and received at least 1 dose of study treatment.		
	Treatment group	Aumolertinib	Gefitinib

Descriptive statistics and estimate variability:	Number of subjects	214	215
	Median PFS (months) 95% CI	19.12 17.74, 20.80	9.72 8.34, 12.45
	ORR (%) 95% CI	73.8 67.4, 79.6	72.1 65.6, 78.0
	Median DoR* (months) 95% CI	19.12 17.74, 20.80	8.28 6.90, 11.07
	Median OS (months)***	NA	NA
	* Subject numbers are n = 158 and n = 155 for the aumolertinib and gefitinib group, respectively. ** Best percentage change from baseline in target lesion size (calculated as follows: the best change from baseline in target lesion tumour size/baseline target lesion tumour size × 100%). *** 123 subjects from the FAS had died (28.7%), including 54 subjects (25.2% in the aumolertinib group and 69 subjects (32.1%) in the gefitinib group, by the time of the primary analysis DCO of 15 Jan 2021.		
Effect estimates per comparison:	PFS	Comparison groups:	Aumolertinib versus gefitinib
		HR:	0.460
		95% CI:	0.358, 0.591
		p-value (log-rank	< 0.0001
	ORR	Comparison groups:	Aumolertinib versus gefitinib
		OR:	1.092
		95% CI:	0.704, 1.693
		p-value (CMH test):	0.6939
	DoR	Comparison groups:	Aumolertinib versus gefitinib
		HR:	0.368
		95% CI:	0.272, 0.498
		p-value (log-rank test):	< 0.0001
	OS	Comparison groups:	Aumolertinib versus gefitinib
		HR:	0.820

		95% CI:	0.573, 1.173
		p-value (log-rank test):	0.2760
Notes:	Reasons for treatment discontinuations other than due to disease progression were as follows: - Aumolertinib group (n = 27): AE (n = 10), subject decision (n = 13), Investigator decision (n = 2), and other reasons (n = 2). - Gefitinib group (n = 31): AE (n = 13), subject decision (n = 15), Investigator		
	Critical findings: - The primary endpoint was met with a statistically significant and clinically meaningful improvement in PFS for aumolertinib over gefitinib but the magnitude of the effect to be weighed against the inadequate comparator - Cross-over to aumolertinib in 41 subjects in gefitinib group that could potentially confounded OS, post-hoc sensitivity analyses to adjust for CO treatment performed, with no statistically significant benefit for aumolertinib-treated subjects.		
Analysis description:	**Updated analysis (DCO 06 Aug 2021)**		
Analysis population and time point descriptions:	Analysis population: - FAS: All subjects who were enrolled, randomized, and received at least 1 dose of study treatment.		
Descriptive statistics and estimate variability:	Treatment group	Aumolertinib	Gefitinib
	Number of subjects	214	215
	Median PFS (months) 95% CI	19.81 17.74, 23.39	9.72 8.34, 12.45
	ORR (%) 95% CI	74.8 68.4, 80.4	72.1 65.6, 78.0
	Median DoR* (months) 95% CI	19.19 15.54, 22.11	8.28 6.90, 11.07
	Median OS (months)***	NA	NA

	* Subject numbers are n = 160 and n = 155 for the aumolertinib and gefitinib group, respectively. ** Best percentage change from baseline in target lesion size (calculated as follows: the best change from baseline in target lesion tumour size/baseline target lesion tumour size × 100%). *** 123 subjects from the FAS had died (28.7%), including 54 subjects (25.2% in the aumolertinib group and 69 subjects (32.1%) in the gefitinib group, by the time of the primary analysis DCO of 15 Jan 2021.		
Effect estimates per comparison:	PFS	Comparison groups:	Aumolertinib versus gefitinib
		HR:	0.450
		95% CI:	0.354, 0.572
		p-value (log-rank test):	< 0.0001
	ORR	Comparison groups:	Aumolertinib versus gefitinib
		OR:	1.092
		95% CI:	0.704, 1.693
		p-value (CMH test):	0.6939
	OS	Comparison groups:	Aumolertinib versus gefitinib
		HR:	0.885
		95% CI:	0.651, 1.203
		p-value (log-rank test):	0.4340
Analysis description:	**Updated analysis (DCO 30 Sep 2022)**		
Descriptive statistics and estimate variability:	Treatment group	Aumolertinib	Gefitinib
Number of subjects		214	215
Median OS (months) 95% CI		39.16 (34.10, NA)	31.15 (27.89, 36.50)
Effect estimates per comparison:			
OS		Comparison groups:	Aumolertinib versus gefitinib
		HR:	0.816
		95% CI:	0.631, 1.056

Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; cEFR = CNS Evaluable for Response set; cFAS = CNS Full Analysis Set; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CNS = central nervous system; CR = complete response; DCO = data cutoff; DCR = disease control rate; DepOR = depth of response; DoR = duration of response; EGFR = epidermal growth factor receptor; FAS = Full Analysis Set; HR = hazard ratio; HR = hazard ratio; H_0 = null hypothesis; H_1 = alternative hypothesis; ICR = independent

central review; max = maximum; min = minimum; n = number; NA = not applicable; NSCLC = non-small cell lung cancer; OR = odds ratio; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS =
progression-free survival; PFS2 = time from randomization to second progression; PK = pharmacokinetic(s); PR = partial response; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SS = Safety Set; TFST = time to first subsequent (anticancer) therapy; TKI = tyrosine kinase inhibitor; TTR = time to response.

Table 82 Summary of efficacy for trial HS-10296-12-01

Study identifiers:	HS-10296-12-01 NCT02981108	
Study design:	Phase 1/2, open-label, multicenter, single-group clinical study to evaluate the safety, tolerability, PK, and efficacy of oral QD administration of aumolertinib in subjects with locally advanced or metastatic NSCLC who have progressed after previous treatment with EGFR TKIs. The study comprises 3 parts: - Part 1: Phase 1 (dose-escalation) portion to further evaluate 4 doses of aumolertinib (55 mg, 110 mg, 220 mg, and 260 mg), each administered orally QD. - Part 2: Phase 1 (dose-expansion) portion to further evaluate 3 doses of aumolertinib (55 mg, 110 mg, and 220 mg), each administered orally QD, to determine the recommended Phase 2 dose. - Part 3 (main study part): Phase 2 (dose-extension) portion to evaluate the safety and efficacy of aumolertinib 110 mg administered orally QD. Subjects were required to have a known EGFR TKI-sensitizing mutation (i.e., G719X, ex19del, L858R, L861Q) or to have derived prior clinical benefit from treatment with an EGFR TKI to be included in the study. In Parts 2 and 3, subjects were required to be positive for the T790M mutation. Note: As the main study part, Part 3 is the focus of this table.	
	Duration of main (treatment) phase:	From first dose of study treatment until treatment discontinuation due to disease progression (per RECIST v1.1) or other protocol-specified treatment termination criteria were met. Part 3 also included a survival follow-up period after treatment discontinuation (collection of survival information every 6 weeks).
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable; however, there was a survival follow-up period for subjects in Part 3, as described above.
Part 3 hypotheses (for the primary endpoint of	H_0: $P \leq 0.3$ ($P0 = 0.3$). H_1: $P > 0.3$ ($P1 = 0.4$).	

<table>
<tr><td>ICR-assessed ORR):</td><td colspan="3"></td></tr>
<tr><td>Part 3 treatment groups:</td><td colspan="3">For all subjects in Part 3, treatment with aumolertinib 110 mg QD until disease progression or other termination criteria were met as per protocol (n = 244).</td></tr>
<tr><td rowspan="2">Part 3 endpoints and definitions:</td><td>Primary endpoint</td><td>(Confirmed) ORR, as evaluated by ICR</td><td>Percentage of subjects with at least 1 confirmed CR or PR before progression.</td></tr>
<tr><td>Secondary endpoint</td><td>DoR</td><td>Interval (in months) between the first date on which response was achieved and the date of disease progression or death.</td></tr>
<tr><td>Database lock:</td><td colspan="3">05 Jan 2019</td></tr>
<tr><td colspan="4"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description:</td><td colspan="3">Primary analysis</td></tr>
<tr><td>Part 3 analysis populations and time point descriptions:</td><td colspan="3">Analysis populations:
- FAS (for ORR, DCR, PFS, DoR, and DepOR)
1. Subjects who have received at least 1 dose of aumolertinib and have a RECIST evaluation at baseline.
2. All subjects were included in the FAS.</td></tr>
<tr><td rowspan="6">Part 3 descriptive statistics and estimate variability:</td><td rowspan="2">Part 3 (110 mg)</td><td colspan="2">Assessed by:</td></tr>
<tr><td>ICR</td><td>Investigator</td></tr>
<tr><td>Number of subjects</td><td>244</td><td>244</td></tr>
<tr><td>Confirmed ORR (n [%])
95% CI</td><td>160 (65.6)
59.2, 71.5</td><td>137 (56.1)
49.7, 62.5</td></tr>
<tr><td>Median DoR (months)*
95% CI</td><td>NA
5.6, NA</td><td>NA
NA, NA</td></tr>
<tr><td colspan="3">* Subject numbers are n = 160 and n = 137 for ICR and Investigator assessment, respectively.
** 11 (4.5%) subjects had died by the time of the primary analysis DCO of 05 Jan 2019.</td></tr>
<tr><td>Effect estimates per comparison:</td><td colspan="3">Not applicable</td></tr>
<tr><td>Notes:</td><td colspan="3">Reasons for treatment discontinuations other than due to disease progression in Part 3 (n = 11) were as follows:</td></tr>
</table>

	- AE (n = 6), subject decision (n = 3), lost to follow-up (n = 1), and poor compliance (n = 1).
	Critical findings in the pivotal Part 3: The ORR of aumolertinib consistent with other EGFR-TKIs. However the single arm design prevents the interpretation of efficacy results.

Abbreviations: AE = adverse event; cEFR = CNS Evaluable for Response set; cFAS = CNS Full Analysis Set; CI = confidence interval; CNS = central nervous system; CR = complete response; DCO = data cutoff; DCR = disease control rate; DepOR = depth of response; DoR = duration of response; EGFR = epidermal growth factor receptor; FAS = Full Analysis Set; H_0 = null hypothesis; H_1 = alternative hypothesis; ICR = independent central review; max = maximum; min = minimum; n = number; NA = not applicable; NMPA = National Medical Products Administration; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; P = proportion of a population; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumours; SS = Safety Set; SD = stable disease; T790M = threonine to methionine substitution at position 790 in exon 20 of the epidermal growth factor receptor; TKI = epidermal growth factor receptor tyrosine kinase inhibitor; TTR = time to response.

2.6.5.5. Clinical studies in special populations

Table 83 Elderly patients included in clinical efficacy trials

	Age 65-74 (Older Subjects Number /Total Number)	**Age 75-84 (Older Subjects Number /Total Number)**	**Age 85+ (Older Subjects Number /Total Number)**
Controlled Trials	118/429	17/429	0/429
HS-10296	54/214	5/214	0/214
Gefitinib	64/215	12/215	0/215
Non Controlled Trials	97/364	35/364	4/364
Escalation: Cohort 1 (55 mg)	2/6	1/6	0/6
Escalation: Cohort 2 (110 mg)	2/6	0/6	0/6
Escalation: Cohort 3 (220 mg)	2/8	1/8	0/8
Escalation: Cohort 4 (260 mg)	2/6	0/6	0/6
Expansion: Cohort 55 mg	4/30	3/30	1/30
Expansion: Cohort 110 mg	15/33	2/33	0/33

Expansion: Cohort 220 mg	6/31	4/31	0/31
Extension Cohort 110 mg	64/244	24/244	3/244

2.6.5.6. In vitro biomarker test for patient selection for efficacy

EGFR mutation status in the HS-10296-03-01 and HS-10296-12-01 studies was assessed by the central testing of tumour or blood samples, using the real-time PCR-based **cobas® EGFR Mutation Test v2** (Roche Diagnostics) to identify mutations in exons 18, 19, 20 and 21 in the EGFR gene.

FFPE specimens were processed using the cobas® 4800 DNA Sample Preparation Kit (Roche Diagnostics), and plasma specimens were processed using the cobas® cfDNA Sample Preparation Kit (Roche Diagnostics). Real-time PCR amplification and detection was performed via cobas® z 480 Analyzer (Roche Diagnostics). DNA quantification was performed via NanoDrop™ 2000 spectrophotometer (ThermoFisher Scientific) by measuring sample absorbance at 260/280 nm and 260/230 nm (DNA stock concentration ≥ 2 ng/L).

The cobas® EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the EGFR gene in DNA derived from FFPET or cfDNA in plasma from NSCLC patients. The test has been analytically and clinically validated by Roche Diagnostics (O'Donnell 2013, Benlloch 2014) and is commercially available in the EU as a CE-marked IVD (Roche 2011). This assay was validated by the central testing laboratory in accordance with the CE-marked product IFU prior to use in the clinical studies for aumolertinib.

2.6.5.7. Analysis performed across trials (pooled analyses and meta-analysis)

Comparison of Efficacy Results from the Primary HS-10296-03-01 Analysis and Phase 3 Clinical Studies with Gefitinib and Osimertinib

As compared with the China population in the Phase 3, randomized, first-line clinical trial for gefitinib (IPASS), which was conducted in previously untreated subjects with advanced NSCLC who were either never-smokers or former light smokers, Study HS-10296-03-01 was essentially consistent in terms of subject demographics and baseline disease characteristics (Mok 2009).

Subject baseline characteristics in HS-10296-03-01 were comparable to those within the global population (Soria 2018), the population in Asia (Cho 2019), and the population in China (Cheng 2021) included in the Phase 3, double-blind registrational trial for osimertinib as 1L treatment for advanced NSCLC (FLAURA). In terms of the phenotype distribution of the EGFR mutation in the China population receiving aumolertinib within HS-10296-03-01 and the China population receiving osimertinib in the FLAURA trial, the proportions of ex19del were 65.4% and 62.8%, respectively; the proportions of L858R were, correspondingly, 34.6% and 37.2%.

Table 84: Summary of Efficacy Data for Aumolertinib in Study HS-10296-03-01 (Primary Analysis) and for Osimertinib in the FLAURA Trial

		Aumolertinib		**Osimertinib**			
		HS-10296-03-01		**FLAURA Trial China Population**		**FLAURA Trial Asia Population**	
		Aumolertinib N = 214	**Gefitinib N = 215**	**Osimertinib N = 71**	**1st-generation TKI N = 65**	**Osimertinib N = 162**	**1st-generation TKI N = 160**
PFS as evaluated by Investigator (months)	Median (95% CI)	19.12 (17.74, 20.80)	9.72 (8.34, 12.45)	17.8 (13.6,20.7)	9.8 (8.3,13.8)	16.5 (13.8,20.7)	11.0 (9.5,12.6)
	HR (95% CI)	0.460 (0.3548, 0.591)		0.56 (0.37,0.85)		0.54 (0.41,0.72)	
	p-value	< 0.0001		0.007		< 0.0001	
PFS as evaluated by ICR (months)	Median (95% CI)	17.94(15.18,20.50)	9.72 (9.53,11.14)	15.0 (10.8,18.0)	11.0 (8.4,12.3)	--	--
	HR (95% CI)	0.490 (0.383, 0.628)		0.54 (0.36,0.81)		--	
	p-value	< 0.0001		< 0.05		--	
Subgroup analysis of PFS as evaluated by Investigator	HR of male subjects (95% CI)	0.528 (0.364, 0.767)		0.60 (0.31,1.17) No statistical difference		0.63 (0.41,0.96)	

		Aumolertinib		**Osimertinib**			
		HS-10296-03-01		**FLAURA Trial China Population**		**FLAURA Trial Asia Population**	
		Aumolertinib N = 214	**Gefitinib N = 215**	**Osimertinib N = 71**	**1st-generation TKI N = 65**	**Osimertinib N = 162**	**1st-generation TKI N = 160**
	HR of subjects with smoking history (95% CI)	0.540 (0.354, 0.823)		0.58 (0.26,1.29) No statistical difference		0.57 (0.37,0.87)	
	HR of subjects with baseline brain metastasis (95% CI)	0.369 (0.237, 0.577)		0.66 (0.30,1.38) No statistical difference		0.68 (0.37,1.22) No statistical difference	
	HR of subjects with L858R mutation (95% CI)	0.575 (0.392, 0.844)		0.69 (0.39, 1.21) No statistical difference		0.48 (0.31, 0.74)	
ORR	% (95% CI)	74.8 (68.4, 80.4)	72.1 (65.6, 78.0)	--	--	80 (73,86)	75 (68,82)
DCR	% (95% CI)	93.0 (88.7, 96.0)	96.7 (93.4, 98.7)	--	--	98 (95,100)	93 (87,96)

		Aumolertinib		Osimertinib			
		HS-10296-03-01		FLAURA Trial China Population		FLAURA Trial Asia Population	
		Aumolertinib N = 214	Gefitinib N = 215	Osimertinib N = 71	1st-generation TKI N = 65	Osimertinib N = 162	1st-generation TKI N = 160
DoR (months)	Median (95% CI)	19.19 (15.54, 22.11)	8.28 (6.90, 11.07)	--	--	18 (12.5,21.9)	9 (7.0,11.0)
OS (months)	Median (95% CI)	NA (29.50, NA)	NA (27.70, NA)	33.1 (26.0, 35.9)	25.7 (19.6, 32.8)	NA (NA, NA)	NA (NA, NA)

CI = confidence interval; DCR = disease control rate; DoR = duration of response; HR = hazard ratio; ICR = independent central review; L858R = substitution of a leucine (L) with an arginine (R) at position 858 in exon 21; NA = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
Data cutoff date for HS-10296-03-01 (primary analysis): 15 January 2021.

Source: HS-10296-03-01 CSR, Table 14.2.1.1, Table 14.2.5.1, Table 14.2.3.1, Table 14.2.8.1, Table 14.2.13.2, and Table 14.2.11.1;

2.6.5.8. Supportive study

Not applicable.

2.6.6. Discussion on clinical efficacy

The efficacy of aumolertinib is based on two pivotal studies: a Phase 3 study HS-10296-03-01 supporting the claimed indication in the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations, and a Phase1/2 study HS-10296-12-01 (Part 3) supporting the claimed indication in the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Design and conduct of clinical studies

Study HS-10296-03-01

Study HS-10296-03-01 is a randomised, controlled and double-blind phase 3 study comparing aumolertinib versus gefitinib in patients with EGFR mutation, locally advanced or metastatic NSCLC supporting the claimed indication of aumolertinib in 1L treatment. The design allowed patients randomised in the gefitinib arm to cross over to aumolertinib post-progression, provided that the T790M mutation was identified in a post progression tumour sample.

Overall the inclusion and exclusion criteria adequately address the intended population. The study population includes patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC (grade IIIb/IV) who have not received any systemic therapy for their advanced cancer, harbouring a documented EGFR mutation including exon 19 deletion or L858R mutation and at least 1 measurable lesion at baseline. Subjects were to be ECOG PS score 0-1; it is unfortunate that subjects score of 2 were not included considering the advanced stage setting. Patients with asymptomatic, stable brain metastasis not requiring steroids for at least 2 weeks prior to the first dose of study treatment were eligible to the study; this is in line with the claimed pre-clinical demonstration of brain penetration of aumolertinib.

The EGFR-sensitive mutation was tested by a central laboratory only using a tumour tissue or blood sample according to the inclusion criteria, which is acceptable. The EGFR-sensitive mutations eligible for inclusion were exon 19 deletion or L858R mutation, either alone or in combination with other EGFR site mutations. Exon 19 deletion or L858R mutation constitute the large majority of the EGFR mutations, and the non-inclusion of other EGFR site mutations was justified based on the sparse efficacy data of the comparator gefitinib on the less common mutations, which was accepted by the CHMP and consistent with the selected mutations in the FLAURA study for osimertinib.

The standard of care in 1L advanced EGFR-mutated NSCLC is osimertinib, based on ESMO guideline, and its use as comparator to demonstrate non-inferiority would have been preferred. The applicant's justification for not having used osimertinib as comparator was its non-availability at the time of the planning of this study and throughout the enrolment to last subject in, gefitinib was a recommended option for first-line treatment in China. Despite the aforementioned limitations, the use of gefitinib, an active comparator, was found acceptable to assess efficacy in the context of a superiority trial.

The primary and secondary objectives are overall endorsed. PFS as primary endpoint is acceptable considering that the expected prolonged PFS is of benefit to the patient and OS has been reported as a secondary endpoint in line with the guideline on the evaluation of anticancer medicinal product in man (EMA/CHMP/205/95 Rev.6). The tumour response was assessed based on RECIST v1.1 which is agreed. The PFS was evaluated by the Investigator for the primary analysis, which was considered

acceptable in the context of a double blind trial; the planned sensitivity analysis with evaluation by ICR is supported to objectify the results. The possible cross-over from gefitinib to aumolertinib treatment is likely to hamper any subsequent comparisons in terms of OS.

Post-progression endpoints such as PFS2 and TFST were considered of relevance since it cannot be excluded that the tumour's drug resistance profile is affected by aumolertinib with development of secondary resistance mechanisms, especially in a first line treatment setting where first- or second-generation EGFR-TKI is likely not to be effective after aumolertinib, while interpretation of OS would likely be affected by the cross over. The analyses of PFS2 and TFST were however provided in a post-hoc addendum of the CSR after study unblinding.

The lack of patient reported outcomes (PRO) in the planned analysis is noted, despite PRO objectives being frequently incorporated in confirmatory oncology study, especially in advanced cancers.

The date of DCO was event-driven (n=262 events). The second DCO was triggered to support global regulatory submission. The absence of a pre-defined determination rule highlights its exploratory nature.

There were several aspects of the Applicant's documentation for trial HS-10296-03-01 that raised serious concerns over the reliability of study results i.e. discrepancies between original CSR outputs and re-run analyses in the translated CSR, discrepancies in randomisation file. Therefore, a GCP inspection was conducted and confirmed the reliability of the data generated during both clinical trials, and the fact that this data can be used for the evaluation of the current application.

The translation of the datasets into English and the conversion to CDISC-compliant datasets resulted in differences between the original CSR outputs and the re-run analyses in the translated CSR that are included with the present submission. The discrepancies in specification resulted in minor differences, and overall did not lead to different conclusions.

According to the summary of major protocol deviations (see Table 40), many patients had major protocol deviations listed as not meeting inclusion or exclusion criteria, with poor compliance or other deviations with a potential impact on efficacy. A sensitivity analysis was also performed where all patients with any major protocol deviations were excluded. The results were consistent with the main analysis results, and provided reassurance on the robustness of the primary analysis results with regard to protocol deviations.

There is no multiplicity adjustment procedure defined in the study protocol or SAP. As a consequence, apart from the primary endpoint hypothesis test, there is no formal type I error control for the analyses of secondary endpoints.

The censoring rules of the primary PFS analysis are not in line with the general recommendations in Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (CHMP/27994/2008 Rev. 1), as they do not closely follow the ITT principle. Censoring was planned before treatment discontinuation or subsequent systemic therapy, or in case of 2 or more missed consecutive visits. Nevertheless, the sensitivity analysis #3 (Table 35), was more in line with the ITT principle, allowing the assessment of the primary analysis under different assumptions.

The SAP was updated less than 3 months prior to DCO, in which the timing of PFS was redefined from time since randomisation instead of time since first dose. The update was based on input from NMPA and is recognised to be according to standard definition. The change had no impact on the results of the comparison.

The sample size was increased with version 2 of the protocol, from 350 patients providing 191 PFS events to 410 patients providing 262 events. At the time of the sample size increase, 18 events had occurred in 318 randomised patients, i.e. representing less than 10% of the originally targeted number

of events. A requested sensitivity analysis was also provided using a cut-off date corresponding to the originally planned target of 191 PFS events, with consistent results. A partially informed decision is considered unlikely and would not affect the study conclusions.

A number of post-hoc analyses (CNS efficacy analyses, PFS2, TFST, RMST PFS, OS analyses with alternative handling of cross-over) have been performed using the more recent data cut-off.

Almost no details were provided in the addendum CSR or SAP regarding the statistical models used for the OS sensitivity analyses based on the IPCW, 2-stage AFT, and RPSFT methods (e.g. no specification provided for censoring rules, baseline and post-baseline characteristics used in models where applicable). Considering this lack of specification, these analyses are deemed highly exploratory and to be interpreted with caution. These analyses aiming at estimating the treatment effect on OS, if no cross-over had occurred in the trial are considered of limited relevance for regulatory decision-making, as pointed out in the EMA Q&A on adjustment for cross-over in oncology trials (EMA/845963/2018).

Study HS-10296-12-01

Study HS-10296-12-01 is a Phase 1/2 open-label, single-arm clinical study that consists of 3 parts: Part 1 dose-escalation that evaluated 4 doses of aumolertinib (55, 110, 220, and 260 mg QD), Part 2 dose-expansion to determine the recommended Phase 2 dose and Part 3 dose-extension that evaluated the safety, efficacy, and PK characteristics of aumolertinib 110 mg QD. Both Parts 2 and 3 included exclusively EGFR-mutated NSCLC patients (no restriction on cancer stage) with confirmed T790M+ mutation.

The claimed indication in T790M mutated advanced NSCLC was supported by the Part 3 at the intended dosage. The main limitation for the evaluation of the efficacy estimands remains the open-label uncontrolled study design and a rather limited follow-up (particularly at the time of primary CSR). A randomised study even if not sufficiently powered, is usually preferred as it might allow obtaining an unbiased treatment effect (Guideline on the clinical evaluation of anticancer medicinal products, EMA/CHMP/205/95 Rev 6). Nevertheless, when taking into consideration the availability of an earlier-line randomized controlled trial (RCT) HS-10296-03-01, the overall data package was deemed comprehensive.

The inclusion and exclusion criteria appeared adequate to address the intended population for the claimed indication.

ORR by ICR is reported as primary outcome and considered acceptable for a Phase II study as a rather convincing measure of anti-tumour activity (Guideline on the clinical evaluation of anticancer medicinal products, EMA/CHMP/205/95 Rev.6). Data on DCR, PFS and OS and tumour shrinkage are reported as secondary outcomes and DoR and PRO as exploratory outcomes. In the absence of randomised comparator the time-to-event data are difficult to interpret. The tumour assessment was performed according to RECIST v1.1 and assessed by an independent central review which is supported to limit bias.

The primary analysis DCO date (5 January 2019) was agreed with the China NMPA, but was not based on a pre-defined rule. The DCO for the CSR addendum was based on the anticipated time for median OS, but was not pre-specified either. A set of ORR and PFS results for a relatively wide range of cut-off dates were provided (data not shown) and did not indicate a potential bias.

Despite the restricted definition of the FAS (treated patients with a baseline RECIST assessment), all enrolled patients were included in all analyses (i.e. there were no untreated patients or without a baseline assessment).

There was no multiplicity adjustment procedure in place across primary and secondary analyses. Moreover, the lack of specification for the cut-off dates adds to the exploratory nature of the trial.

Efficacy data and additional analyses

Study HS-10296-03-01

A total of 429 subjects were randomized in the study: 214 in the aumolertinib group and 215 in gefitinib group. At the primary DCO (15 Jan 2021), the discontinuation of treatment study was mainly due to imaging progression in both treatment groups, with a higher rate in gefitinib arm compared to aumolertinib arm, i.e. 53.0% and 34.1%, respectively. Death was the main reason of study discontinuation in both treatment arms, i.e. 25.2% in aumolertinib groups and 32.1% in gefitinib group. The lost to follow up was comparable with 4 (1.9%) subjects in aumolertinib group and 3 (1.4%) subjects in gefitinib group. A total of 41 (19.1%) subjects in gefitinib arm proceeded to a crossover to aumolertinib after progression.

The protocol has been amended two times. Overall the protocol changes were not expected to impact the efficacy assessment.

Serious protocol deviations were more reported in subjects treated with aumolertinib than gefitinib, i.e. 36.9% vs 30.2%, respectively. For both treatment groups, the most common reason was overall missing visits during medication and occurred more in the aumolertinib arm (22.0%) compared to gefitinib arm (16.7%). Sensitivity analyses of PFS (excluding subjects with missing visits during study treatment, before imaging progression and before imaging progression or discontinuation of study treatment) were consistent with the primary analysis (data not shown).

The majority of subjects were female (62.6% in aumolertinib group and 62.8% in gefitinib group) and non-smokers (300/429, 70%) consistently with the target population, however the global rate of non-smokers in the study is higher than the study population of other EGFR-TKIs. An imbalance on age is observed with a higher percentage of subjects ≥65 in the gefitinib arm (35.3%) than aumolertinib arm (27.6%) with median age of 59.0 years in aumolertinib group and 62.0 y.o. in gefitinib group. There was also imbalance on smoking history, that may affect the efficacy outcomes, with higher rate of never smoked subjects in aumolertinib group compared to gefitinib group (72.9% vs 67.0%).

There were 5 subjects that harboured an EGFR T790M mutation at baseline, i.e. 2 (0.9%) treated with aumolertinib and 3 (1.4%) treated with gefitinib for which a lack of treatment response is expected.

There is an imbalance in the prior anticancer therapy across the treatment arms with a higher rate in subjects from the aumolertinib group than the gefitinib group (17.8% vs 12.1%), mainly driven by traditional Chinese plant-based medicine, which was the most reported prior anticancer therapy, i.e. 22 (10.3%) and 9 (4.2%) subjects in aumolertinib and gefitinib arms, respectively. A PFS sensitivity analysis was consistent with the primary analysis suggesting a negligible impact of prior anticancer traditional Chinese medicines on PFS outcomes. The other prior anticancer treatments used were well-balanced.

There was 6.1% of patients in the aumolertinib and 26.0% in the gefitinib who received bicyclol, a China approved hepatoprotective medicine, and different herbal preparations. In addition, other herbal preparations were listed in other ATC level 3. The majority of ATC level 3 uncoded and herbal preparations concomitant medications were used to treat AEs (45.2% and 11.7%, respectively) with a higher rate in gefitinib compared to aumolertinib group for both treatments. Overall the sensitivity analyses of PFS suggested a limited impact of the use of these concomitant medicines on the outcome.

At the 06 Aug 2021 DCO, a higher rate of subjects in gefitinib compared to aumolertinib group received one subsequent anticancer treatment (61.4% vs 35.5%, respectively), mainly driven by the 3rd generation EGFR TKI therapy (27.4% in gefitinib including the crossover to aumolertinib and 2.8% in aumolertinib). The majority of aumolertinib-treated subjects that progressed received platinum-based therapy (34.1%) in line with the current recommendations.

At the DCO date of the primary analysis (05 January 2021), a total of 266 PFS events had occurred and the maximum follow-up period was 20.63 months, i.e. approximately 3 months less than planned. The primary endpoint PFS is met with a statistically significant and clinically relevant 9.4 month improvement of the median PFS by investigator in subjects treated with aumolertinib compared to gefitinib, i.e. 19.12 (95%CI 17.74, 20.80) months vs 9.72 (95% CI 8.34, 12.45) months and a HR of 0.460 (95%CI 0.358, 0.591), p<0.0001. In the updated analysis (DCO 06 August 2021), the mPFS was 19.81 (95%CI 17.74, 23.39) months in aumolertinib vs 9.72 (95%CI 8.34, 12.45) months in gefitinib group. The sensitivity analyses were consistent with the primary analysis. The magnitude of the PFS benefit should be considered in the context of a comparison against gefitinib, a first generation TKI against which another 3rd generation EGFR TKI has also demonstrated large superiority over. Indeed, a difference in PFS of comparable magnitude was reported for osimertinib versus 1st generation EGFR-TKI (either gefitinib or erlotinib) in FLAURA study (Phase III, double-blind, randomised study) with mPFS by investigator of 18.9 months [95% CI: 15.2, 21.4] in osimertinib arm vs. 10.2 months [95% CI: 9.6, 11.1]) in the comparator arm. In subgroup analyses conducted at the primary and updated analysis, a PFS benefit of aumolertinib over gefitinib was observed across subgroups. Subjects were stratified by EGFR mutation and brain metastasis status. The subgroup analysis by EGFR mutation status supports a better efficacy in patients with Exon19 deletion mutation compared to those with L858R mutations, i.e. HR of 0.383 (95% CI 0.276, 0.531) and HR of 0.605 (0.409, 0.894), respectively, which is in line with the trend showed for the other EGFR-TKI. The mPFS in subjects with brain metastasis was improved of approximately 7 months with aumolertinib compared to gefitinib in subjects (15.28 [95%CI 10.84, 20.76] vs 8.18 [95%CI 6.51, 8.34] months) with a HR of 0.367 (95% CI 0.232, 0.579). In comparison, the HR in subjects with no brain metastasis was 0.509 (95% CI 0.377, 0.687) suggesting an adequate efficacy of aumolertinib via CNS penetration. In a sensitivity analysis excluding patients with RT within 3 months, results were in concordance with original results. The mPFS of aumolertinib was longer in female subjects, with no smoking history and a baseline ECOG PS of 0.

A summary of the concordance between IRC and investigator response assessments was provided, together with concordance rates and kappa coefficients (Table 55). The concordance rates were indicating substantial but not perfect agreement. Regarding BOR, the agreement between IRC and investigator assessments was more moderate. The largest divergence (in proportion of patients) appears to be between SD and PR categories (with more SD by IRC than by investigator).

The Median OS at the primary analysis (DCO date of 15 Jan 2021) and the updated analysis (DCO date of 06 Aug 2021) were not reached in each treatment arm due to immaturity of OS data. An updated OS analysis at the DCO date of 30 Sept 2022 with more than 1 year of additional follow-up was provided during the procedure. There was no statistically significant difference on OS between the two treatment arms with a HR of 0.820 (95%CI 0.573, 1.173; p=0.2760) for the primary analysis and a HR of 0.885 (95%CI 0.651, 1.203; p=0.4340) for the updated analysis (DCO date of 06 Aug 2021). The KM OS curves for both analyses crossed at approximately 8 months after randomisation preventing any interpretation of the OS. It is acknowledged that OS was potentially confounded with the crossover; the ad-hoc sensitivity analysis for adjustment on crossover was consistent with the primary analysis with no demonstration of a statistically significant longer OS of aumolertinib compared to gefitinib. As of 30 Sept 2022, the median OS as of the updated DCO date was numerically higher in aumolertinib than gefitinib, i.e. 39.16 months and 31.15 months, respectively, suggesting a favourable trend without demonstration of an improved survival of aumolertinib over gefitinib. The OS HR was 0.816 (95% CI: 0.631, 1.056) which is consistent with the primary analysis.

The **ORR** were comparable across the two treatment groups, i.e. 73.8% (95%CI 67.4, 79.6) in aumolertinib arm and 72.1% (95%CI 65.6, 78.0) in gefitinib arm, showing a convincing anti-tumour activity as expected with EGFR-TKIs in the claimed indication.

Despite comparable ORR across treatment groups, a clinically relevant benefit of aumolertinib on the duration of responses is observed with a median **DoR** by the Investigator close to 10 months longer with aumolertinib compared to gefitinib, i.e. 18.14 (95% CI 15.21, NA) vs 8.28 (95%CI 6.90, 11.07) months and a HR of 0.368 (95%CI 0.272, 0.498), supported by the updated analysis. Median DoR of aumolertinib is consistent with the mDoR of osimertinib in FLAURA study.

In the updated PFS2 by investigator analysis as of DCO date of 30 Sept 2022, 77 (36.0%) patients in the aumolertinib and 113 (52.6%) patients in the gefitinib arm had second progression events during the first subsequent therapy or died. The median PFS2 was longer with aumolertinib compared to gefitinib, i.e. 40.25 (35.55, NA) and 25.82 (21.16, 28.19) months, respectively, with a HR of 0.519 (95% CI: 0.386, 0.7697), favouring a longer PFS2 in the aumolertinib arm consistently with the primary analysis.

The **post-hoc CNS analyses** were performed at a DCO date of 06 Aug 2021 and included CNS PFS, ORR, DCR, DoR and percentage change from baseline in CNS lesion size, which are considered adequate outcomes. The main goal of these analyses was to assess the efficacy of aumolertinib on brain metastasis based on disease assessment of the CNS scans. The CNS analysis set (cFAS and cEFR) were based on the presence of brain lesion identified on screening or baseline brain scan and confirmed by ICR and 105/106 (99.1%) subjects included in cFAS had brain metastasis. The large difference between the cFAS (n=106) and cEFR (n=60) was due to measurable disease burden within the CNS analysis set. In addition, differences in the number of subjects with brain metastasis between the FAS (n=115) and the cFAS (n=105) were based on Investigator assessments at baseline (FAS) and a retrospective IRC assessment of the baseline images (cFAS). The baseline demographic characteristics in cFAS were imbalanced with regard to the age, with higher rate of <65 in aumolertinib compared to gefitinib (78.4% vs 65.5%) and lower rate of 65-74 (19.6% vs 30.9%). Such age imbalances were observed in the FAS of primary analyses, however they were more marked in the cFAS despite the stratification by brain metastasis status. A greater imbalance in age was observed across treatment arms in the cEFR with rates of <65 of 82.1% in aumolertinib group vs 62.5% in gefitinib group. Regarding the baseline disease characteristics, the Ex19del EGFR mutation was more frequently reported in the gefitinib group (63.6%) compared to the aumolertinib group (58.8%) in the cFAS. Imbalances in ECOG PS were also observed, with a higher proportion of subjects with ECOG PS 0 in gefitinib compared to aumolertinib arms (i.e. 23.6% and 13.7% in cFAS, respectively). Additional information on patients who received radiation for their brain metastases was provided and reflects the overall trend that aumolertinib shows efficacy against gefitinib.

The median CNS PFS by ICR (cFAS) was improved by 20.76 months with aumolertinib compared to gefitinib with a mPFS of 29.01 (95%CI 12.32, NA) months in the aumolertinib group vs 8.25 (95%CI 6.90, 9.72) months in the gefitinib group and a HR of 0.308 (95%CI 0.170, 0.558; p<0.0001). The CNS PFS results in the cEFR were consistent with cFAS. The large magnitude of improved CNS PFS with aumolertinib can be considered encouraging despite the post-hoc setting of the analysis and the limited analysis sets.

The CNS ORR (cFAS) also favoured aumolertinib compared to gefitinib, i.e. 62.7% vs 49.1% respectively, mainly driven by the higher rate of complete response in the aumolertinib group, i.e. 23.5% vs 5.5% in gefitinib group. The CNS mDoR was longer in aumolertinib arm compared to gefitinib arm, i.e. 27.70 (NA, NA) and 6.93 (5.52, 9.43) months, respectively. More subjects had ≥50% reduction of CNS lesion size from baseline in aumolertinib group compared to gefitinib group, i.e. 71.4% and 56.3%, respectively, and 28.6% of subjects treated with aumolertinib had ≥75% reduction of CNS lesion size from baseline vs 0 in gefitinib group.

In conclusion, the CNS analyses support a favourable trend of aumolertinib over gefitinib on brain metastasis with a large nominal statistically significant improvement of median CNS PFS of approximately 21 months with aumolertinib over gefitinib in cFAS.

Study HS-10296-12-01

A total of 244 subjects were included in the Part 3 of the study. All the enrolled subjects received the study treatment. There were 62 (25.4%) subjects that discontinued the study treatment at the DCO date of 05 January 2019 mainly due to disease progression (20.5%). The treatment discontinuation increased up to 87.7% at DCO date of 01 August 2021. The rates of loss to follow-up and poor compliance are considered very low, i.e. 1 (0.4%) subject for each at both the DCO dates. The part 3 of the study was exclusively conducted in China and Taiwan.

A total of 25 (10.2%) subjects reported major protocol deviations including study procedures criteria in 11 (4.5%) subjects and inclusion/exclusion criteria in 7 (2.9%) subjects.

The median follow-up time for the patients in study 12-01, part 3 was 4.7 (min, max 0.2, 7.7) months at initial DCO date of 05 Jan 2019 and 11.1 (min, max 0.2, 38.6) months at updated DCO date of 01 Aug 2021.

The majority of subjects were female (58.2%), non-smoking history (73.0%) and all were Chinese; the extrapolation of efficacy and safety data was mainly based on a PK bridging study. The median age was 61 years (range 27-87), with a rate of 62.7% (153/244) of subjects <65 and 37.3% (91/244) of subjects ≥65 years.

Adenocarcinoma was the most reported histology (99.2%). The majority of subjects had a metastatic cancer (i.e. 95%, including 70.9% of stage IV, 12.3% of stage IV A, 11.1% of stage IV B and 0.8% of stage IV C) and 3.3% of subjects were stage III B, which is consistent with the intended population that received prior EGFR-TKI. Brain metastases were present in 36.9% of subjects at baseline. There were 26.2% of subjects that had previous radiotherapy and 26.2% a previous surgical history.

There was 63.5% of subjects harbouring an EGFR Ex19del mutation and 34.8% of subjects harboured a L858R mutation. All enrolled subjects were tested T790M positive. While the patients must have confirmation of tumour T790M+ mutation status from a biopsy sample and EGFR mutation subtypes described are consistent with what is observed in this pathology.

All subjects included in Part 3 of study HS-10296-12-01 were previously treated with EGFR TKI, mainly with gefitinib (120/244 [49.2%]). The large majority of subjects received one line of prior EGFR TKI (221/244 [90.6%]), 18 (7.4%) subjects had 2 prior lines and 5 (2.0%) subjects had 3 prior lines.

The treatment compliance was unknown; this, combined with the uncontrolled study design, added uncertainties on the evaluation of the treatment effect. All enrolled subjects were included in the FAS, i.e. evaluable for response and received at least one dose.

At the DCO date of 05 January 2019, the confirmed **ORR** by ICR was 65.6% (95%CI 59.2, 71.5) in the FAS. The ORR by Investigator was 9.5% lower than the primary analysis, i.e. 56.1% (95%CI 49.7, 62.5). In the updated analysis (DCO 01 August 2021), the ORR by ICR was 68.9% (95%CI 62.6, 74.6). All treatment responses were partial response with no CR which is expected in an advanced cancer and consistent with the other EGFR-TKIs. Subgroup analyses of ORR by ICR were performed as planned in the SAP. None of the investigated subgroups appeared not to derive benefit from aumolertinib. The ORR were comparable across the subgroups by gender and age group (<65 and ≥65). A higher ORR was observed in subjects with ECOG 0 compared to 1 (69.4% vs 63.5%), absence of brain metastasis at entry compared to presence (69.3% vs 59.3%), never smoked compared to smoker (68.0% vs 59.1%) and EGFR Ec19del compared to L858R mutations (69.0% vs 59.1%). The primary outcome of ICR assessed ORR in study 12-01 is slightly lower; 65.6% (ICR)/56.1 (Inv)

compared to the ORR observed in study 03-01; 73.8% (primary)/74.8% (updated). This outcome is as it would be expected, as the patients are treated in a later line and a higher fraction of the patients have more advanced disease compared to patients in study 03-01. Nevertheless, the exploratory nature of the study avoids any interpretation of an improved treatment effect in any subgroup. The magnitude of the ORR represents an antitumor activity of aumolertinib likely to translate into a clinically relevant benefit, and was consistent with osimertinib (ORR by BICR of approximately 60% based on pooled Phase 2 studies).

A summary of the agreement between IRC and investigator best overall response assessments was provided (see Table 75), using concordance rates and kappa coefficients. The concordance rate was indicating moderate to substantial agreement. The largest divergence (in proportion of patients) appears to be between SD and PR categories (there was a larger proportion of patients assessed as PR by IRC and SD by investigator than the opposite). This appears to be the main reason for the higher ORR by IRC than by investigator.

Median **DoR** by IRC was not reached at the time of data cutoff of the primary analysis (05 January 2019) and was 15.1 (95%CI 12.9, 16.6) months at the updated DCO (01 August 2021). The median DoR by Investigator at DCO date of 01 August 2021 was slightly shorter, i.e. 13.8 (95%CI 12.5, 15.6) months.

DepOR by ICR (Figure 26) showed a tumour reduction in a large majority of subjects treated with aumolertinib with 78.1% of responders experiencing best tumour shrinkage of at least 50%, supported by the updated analysis. The DepOR analysis was based on 237/240 subjects having evaluable tumour response; 3 subjects were excluded from the evaluation of which 2 with no target lesions at baseline and one with a target lesion that could not be accurately measured. The exclusion of the 3 subjects from the DepOR analysis was related to IRC assessment.

Additional post-hoc analyses of CNS efficacy were performed for the part 3 of the study HS-10296-12-01 based on the data cutoff date of 01 August 2021. The lack of pre-specification in the context of a non-controlled exploratory study leads to major uncertainties on drawing conclusion on clinical efficacy of aumolertinib in brain metastasis in the claimed indication precluding their inclusion in the SmPC.

The cFAS included 88 subjects with consistent baseline characteristics with the FAS; brain metastases were present in 83/88 (94.3%) subjects from the cFAS. A total of 73 subjects were included in cEFR.

Overall the CNS ORR (54.5% in cFAS, 63.0% in cEFR) and DCR (93.2% in cFAS and 93.2% in cEFR) combined with the CNS DepOR (52.1% of subjects achieved at least a 50% reduction from baseline and 28.8% achieved at least a 75% reduction from baseline) suggested an antitumor activity of aumolertinib in brain metastasis in T790M mutation-positive NSCLC patients.

In vitro biomarker test

The EGFR mutation status was determined in a central laboratory using the CE-marked diagnostic test, i.e. cobas® EGFR Mutation Test v2, which is considered acceptable. This test is used as CDx for approved EGFR TKIs gefitinib, erlotinib and osimertinib. The detection of EGFR-sensitive mutations was based on tumour tissue or blood samples in the Phase 3 study HS-10296-03-01 and only on tumour tissue samples in Phase 1/2 study HS-10296-12-01, which is adequate with the intended use of this biomarker test.

Extrapolation of efficacy data to non-Chinese population

The extrapolation of the efficacy data from the 2 pivotal studies to non-Chinese population. was initially based on an "ethnic bridging study" EQ143-101 (see Table 12) with only 30 non-Asian, younger, healthy volunteers who received just 1 dose of 110 mg aumolertinib.

According to the EMA reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population (EMEA/CHMP/EWP/692702/2008) and to the ICH E5 R1 Guideline on ethnic factors in the acceptability of foreign clinical data, the CHMP considered that a PK bridging study was necessary in order to extrapolate the efficacy results from the pivotal studies to the EU population.

The HS-10296-108 study was initiated in Dec 2024 and designed as a Phase 1, Open-label, Multiple-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Aumolertinib in European Participants with Locally Advanced or Metastatic, EGFR-mutated NSCLC. Its primary objective was to study the pharmacokinetics of aumolertinib in European patients. The results of this study were submitted during the procedure.

Based on the additional data from the HS-10296-108 (**Error! Reference source not found.**), PK parameters in non-Asian patients were comparable to Asian patients in the pivotal HS-10296-12-01 trial with 15.3% higher Cmax of aumolertinib in European patients. Differences of other PK parameters were smaller and overall, are not considered clinically relevant.

Safety and tolerability were secondary outcomes and efficacy was not pre-defined in any detail besides a description in the Protocol "Every 6 [± 1] weeks during Cycles 1-17, every 12 (± 1) weeks starting Cycle 18 and beyond relative to first dose of study intervention until RECIST 1.1 defined radiological PD, even if dose is delayed due to toxicity or a participant discontinues treatment prior to progression". A total of 19 patients were included and 10 were treated in the first-line setting and 9 (47.4%) had a history of anti-NSCLC systemic therapy: erlotinib (42.1%), cisplatin (26.3%), docetaxel (10.5%), paclitaxel (10.5%), and pemetrexed (10.5%).

The ORR was 50% (7 out of 14 patients evaluable patients, although 19 patients were included).

These limitations on the assessment of activity in the HS-10296-108 study strongly limits the interpretability of the outcomes and are at best indicative of response.

Review of literature of EGFR-TKI efficacy across different regions and populations show that while differences in magnitude of benefit can be found, pivotal EGFR-TKI trials (EURTAC-trial for erlotinib, LUX-lung trials for afatinib and FLAURA for osimertinib) found comparable benefits in both Asian and non-Asian patients.

Based on these considerations, it is likely that aumolertinib would be efficacious in non-Asians.

Upon request from the CHMP, the wording of the indication was amended to only include "advanced NSCLC" that would encompass both locally advanced and metastatic disease, and to include a cross reference to section 4.2 of the SmPC on the biomarker-based selection.

2.6.7. Conclusions on the clinical efficacy

The Phase 3 study HS-10296-03-01 demonstrated an improved median PFS of aumolertinib over gefitinib in 1L treatment of EGFR-mutated NSCLC.

For treatment of EGFR T790M-mutated NSCLC, the efficacy data are derived from a single arm Phase 1/2 study HS-10296-12-01. However, these data are considered comprehensive to support a clinical benefit in patients with EGFR T790M-mutated NSCLC, in the presence of comparative data in an earlier-line setting (study HS-10296-03-01). The ORR by ICR of 68.9% supported an antitumour activity of aumolertinib in the claimed indication.

2.6.8. Clinical safety

The safety of aumolertinib was reported in 9 clinical studies. There are 2 pivotal studies and 7 clinical pharmacology studies. The safety data are presented in a table with populations included in the pivotal studies and pooled safety summaries separately. Thus, the safety assessment presented in this AR will exclusively be based on the 545 subjects included in the HS-10296-03-01 and HS-10296-12-01 studies.

Populations Included in the Pivotal Studies and Pooled Safety Summaries

Table 85: Populations Included in the Pivotal Studies and Pooled Safety Summaries

	301a Aumo N = 214	301a Gefi N = 215	1201a 110 mg N = 283	301a Crossover N = 48	All Aumo 110 mg b N = 545
Population	Subjects in the HS-10296-03-01 study randomized to receive aumolertinib[c]	Subjects in the HS-10296-03-01 study randomized to receive gefitinib[c]	Subjects, who received 110 mg in Parts 1, 2 and 3 of the HS-10296-12-01 study	Subjects in the HS-10296-03-01 study randomized to gefitinib who subsequently received aumolertinib after crossover	All subjects who received 110 mg aumolertinib in the HS-10296-03-01 and HS-10296-12-01 studies

[a] Note that Study HS-10296-12-01 is abbreviated to 1201, and Study HS-10296-03-01 is abbreviated to 301 in tables of this kind
[b] The "All 110 mg" group (Pooled Safety Population) includes 214 subjects from the aumolertinib arm of Study HS-10296-03-01, 283 subjects from Study HS-10296-12-01 and 48 subjects who crossed over from the gefitinib arm of Study HS-10296-03-01.
[c] All randomized subjects received at least one dose of allocated treatment.
Aumo = aumolertinib; Gefi = gefitinib.

8 of the 9 clinical studies were conducted primarily in China and Taiwan; 7 subjects from the US were included in the HS-10296-12-01 study. Study EQ143-101, an "ethnic bridging study" (see Table 12), was conducted at sites in the US and New Zealand and the applicant reports the following composition of the 45 included subjects: 15 Caucasian, 7 Black or African American, 8 Hispanic or Latino, and 15 Chinese.

2.6.8.1. Patient exposure

In 545 subjects of Asian origin with advanced NSCLC, overall exposure to aumolertinib 110 mg ranged from 2 to 1274 days with a median exposure of 403 days roughly equivalent to 13 months. 408 subjects (74.9%) were exposed longer than 6 months and 289 subjects (53.0%) more than one year. Within the overall population, 15 subjects (2.8%) had a dose reduction, and 169 subjects (31%) had a dose interruption (for any reason).

Within study HS-10296-03-01, dose reduction was numerically higher for aumolertinib than for gefitinib 2.3% vs. 0.5%, whereas dose interruptions were more frequent for aumolertinib than for gefitinib: 35.5% vs. 4.2%. This trend is also observed in the crossover population (n= 48), since 1 patient (2.1%) had a dose reduction, and 9 patients (18.3%) had a dose interruption (for any reason).

The median exposure time was longer in the aumolertinib arm than in the gefitinib arm, with a 7 months difference (18.5 months versus 11.5 months), and 141 (67.3%) patients had a duration of exposure of over 12 months versus 102 (47.5%) in the gefitinib arm.

Table 86: Overall Exposure to Aumolertinib 110 mg in the Pivotal Studies and Pooled Safety Population or Exposure to Gefitinib 250 mg in the Pivotal Study

	301 Aumo (N = 214)	301 Gefi (N = 215)	1201 110 mg (N = 283)	301 Crossover (N = 48)	All Aumo 110 mg (N = 545)
Duration of Exposure (days)[a]					
Mean (SD)	533.7 (281.17)	378.4 (236.14)	434.8 (338.66)	235.1 (152.71)	456.0 (315.17)
Median	553.5	340.0	337.0	208.5	403.0
Min, Max	18, 928	14, 946	6, 1274	2, 653	2, 1274
Duration of Exposure (n, %)					
≥ 6 months (183 days)	181 (84.6)	159 (74.0)	199 (70.3)	28 (58.3)	408 (74.9)
≥ 1 year (365 days)	141 (67.3)	102 (47.4)	135 (47.7)	10 (20.8)	289 (53.0)
Actual Exposure Time (days)[b]					
Mean (SD)	530.3 (280.51)	374.9 (235.04)	414.7 (331.59)	234.3 (151.60)	444.2 (311.52)
Median	552.5	340.0	334.0	207.5	380.0
Min, Max	18, 928	14, 946	6, 1270	2, 653	2, 1270
Treatment Compliance (%)[c]					
Mean (SD)	99.2 (2.16)	98.7 (3.44)	95.5 (12.82)	99.63 (3.74)	97.33 (9.58)
Median	100.0	100.0	100.0	100.0	100.0
Min, Max	84.9, 100.0	72.5, 100	3.9, 100.0	85.0, 100	3.9, 100
Total dose Received (mg)[d]					
Mean (SD)	58332.4 (30852.92)	93720.9 (58759.74)	45159.9 (36281.41)	25604.8 (16772.81)	48609.9 (34197.37)
Median	60775.0	85000.0	34650.0	22825.0	41690.0
Min, Max	1980, 102080	3500, 236500	660, 139700	220, 71830	220, 139700
Mean Daily Dose (mg/day)[e]					
Mean (SD)	109.11 (2.383)	246.81 (8.592)	104.41 (16.223)	108.71 (7.699)	106.63 (12.213)
Median	110.0	250.0	110.0	110.0	110.0
Min, Max	93.4, 110.8	181.3, 250.7	3.9, 166.1	64.5, 131.1	3.9, 166.1
Actual Mean Daily Dose (mg/day)[f]					
Mean (SD)	110.01 (0.113)	250.01 (0.065)	109.19 (8.011)	109.10 (6.263)	109.50 (6.068)
Median	110.0	250.0	110.0	110.0	110.0
Min, Max	109.5, 111.3	250.0, 250.7	57.7, 179.8	66.6, 110.0	57.7, 179.8
At least one dose reduction (n, %)	5 (2.3)	1 (0.5)	9 (3.2)	1 (2.1)	15 (2.8)
At least one dose interruption (n, %)	76 (35.5)	9 (4.2)	84 (29.7)	9 (18.8)	169 (31.0)

[a] Duration of exposure (days) = (date of last dose of study drug - date of first dose of study drug) + 1.
[b] Actual exposure time (days) = total exposure time – total duration of days not receiving study treatment.
[c] Treatment compliance (%) = Actual exposure time(days) / Duration of exposure (days) × 100%.
[d] Total dose received (mg) = sum of daily dose.
[e] Mean daily dose (mg/day) = Total dose received (mg)/ Duration of exposure (days).
[f] Actual mean daily dose (mg/day) = Total dose received (mg)/ Actual exposure time (days).

The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; Max = maximum; Min = minimum; SD = standard deviation.

At the time of the updated analysis performed with a data cut-off date of 06 August 2021, 142/214 subjects in the aumolertinib group (66.4%) and 195/215 subjects in the gefitinib group (90.7%) had discontinued their assigned study treatment. The most common reason for discontinuation in both groups was disease progression.

Demographic and other characteristics of safety population

Table 87: Demographics of Subjects in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population

	301 Aumo (N = 214)	301 Gefi (N = 215)	1201 110 mg (N = 283)	301 Crossover (N = 48)	All Aumo 110 mg (N = 545)
Age (Years)					
n	214	215	283	48	545
Mean (SD)	58.1 (9.59)	60.6 (9.72)	61.0 (10.67)	58.3 (10.60)	59.6 (10.33)
Median	59.0	62.0	62.0	58.0	60.0
Min, Max	32, 78	25, 81	27, 87	25, 79	25, 87
Age Group (Years), n (%)					
< 65	155 (72.4)	139 (64.7)	173 (61.1)	36 (75.0)	364 (66.8)
65-74	54 (25.2)	64 (29.8)	81 (28.6)	10 (20.8)	145 (26.6)
≥ 75	5 (2.3)	12 (5.6)	29 (10.2)	2 (4.2)	36 (6.6)
Height (cm)					
n	214	215	283	48	545
Mean (SD)	161.29 (8.182)	161.37 (7.457)	161.33 (7.861)	162.4 (7.219)	161.41 (7.928)
Median	160.00	160.00	160.00	162.00	160.00
Min, Max	135.0, 185.0	140.0, 182.0	142.2, 180.0	150.0, 178.0	135.0, 185.0
Weight (kg)					
n	214	215	283	48	545
Mean (SD)	60.33 (10.676)	59.45 (9.575)	60.25 (10.577)	61.74 (10.222)	60.41 (10.575)
Median	59.00	59.00	59.20	63.50	59.60
Min, Max	36.0, 92.0	34.5, 89.0	37.0, 100.0	42.0, 87.0	36.0, 100.0
BMI (kg/m^2)[a]					
n	214	215	283	48	545
Mean (SD)	23.12 (3.306)	22.77 (2.961)	23.07 (3.203)	23.41 (3.623)	23.12 (3.277)
Median	22.73	22.77	23.15	23.23	22.99
Min, Max	16.0, 37.9	14.7, 32.8	15.2, 33.7	16.2, 33.3	15.2, 37.9
Sex, n (%)					
Male	80 (37.4)	80 (37.2)	118 (41.7)	19 (39.6)	217 (39.8)
Female	134 (62.6)	135 (62.8)	165 (58.3)	29 (60.4)	328 (60.2)
Smoking History, n (%)					

	301 Aumo (N = 214)	301 Gefi (N = 215)	1201 110 mg (N = 283)	301 Crossover (N = 48)	All Aumo 110 mg (N = 545)
Never smoked	156 (72.9)	144 (67.0)	203 (71.7)	31 (64.6)	390 (71.6)
Current smoker	9 (4.2)	7 (3.3)	4 (1.4)	3 (6.3)	16 (2.9)
Ex-Smoker	49 (22.9)	64 (29.8)	76 (26.9)	14 (29.2)	139 (25.5)
Smoking History (2 Category), n (%)					
Present	58 (27.1)	71 (33.0)	80 (28.3)	17 (35.4)	155 (28.4)
Absent	156 (72.9)	144 (67.0)	203 (71.7)	31 (64.6)	390 (71.6)

[a] Body Mass Index is derived by baseline weight in kg divided by baseline height in meters squared
The percentages are calculated based on the number of safety population.
Baseline value is defined as the latest valid value before the first use of the study drug (aumolertinib).
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation.

Table 88: Baseline Disease Characteristics in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population

	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
EGFR Gene Mutation Type					
Ex19del	140 (65.4)	141 (65.6)	177 (62.5)	33 (68.8)	350 (64.2)
L858R	74 (34.6)	74 (34.4)	101 (35.7)	15 (31.3)	190 (34.9)
Other	0	1[a] (0.5)	5 (1.8)	0	5 (0.9)
EGFR T790M Mutation					
Positive	2 (0.9)	3 (1.4)	278 (98.2)	41 (85.4)	321 (58.9)
Negative	212 (99.1)	212 (98.6)	1 (0.4)	0	213 (39.1)
Unknown	0	0	4 (1.4)	7 (14.6)	11 (2.0)
Stage at initial diagnosis					
IA	0	1 (0.5)	2 (0.7)	0	2 (0.4)
IB	2 (0.9)	0	2 (0.7)	0	4 (0.7)
IIA	1 (0.5)	0	1 (0.4)	0	2 (0.4)
IIB	1 (0.5)	3 (1.4)	0	0	1 (0.2)
IIIA	2 (0.9)	1 (0.5)	0	0	2 (0.4)
IIIB	11 (5.1)	16 (7.4)	8 (2.8)	1 (2.1)	20 (3.7)
IV	197 (92.1)	194 (90.2)	207 (73.1)	47 (97.9)	451 (82.8)
IVA	0	0	31 (11.0)	0	31 (5.7)
IVB	0	0	29 (10.2)	0	29 (5.3)
IVC	0	0	3 (1.1)	0	3 (0.6)
Brain Metastasis					
Yes	56 (26.2)	59 (27.4)	108 (38.2)	11 (22.9)	175 (32.1)
No	158 (73.8)	156 (72.6)	173 (61.1)	37 (77.1)	368 (67.5)
Unknown	0	0	2 (0.7)	0	2 (0.4)
ECOG Performance Score					

	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
0	54 (25.2)	53 (24.7)	97 (34.3)	13 (27.1)	164 (30.1)
1	159 (74.3)	162 (75.3)	186 (65.7)	34 (70.8)	379 (69.5)
2	0	0	0	1 (2.1)	1 (0.2)
Missing	1 (0.5)	0	0	0	1 (0.2)

[a] One patient had co-mutations of Ex19del and Exon 20 insertion.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; Ex19del = exon 19 deletion; L858R = point mutation in which leucine at amino acid 858 is replaced by arginine; T790M = mutation substitutes a threonine with a methionine at position 790 of exon 20.

2.6.8.2. Adverse events

AEs are analysed and presented in terms of TEASs (treatment emergent AEs).

Overall Summary of TEAEs in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population

Table 89 Overall Summary of TEAEs in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population

TEAE Category	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Number of Subjects Reporting					
Any TEAE	211 (98.6)	214 (99.5)	269 (95.1)	44 (91.7)	524 (96.1)
Any TEAE of CTCAE Grade 3 or higher	87 (40.7)	77 (35.8)	103 (36.4)	14 (29.2)	204 (37.4)
Any serious TEAE	55 (25.7)	49 (22.8)	65 (23.0)	1 (2.1)	121 (22.2)
Any TEAE with outcome of death	5 (2.3)	3 (1.4)	6 (2.1)	0	11 (2.0)
Any TEAE leading to dose reduction	9 (4.2)	10 (4.7)	7 (2.5)	1 (2.1)	17 (3.1)
Any TEAE leading to dose interruption	41 (19.2)	54 (25.1)	42 (14.8)	6 (12.5)	89 (16.3)
Any TEAE leading to dose modification (dose reduction or dose interruption)	43 (20.1)	55 (25.6)	43 (15.2)	6 (12.5)	92 (16.9)
Any TEAE leading to discontinuation of treatment[a]	8 (3.7)	12 (5.6)	15 (5.3)	0	23 (4.2)
Any TEAE related to study treatment[a]	197 (92.1)	207 (96.3)	231 (81.6)	39 (81.3)	467 (85.7)
Any TEAE of CTCAE Grade 3 or higher, related to study treatment[a]	48 (22.4)	56 (26.0)	73 (25.8)	6 (12.5)	127 (23.3)
Any serious TEAE, related to study treatment[a]	11 (5.1)	25 (11.6)	37 (13.1)	0	48 (8.8)
Any TEAE with outcome of death, related to study treatment[a]	1 (0.5)	1 (0.5)	5 (1.8)	0	6 (1.1)
Any TEAE leading to dose reduction, related to study treatment[a]	9 (4.2)	10 (4.7)	7 (2.5)	1 (2.1)	17 (3.1)
Any TEAE leading to dose interruption, related to study treatment[a]	32 (15.0)	52 (24.2)	33 (11.7)	6 (12.5)	71 (13.0)
Any TEAE leading to dose modification (dose reduction or dose interruption), related to study treatment[a]	34 (15.9)	53 (24.7)	34 (12.0)	6 (12.5)	74 (13.6)
Any TEAE leading to discontinuation of treatment, related to study treatment[a]	6 (2.8)	11 (5.1)	9 (3.2)	0	15 (2.8)

MedDRA version 24.0.

[a] Adverse events were counted as drug-related if they had a causality of definitely related, possibly related, probably related, possibly not related, uncertain or unknown causality.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.

Aumo = aumolertinib; CTCAE = Common Terminology Criteria for Adverse Events; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

Common AEs

Table 90 Adverse Events Reported in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population (at ≥ 10% Cut-off) by Preferred Terms

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Investigations	181 (84.6)	183 (85.1)	174 (61.5)	39 (81.3)	394 (72.3)
Blood creatine phosphokinase increased	88 (41.1)	21 (9.8)	61 (21.6)	24 (50.0)	173 (31.7)
Aspartate aminotransferase increased	66 (30.8)	116 (54.0)	41 (14.5)	11 (22.9)	118 (21.7)
Alanine aminotransferase increased	65 (30.4)	120 (55.8)	36 (12.7)	9 (18.8)	110 (20.2)
White blood cell count decreased	57 (26.6)	31 (14.4)	33 (11.7)	11 (22.9)	101 (18.5)
Platelet count decreased	49 (22.9)	18 (8.4)	23 (8.1)	8 (16.7)	80 (14.7)
Neutrophil count decreased	34 (15.9)	21 (9.8)	21 (7.4)	5 (10.4)	60 (11.0)
Electrocardiogram QT prolonged	26 (12.1)	19 (8.8)	18 (6.4)	7 (14.6)	51 (9.4)
Blood bilirubin increased	20 (9.3)	34 (15.8)	16 (5.7)	4 (8.3)	40 (7.3)
Blood lactate dehydrogenase increased	27 (12.6)	15 (7.0)	7 (2.5)	4 (8.3)	38 (7.0)
Gamma-glutamyltransferase increased	19 (8.9)	30 (14.0)	8 (2.8)	4 (8.3)	31 (5.7)
Weight decreased	15 (7.0)	35 (16.3)	8 (2.8)	3 (6.3)	26 (4.8)
Gastrointestinal Disorders	107 (50.0)	120 (55.8)	127 (44.9)	11 (22.9)	245 (45.0)
Diarrhoea	37 (17.3)	77 (35.8)	35 (12.4)	0	72 (13.2)
Constipation	23 (10.7)	15 (7.0)	37 (13.1)	3 (6.3)	63 (11.6)
Vomiting	26 (12.1)	11 (5.1)	29 (10.2)	3 (6.3)	58 (10.6)
Nausea	23 (10.7)	20 (9.3)	29 (10.2)	2 (4.2)	54 (9.9)
Mouth ulceration	22 (10.3)	21 (9.8)	19 (6.7)	2 (4.2)	43 (7.9)
Infections and Infestations	112 (52.3)	100 (46.5)	130 (45.9)	13 (27.1)	255 (46.8)
Upper respiratory tract infection	42 (19.6)	28 (13.0)	57 (20.1)	2 (4.2)	101 (18.5)
Urinary tract infection	50 (23.4)	39 (18.1)	32 (11.3)	10 (20.8)	92 (16.9)
Skin and Subcutaneous Tissue Disorders	77 (36.0)	129 (60.0)	99 (35.0)	11 (22.9)	187 (34.3)
Rash	52 (24.3)	90 (41.9)	47 (16.6)	6 (12.5)	105 (19.3)
Pruritus	14 (6.5)	25 (11.6)	41 (14.5)	2 (4.2)	57 (10.5)
Blood and Lymphatic System Disorders	51 (23.8)	24 (11.2)	73 (25.8)	9 (18.8)	133 (24.4)
Anaemia	47 (22.0)	24 (11.2)	42 (14.8)	9 (18.8)	98 (18.0)
Metabolism and nutrition disorders	95 (44.4)	88 (40.9)	86 (30.4)	14 (29.2)	195 (35.8)
Hypokalaemia	21 (9.8)	33 (15.3)	20 (7.1)	4 (8.3)	45 (8.3)
Decreased appetite	18 (8.4)	28 (13.0)	25 (8.8)	1 (2.1)	44 (8.1)
Hypoalbuminaemia	17 (7.9)	23 (10.7)	11 (3.9)	3 (6.3)	31 (5.7)
Respiratory, Thoracic and Mediastinal Disorders	52 (24.3)	49 (22.8)	100 (35.3)	3 (6.3)	155 (28.4)
Cough	20 (9.3)	13 (6.0)	53 (18.7)	1 (2.1)	74 (13.6)
Musculoskeletal and Connective Tissue Disorders	50 (23.4)	22 (10.2)	87 (30.7)	2 (4.2)	139 (25.5)
Arthralgia	16 (7.5)	7 (3.3)	31 (11.0)	0	47 (8.6)

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Rhabdomyolysis	8 (3.7)	0	5 (1.8)	1 (2.1)	14 (2.6)
Nervous System Disorders	43 (20.1)	33 (15.3)	55 (19.4)	1 (2.1)	99 (18.2)
Headache	22 (10.3)	9 (4.2)	14 (4.9)	0	36 (6.6)
Renal and Urinary Disorders	31 (14.5)	42 (19.5)	63 (22.3)	9 (18.8)	103 (18.9)
Proteinuria	20 (9.3)	19 (8.8)	30 (10.6)	4 (8.3)	54 (9.9)
Hepatobiliary disorders	17 (7.9)	36 (16.7)	18 (6.4)	3 (6.3)	38 (7.0)
Hepatic function abnormal	9 (4.2)	26 (12.1)	8 (2.8)	3 (6.3)	20 (3.7)

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities; QT = interval, time from the start of the Q wave to the end of the T wave.

Table 91: Drug-related Adverse Events Reported in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population (at ≥ 10% Cut-off) by Preferred Terms

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%))
Investigations	159 (74.3)	166 (77.2)	157 (55.5)	36 (75.0)	352 (64.6)
Blood creatine phosphokinase increased	85 (39.7)	15 (7.0)	61 (21.6)	23 (47.9)	169 (31.0)
Aspartate aminotransferase increased	60 (28.0)	115 (53.5)	38 (13.4)	11 (22.9)	109 (20.0)
Alanine aminotransferase increased	62 (29.0)	119 (55.3)	34 (12.0)	9 (18.8)	105 (19.3)
White blood cell count decreased	46 (21.5)	26 (12.1)	33 (11.7)	9 (18.8)	88 (16.1)
Platelet count decreased	37 (17.3)	12 (5.6)	23 (8.1)	6 (12.5)	66 (12.1)
Neutrophil count decreased	28 (13.1)	20 (9.3)	21 (7.4)	2 (4.2)	51 (9.4)
Electrocardiogram QT prolonged	26 (12.1)	19 (8.8)	18 (6.4)	7 (14.6)	51 (9.4)
Blood bilirubin increased	16 (7.5)	31 (14.4)	15 (5.3)	3 (6.3)	34 (6.2)
Blood lactate dehydrogenase increased	24 (11.2)	12 (5.6)	4 (1.4)	4 (8.3)	32 (5.9)
Gamma-glutamyltransferase increased	15 (7.0)	27 (12.6)	6 (2.1)	3 (6.3)	24 (4.4)
Skin and Subcutaneous Tissue Disorders	68 (31.8)	124 (57.7)	89 (31.4)	9 (18.8)	166 (30.5)
Rash	46 (21.5)	88 (40.9)	44 (15.5)	6 (12.5)	96 (17.6)
Pruritus	14 (6.5)	25 (11.6)	37 (13.1)	2 (4.2)	53 (9.7)
Gastrointestinal Disorders	73 (34.1)	90 (41.9)	95 (33.6)	4 (8.3)	172 (31.6)
Diarrhoea	31 (14.5)	63 (29.3)	30 (10.6)	0	61 (11.2)
Blood and Lymphatic System Disorders	33 (15.4)	12 (5.6)	64 (22.6)	5 (10.4)	102 (18.7)
Anaemia	32 (15.0)	12 (5.6)	36 (12.7)	5 (10.4)	73 (13.4)
Hepatobiliary disorders	13 (6.1)	32 (14.9)	16 (5.7)	2 (4.2)	31 (5.7)

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%))
Hepatic function abnormal	8 (3.7)	25 (11.6)	8 (2.8)	2 (4.2)	18 (3.3)

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities; QT = interval, time from the start of the Q wave to the end of the T wave.

TEAEs Grade ≥3

Table 92 Adverse Events Grade ≥ 3 Reported in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population (at incidence ≥ 2% Cutoff) by Preferred Terms

System organ class Preferred term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Investigations	44 (20.6)	41 (19.1)	38 (13.4)	12 (25.0)	94 (17.2)
Blood creatine phosphokinase increased	17 (7.9)	1 (0.5)	20 (7.1)	4 (8.3)	41 (7.5)
Alanine aminotransferase increased	6 (2.8)	26 (12.1)	5 (1.8)	2 (4.2)	13 (2.4)
Blood pressure increased	1 (0.5)	1 (0.5)	3 (1.1)	3 (6.3)	7 (1.3)
Lymphocyte count decreased	4 (1.9)	1 (0.5)	3 (1.1)	1 (2.1)	8 (1.5)
Neutrophil count decreased	5 (2.3)	0	2 (0.7)	0	7 (1.3)
Platelet count decreased	4 (1.9)	3 (1.4)	2 (0.7)	1 (2.1)	7 (1.3)
White blood cell count decreased	6 (2.8)	0	0	1 (2.1)	7 (1.3)
Aspartate aminotransferase increased	3 (1.4)	20 (9.3)	1 (0.4)	1 (2.1)	5 (0.9)
Gamma-glutamyltransferase increased	2 (0.9)	5 (2.3)	0	0	2 (0.4)
Weight decreased	0	1 (0.5)	0	1 (2.1)	1 (0.2)
Infections and Infestations	7 (3.3)	13 (6.0)	14 (4.9)	1 (2.1)	22 (4.0)
Pneumonia	2 (0.9)	7 (3.3)	7 (2.5)	1 (2.1)	10 (1.8)
Vascular Disorders	11 (5.1)	2 (0.9)	10 (3.5)	0	21 (3.9)
Hypertension	9 (4.2)	2 (0.9)	6 (2.1)	0	15 (2.8)
Metabolism and Nutrition Disorders	13 (6.1)	13 (6.0)	10 (3.5)	2 (4.2)	25 (4.6)
Hyponatraemia	2 (0.9)	1 (0.5)	4 (1.4)	1 (2.1)	7 (1.3)
Hypokalaemia	4 (1.9)	7 (3.3)	2 (0.7)	0	6 (1.1)
Hypertriglyceridaemia	1 (0.5)	2 (0.9)	0	1 (2.1)	2 (0.4)
Blood and Lymphatic System Disorders	6 (2.8)	0	5 (1.8)	1 (2.1)	12 (2.2)
Anaemia	4 (1.9)	0	4 (1.4)	1 (2.1)	9 (1.7)

System organ class Preferred term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Investigations	44 (20.6)	41 (19.1)	38 (13.4)	12 (25.0)	94 (17.2)
Respiratory, Thoracic and Mediastinal Disorders	9 (4.2)	4 (1.9)	12 (4.2)	1 (2.1)	22 (4.0)
Pulmonary embolism	6 (2.8)	0	8 (2.8)	1 (2.1)	15 (2.8)
Hepatobiliary Disorders	3 (1.4)	11 (5.1)	2 (0.7)	0	5 (0.9)
Hepatic function abnormal	2 (0.9)	9 (4.2)	0	0	2 (0.4)

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities;

Grade ≥ 3 Drug-related Adverse Events Reported in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population (at ≥ 2% Cut-off) by Preferred Terms

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Investigations					
Blood creatine phosphokinase increased	17 (7.9)	0	20 (7.1)	4 (8.3)	41 (7.5)
Alanine aminotransferase increased	6 (2.8)	26 (12.1)	5 (1.8)	1 (2.1)	12 (2.2)
Aspartate aminotransferase increased	3 (1.4)	20 (9.3)	1 (0.4)	0	4 (0.7)
Blood pressure increased	0	0	3 (1.1)	1 (2.1)	4 (0.7)
Respiratory, Thoracic and Mediastinal Disorders					
Pulmonary embolism	2 (0.9)	0	6 (2.1)	0	8 (1.5)
Hepatobiliary Disorders					
Hepatic function abnormal	2 (0.9)	9 (4.2)	0	0	2 (0.4)
Musculoskeletal and connective tissue disorders					
Rhabdomyolysis	8 (3.7)	0	5 (1.8)	1 (2.1)	14 (2.6)

A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population. Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021. Aumo = aumolertinib; Gefi = gefitinib; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Adverse drug reaction

All TEAEs regardless of assessed causality, and all TEAEs assessed as treatment-related by the Investigator, from the pooled safety population at the recommended dose of 110 mg were reviewed to determine ADRs. A frequency threshold of ≥ 5% for all TEAEs regardless of causality assessment and ≥ 1% for TEAEs ≥ Grade 3 regardless of causality was applied to identify possible ADRs.

All TEAEs meeting the defined threshold were evaluated individually and if the available evidence was sufficient to support a causal association, the event was included as an ADR. In addition to the pooled 110 mg aumolertinib population data, the frequency of TEAEs, all TEAEs regardless of causality and events assessed as related, were evaluated from Study HS 10296 03 01, comparing the aumolertinib 110 mg arm to the gefitinib arm.

Although the reported frequency met the defined threshold of ≥ 5% for all TEAEs regardless of causality assessment and ≥ 1% for TEAEs ≥ Grade 3 regardless of causality, the following events were excluded as ADRs due to insufficient evidence supporting a causal association, no apparent class effect or target-related side effect, and the relatively common frequency of these events in the general population:

- Constipation
- Weight increased
- Back pain
- Headache

TEAEs that were reported at a frequency that did not meet the defined threshold were evaluated to identify rare and potentially severe ADRs and, if available evidence supported a causal association, these events were considered ADRs. Although changes in myocardial contractility, eye diseases, and interstitial lung disease did not meet the defined threshold, these events were included as ADRs based on the available evidence supporting a causal association, including the known effects of EGFR TKIs.

The ADRs are included in the tabulated list of adverse reactions (frequencies presented by all assessed causalities) as either a single PT or a pooled term, based on the medical concept and the data reported from the 110 mg pooled safety population (N=545).

Table 93 Adverse reactions reported in subjects treated with Aumseqa

		Adverse reactions	
System organ class	**MedDRA preferred term**	**Frequency of all grades n (%)**	**Frequency of grade ≥ 3 n (%)**
Infections and infestations	Upper respiratory tract infections [a]	Very common 127 (23.3)	Uncommon 1 (0.2)
	Urinary tract infections [b]	Very common 100 (18.3)	Uncommon 4 (0.7)
	Lower respiratory tract and lung infection [c]	Common 43 (7.9)	Common 10 (1.8)
	Conjunctivitis [d]	Common 17 (3.1)	- 0
Blood and lymphatic system disorders	Anaemia	Very common 98 (18.0)	Common 9 (1.7)
Immune system disorders	Hypersensitivity	Common 7 (1.3)	- 0

System organ class	MedDRA preferred term	Adverse reactions	
		Frequency of all grades n (%)	Frequency of grade ≥ 3 n (%)
Metabolism and nutrition disorders	Hyponatraemia *[e]	Very common 203 (37.2)	Common 26 (4.8)
	Hypokalaemia *[f]	Very common 100 (18.3)	Common 13 (2.4)
	Decreased appetite	Common 44 (8.1)	Uncommon 4 (0.7)
	Hyperuricaemia	Common 35 (6.4)	- 0
Eye disorders	Dry eye [g]	Common 19 (3.5)	- 0
	Blurred vision [h]	Common 14 (2.6)	- 0
	Ocular discomfort [i]	Uncommon 5 (0.9)	- 0
	Ocular hyperaemia [j]	Uncommon 5 (0.9)	- 0
	Abnormal sensation in eye [k]	Uncommon 2 (0.4)	- 0
	Corneal changes [l]	Uncommon 2 (0.4)	- 0
	Eyelid oedema [m]	Uncommon 2 (0.4)	- 0
Cardiac disorders	Cardiac failure [n]	Uncommon 4 (0.7)	Uncommon 2 (0.4)
Vascular disorders	Hypertension [o]	Common 46 (8.4)	Common 22 (4.0)
	Venous thromboembolism [p]	Common 39 (7.2)	Common 17 (3.1)
Respiratory, thoracic and mediastinal disorders	Cough [q]	Very common 84 (15.4)	- 0
	Interstitial lung disease [r]	Common 16 (2.9)	Uncommon 1 (0.2)
Gastrointestinal disorders	Diarrhoea	Very common 72 (13.2)	Uncommon 4 (0.7)
	Mouth ulceration [s]	Very common 68 (12.5)	- 0
	Vomiting	Very common 58 (10.6)	Uncommon 3 (0.6)
	Nausea	Common 54 (9.9)	Uncommon 2 (0.4)
Skin and subcutaneous tissue disorders	Rash [t]	Very common 124 (22.8)	Uncommon 2 (0.4)
	Pruritus	Very common 57 (10.5)	- 0
	Paronychia	Common 12 (2.2)	- 0

System organ class	MedDRA preferred term	Adverse reactions	
		Frequency of all grades n (%)	Frequency of grade ≥ 3 n (%)
	Dry skin	Common 11 (2.0)	- 0
	Dermatitis [u]	Common 10 (1.8)	- 0
	Erythema [v]	Uncommon 5 (0.9)	- 0
	Palmar-planar erythrodysaesthesia syndrome	Uncommon 3 (0.6)	- 0
	Folliculitis	Uncommon 2 (0.4)	- 0
Musculoskeletal and connective tissue disorders	Blood creatine phosphokinase increased	Very common 173 (31.7)	Common 41 (7.5)
	Rhabdomyolysis	Common 14 (2.6)	Common 14 (2.6)
	Pain in extremity	Common 42 (7.7)	Uncommon 1 (0.2)
	Myalgia	Common 12 (2.2)	- 0
	Muscular weakness	Common 6 (1.1)	Uncommon 1 (0.2)
Renal and urinary disorders	Blood creatinine increased *	Very common 133 (24.5)	Uncommon 2 (0.4)
	Proteinuria	Common 54 (9.9)	Uncommon 1 (0.2)
Investigations	Aspartate aminotransferase (AST) increased *	Very common 220 (40.4)	Common 7 (1.3)
	White blood cell (WBC) count decreased *[w]	Very common 167 (30.6)	Common 11 (2.0)
	Alanine aminotransferase (ALT) increased *	Very common 180 (33.0)	Common 15 (2.8)
	Platelet count decreased *[x]	Very common 160 (29.4)	Common 8 (1.5)
	Blood bilirubin increased *[y]	Very Common 89 (16.3)	Uncommon 1 (0.2)
	Electrocardiogram QT prolonged	Common 51 (9.4)	Uncommon 4 (0.7)
	Blood lactate dehydrogenase increased	Common 38 (7.0)	- 0
	Gamma-glutamyltransferase increased	Common 31 (5.7)	Uncommon 2 (0.4)
	Lymphocyte count decreased	Common 25 (4.6)	Common 8 (1.5)

Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
The severity of adverse reactions was assessed based on the CTCAE, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening, and Grade 5 = death.
a Includes: acute sinusitis, laryngopharyngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, and upper respiratory tract infection.

b Includes: cystitis, pyelonephritis acute, urethritis, and urinary tract infection.
c Includes: atypical pneumonia, bronchitis, pneumonia, and sputum purulent.
d Includes: conjunctivitis and conjunctivitis allergic.
e Includes: blood sodium decreased, hyponatraemia*.
f Includes: blood potassium decreased, hypokalaemia*.
g Includes: dry eye and xerophthalmia.
h Includes: visual impairment and blurred vision.
i Includes: eye pain, and ocular discomfort.
j Includes: ocular hyperaemia, conjunctival haemorrhage, and eye haemorrhage.
k Includes: abnormal sensation in eye, and foreign body sensation in eyes.
l Includes: corneal exfoliation and corneal opacity.
m Includes: eyelid oedema and swelling of eyelid.
n Includes: cardiac failure, cardiac failure chronic, ejection fraction decreased, and pulmonary oedema.
o Includes: blood pressure increased, hypertension.
p Includes: deep vein thrombosis, pulmonary embolism, venous thrombosis limb, cerebral infarction and cerebral thrombosis.
q Includes: cough, productive cough, and upper-airway cough syndrome.
r Includes: bronchiolitis, interstitial lung disease, and pneumonitis.
s Includes: aphthous ulcer, dry mouth, glossodynia, mouth ulceration, oral pain, stomatitis, and tongue ulceration.
t Includes: drug eruption, papule, macule, rash, rash maculo-papular, rash papular, rash pruritic, rash pustular, and urticaria.
u Includes: dermatitis and dermatitis acneiform.
v Includes: erythema and erythema nodosum.
w Includes: neutropenia, neutrophil count decreased, and white blood cell count decreased*.
x Includes: platelet count decreased*, and thrombocytopenia.
y Includes: blood bilirubin increased, and hyperbilirubinemia.
* Represent incidence of laboratory findings, not of adverse events

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

A similar proportion of patients experienced SAEs in the aumolertinib and gefitinib treatment arms (22.0% vs 21.4%). SAEs reported in ≥ 3 subjects in both arms were Pneumonia (n=6, 2.8% in aumolertinib arm versus n=8, 3.7% in gefitinib arm).

Table 94 Serious Adverse Events by Preferred Terms in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population (at ≥ 1% Cutoff)

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Infections and Infestations	10 (4.7)	13 (6.0)	19 (6.7)	1 (2.1)	30 (5.5)
Pneumonia	6 (2.8)	9 (4.2)	7 (2.5)	1 (2.1)	14 (2.6)
Urinary tract infection	1 (0.5)	0	3 (1.1)	0	4 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	8 (3.7)	8 (3.7)	13 (4.6)	1 (2.1)	22 (4.0)
Pulmonary embolism	4 (1.9)	0	8 (2.8)	1 (2.1)	13 (2.4)
Pneumonitis	1 (0.5)	3 (1.4)	1 (0.4)	0	2 (0.4)
Nervous system disorders	7 (3.3)	3 (1.4)	10 (3.5)	0	17 (3.1)
Cerebral infarction	3 (1.4)	1 (0.5)	0	0	3 (0.6)
Vascular Disorders	8 (3.7)	0	9 (3.2)	0	17 (3.1)
Deep vein thrombosis	3 (1.4)	0	3 (1.1)	0	6 (1.1)
Venous thrombosis limb	4 (1.9)	0	2 (0.7)	0	6 (1.1)
General disorders and administration site conditions	2 (0.9)	2 (0.9)	6 (2.1)	0	8 (1.5)
Death	1 (0.5)	1 (0.5)	4 (1.4)	0	5 (0.9)
Investigations	1 (0.5)	6 (2.8)	3 (1.1)	0	4 (0.7)

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Alanine aminotransferase increased	0	4 (1.9)	0	0	0
Aspartate aminotransferase increased	0	4 (1.9)	0	0	0
Hepatobiliary disorders	2 (0.9)	12 (5.6)	1 (0.4)	0	3 (0.6)
Hepatic function abnormal	2 (0.9)	9 (4.2)	0	0	2 (0.4)

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Deaths

Summary of Deaths (All Causes)

Table 95 Early and Late Deaths in the Pivotal Studies and Pooled Safety Population

	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Within 28 days of last dose					
Total number of deaths	17 (7.9)	12 (5.6)	18 (6.4)	4 (8.3)	39 (7.2)
Primary cause of death					
Disease Progression	10 (4.7)	9 (4.2)	12 (4.2)	4 (8.3)	26 (4.8)
Adverse Events	6 (2.8) *	3 (1.4)	1 (0.4) *	0	7 (1.3)
Other	1 (0.5)	0	5 (1.8)	0	6 (1.1)
More than 28 days after last dose					
Total number of deaths	60 (28.0)	76 (35.3)	118 (41.7)	8 (16.7)	186 (34.1)
Primary cause of death					
Disease Progression	49 (22.9)	63 (29.3)	85 (30.0)	7 (14.6)	141 (25.9)
Adverse Events	1 (0.5)	0	2 (0.7)	0	3 (0.6)
Other	10 (4.7)	13 (6.0)	31 (11.0)	1 (2.1)	42 (7.7)

MedDRA version 24.0;
Data cutoff of HS-10296-12-01: January 5, 2019; Data cutoff of HS-10296-03-01: January 15, 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities.
* One Subject from the 1201 110mg group) and one subject (from the 301 Aumo group) died with disease progression, concurrent with pneumonia and interstitial lung disease (ILD), respectively. The potential contribution of these conditions to death could not be completely ruled out, and therefore these cases were counted in the Adverse Event category only.

In the overall population, at the time of the updated data cut-off (August 2021), grade 5 AEs occurred in 225 (41.3%) patients. AEs with a fatal outcome were reported in 11 of 545 subjects (2.0%); and 1.1% (n=6) were adjudicated as treatment-related by the Investigator.

The majority of deaths (169/225; 75%) were attributed by the Investigator to disease progression, ~22% (48/225) to "other" and ~3% (6/225) were attributed to AEs.

A total of 77 subjects (36%) died in the aumolertinib arm at the time of data cut-off (August 2021). In comparison, 88 subjects (40.9%) died in the gefitinib arm. Nine (9) subjects experienced AEs leading to death: 6 in the aumolertinib and 3 in the gefitinib arm. Fatal TEAEs were mostly thromboembolic events.

Adverse events of special interest (AESIs)

The study protocols of the pivotal studies did not include a pre-specified list of AESIs subject to specific reporting, instead, a list of AE of clinical interest (AECI) based on "consolidated analyses of similar items by medical logic" was defined by the sponsor and included in the HS-10296-03-01 CSR to characterize risks.

To characterize key risks, based on known class effects of EGFR TKIs, emerging preclinical, and clinical data from the aumolertinib studies, the following AECIs were selected for further characterisation in the safety pool (N=545): hepatotoxicity, elevated blood CPK, interstitial lung disease, cardiac failure, QT prolongation, ocular toxicity and diarrhoea, and were completed with a description of rhabdomyolysis and venous thromboembolism.

Interstitial lung disease (ILD)

ILD was reported in 16 subjects (2.9%) treated with Aumseqa 110 mg in the safety pool (N=545). One (0.2%) subject reported grade 3 ILD (pneumonitis) and died during the study concurrent with disease progression. The median time to onset of ILD was 124 days (range: 2 days – 932 days). The median time to resolution of ILD was 41 days (range: 14 days - 702 days).

Cardiac failure

Cardiac failure was reported in 4 subjects (0.7%) in the safety pool (N=545). Two subjects (0.4%) reported cardiac failure of Grade ≥ 3. The median time to onset of any Grade cardiac failure was 249 days (range: 84 days – 381 days), and the median time to resolution was 35 days (range: 22 days – 160 days). One subject with cardiac failure died due to pulmonary oedema and upper gastrointestinal haemorrhage. Four subjects (0.7%) had a decline in LVEF of ≥ 10% to an absolute value < 50%. Nineteen subjects (3.5%) had a decline in LVEF of ≥ 15% but the absolute LVEF remained ≥ 50% in these subjects.

QTc prolongation

QT prolongation was reported in 51 subjects (9.4%) treated with Aumseqa 110 mg in the safety pool (N=545). In 4 subjects (0.7%) the events were Grade ≥ 3. The median time to onset of any Grade QT prolongation was 22 days (range: 1 day – 839 days) and the median time to resolution was 100 days (1 day – 1,068 days). Seven subjects (1.3%) had symptomatic events, 4 (0.7%) of which were Grade ≥ 3. The reported symptomatic events were cardiac arrest, cardiorespiratory arrest, sudden cardiac death, syncope (n = 2), and ventricular arrhythmia (n = 2). The median time to onset of syncope and ventricular arrhythmia was 204 days and 252 days, respectively. Two subjects with QT prolongation died: 1 due to sudden cardiac death and 1 due to cardiorespiratory arrest. 5 subjects (0.9%) had a maximum absolute QTcF interval > 500 msec and 23 subjects (4.2%) had a maximum change in QTcF from baseline > 60 msec.

Diarrhoea

Diarrhoea was reported in 72 subjects (13.2%) treated with Aumseqa 110 mg in the safety pool (N=545). In 4 subjects (0.7%) the events were Grade ≥ 3. The median time to onset of any Grade diarrhoea was 27 days (range: 1 day – 1,046 days) and the median time to resolution was 13 days (1 day – 846 days). Three subjects (0.6%) experienced SAEs of diarrhoea. One subject reported potassium imbalance. Six subjects reported hypokalaemia of Grade 3.

Elevated blood creatinine phosphokinase (CPK) and rhabdomyolysis

Table 96: TEAEs in the Rhabdomyolysis Broad SMQ of Any Grade in the Pooled Safety Population (Aumolertinib 110 mg)

AECI **PT**	All Aumo 110 mg [a] **(N = 545)**			
	n, any Grade (%) [b]	**median time-to-onset [c] (day), min – max**	**median duration [d] (day), min – max**	**median time-to-resolution [e] (day), min – max**
Any AE in the Rhabdomyolysis Broad SMQ	223 (40.9)	64, 1 – 926	127, 4 – 1060	169, 4 – 1212
Blood creatine phosphokinase increased	173 (31.7)	64, 1 – 926	130, 4 – 1060	215, 4 – 1156
Blood creatinine increased	32 (5.9)	74, 7 – 820	59.5, 9 – 1047	59.5, 9 – 1047
Hypocalcaemia	25 (4.6)	96, 8 – 632	45, 5 – 331	57, 5 – 793
Myalgia	12 (2.2)	34.5, 4 – 610	77.5, 2 – 1009	88, 2 – 1204
Myoglobin blood increased	11 (2.0)	47, 23 – 217	33, 6 – 251	37, 6 – 764
Muscular weakness	6 (1.1)	292.5, 2 – 671	45, 3 – 497	45, 3 – 497
Chronic kidney disease	3 (0.6)	68, 22 – 253	197, 168 – 448	197, 168 – 448
Glomerular filtration rate decreased	3 (0.6)	630, 8 – 632	84, 8 – 117	84, 8 – 117
Myositis	2 (0.4)	241.5, 22 – 461	334, 80 – 588	342.5, 97 – 588
Renal failure	2 (0.4)	29, 15 – 43	59.5, 6 – 113	59.5, 6 – 113
Musculoskeletal pain	1 (0.2)	243, 243 – 243	110, 110 – 110	110, 110 – 110
Renal impairment	1 (0.2)	415, 415 – 415	126, 126 – 126	126, 126 – 126
Musculoskeletal discomfort	0	--	--	--

a All Aumo 110 mg is defined as all NSCLC subjects treated with aumolertinib at 110 mg, qd dose level.
b The percentages are calculated based on the number of safety population.
c Time-to-onset is defined as from the first dose date to the onset date of the first AECI category/PT.
d Duration is defined as the sum of the duration of each record. If last record is ongoing (without ending date) and the treatment discontinuation date is available, the ending date of safety follow-up (i.e., min (last dose date of study drug + 28, start date of HS-10296 crossover treatment – 1, end of study date, death date) was used, or if the subject is still on study treatment, data cutoff date was u
ed.
e Time-to-resolution is defined as the duration from the onset date (or the earliest onset date within AECI) to the ending date (or the latest ending date within AECI). If the event (or any one event within AECI) is ongoing, the ending date will be the end date of safety follow up (i.e., min (last dose date of study drug + 28, start date of HS-10296 crossover treatment – 1, end of study date, death date) if the treatment is discontinued, or data cutoff date if the subject is still on study treatment.
MedDRA version 24.0. Data cutoff of HS-10296-12-0: 01 Aug 2021; Data cutoff of HS-10296-03-0: 06 Aug 2021.
AE = adverse event; AECI = adverse event of clinical interest; Aumo = aumolertinib; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; qd = once a day; SMQ = standardized MedDRA query.

Elevated blood CPK was reported in 173 subjects (31.7%) treated with Aumseqa 110 mg in the safety pool (N=545). In 41 subjects (7.5%), the events were Grade ≥ 3. The median time to onset of any Grade blood CPK increased was 64 days (range: 1 day – 926 days) and the median time to resolution

was 215 days (4 days – 1,156 days). Elevated blood CPK led to treatment discontinuation in 1 subject (0.2%). Events of elevated Blood CPK were considered rhabdomyolysis if they were Grade 3 with muscle related symptoms or Grade 4 with or without muscle related symptoms. In total, 14 subjects (2.6%) treated with Aumseqa 110 mg were considered to have experienced rhabdomyolysis.

Hepatic dysfunction

Table 97: Grade ≥ 3 Hepatotoxicity in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population

Standardized MedDRA Queries Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Number of subjects with at least 1 Grade ≥ 3 AE of hepatotoxicity	12 (5.6)	42 (19.5)	6 (2.1)	2 (4.2)	20 (3.7)
Alanine aminotransferase increased	6 (2.8)	26 (12.1)	5 (1.8)	2 (4.2)	13 (2.4)
Aspartate aminotransferase increased	3 (1.4)	20 (9.3)	1 (0.4)	1 (2.1)	5 (0.9)
Gamma-glutamyltransferase increased	2 (0.9)	5 (2.3)	0	0	2 (0.4)
Hepatic function abnormal	2 (0.9)	9 (4.2)	0	0	2 (0.4)
Drug-induced liver injury	1 (0.5)	2 (0.9)	0	0	1 (0.2)
Hepatic cancer	1 (0.5)	0	0	0	1 (0.2)
Hepatitis	0	0	1 (0.4)	0	1 (0.2)

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities.

ALT increased are presented in Table 98.

Table 98: AST increased and ALT increased AEs of any Grade in the Pooled Safety Population (Aumolertinib 110 mg)

SOC **PT**	All Aumo 110 mg [a] (N = 545)					
	Any Grade AEs			Grade ≥ 3 AEs		
	n, (%)b	median time-to-onset [c] (day), min-max	median time-to-resolution [d] (day), min-max	n, (%)b	median -to-time onset [c] (day), min-max	median time-to-resolution [d] (day), min-max
Hepatotoxicity						
Aspartate aminotransferase increased	118 (21.7)	43, 1-841	57.5, 2-987	13 (2.4)	63, 15-505	7, 5-22
Alanine aminotransferase increased	110 (20.2)	43, 1-715	42, 6-765	5 (0.9)	22, 8-262	8, 6-62

a All Aumo 110 mg is defined as all NSCLC patients treated with aumolertinib at 110 mg, qd dose level.
b Percentages are calculated based on the number of subjects in the safety population (n=545).
c Time-to-onset is defined as from the date of first dose to the onset date of the first PT.

d Time-to-resolution is defined as the duration from the onset date (or the earliest onset date of the PT when a patient experienced more than one event) to the end date (or the latest end date of the PT if the subject experienced more than one event). If the event was ongoing, the end date will be the end date of safety follow up (i.e., min (last dose date of study drug + 28, start date of HS-10296 crossover treatment - 1, end of study date, death date) if the treatment is discontinued, or data cutoff date if the patient is still on study treatment.
MedDRA version 24.0. Data cutoff of HS-10296-12-01: August 1, 2021; Data cutoff of HS-10296-03-01: August 6, 2021.
ALT = alanine aminotransferase; Aumo = aumolertinib; AST = aspartate aminotransferase; PT = preferred term; qd = once a day; SOC = system organ class.

Hepatic dysfunction was reported in 204 subjects (37.4%) treated with Aumseqa 110 mg in the safety pool (N=545). In 20 (3.7%) of these subjects the events were Grade ≥ 3. The median time to onset of any Grade hepatic dysfunction was 44 days (range: 1 day – 841 days) and the median time to resolution was 62 days (2 days – 1,036 days). AST and ALT elevations were reported in 118 (21.7%) and 110 (20.2%) subjects, respectively. Thirteen subjects (2.4%) reported AST increased of Grade ≥ 3 and 5 subjects (0.9%) reported ALT increased of Grade ≥ 3. One subject (0.2%) reported drug induced liver injury of Grade ≥ 3 with a time to onset of 8 days and a time to resolution of 6 days.

Venous thromboembolism (VTE)

VTE (including deep vein thrombosis, pulmonary embolism, and venous thrombosis limb) was reported in 39 subjects (7.2%) treated with Aumseqa 110 mg in the safety pool (N=545). In 17 subjects (3.1%) the events were Grade ≥ 3. The median time to onset of any Grade VTE was 229 days (range: 8 days – 1,087 days) and the median time to resolution was 142 days (7 days – 830 days). Pulmonary embolism was reported by 21 subjects (3.9%), with 15 (2.8%) of the events being Grade ≥ 3. Venous thrombosis limb was reported by 16 subjects (2.9%), with 2 (0.4%) of the events being Grade ≥ 3. Deep vein thrombosis was reported by 9 subjects (1.7%), with 1 (0.2%) of the events being Grade ≥ 3. In addition, cerebral infarction and cerebral thrombosis were respectively reported in 4 (0.7%) and 1 (0.2%) subject, with 3 (0.6%) of the events being Grade ≥ 3.

2.6.8.4. Laboratory findings

Table 99 Significant findings under investigation SOC with cut-off of less than 10%

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Investigations					
Blood creatinine increased	12 (5.6)	14 (6.5)	16 (5.7)	4 (8.3)	32 (5.9)
Blood CPK MB increased	13 (6.1)	3 (1.4)	0	3 (6.3)	16 (2.9)
Alpha hydroxybutyrate dehydrogenase increased	8 (3.7)	3 (1.4)	0	3 (6.3)	11 (2.0)
Myoglobin blood increased	8 (3.7)	1 (0.5)	2 (0.7)	1 (2.1)	11 (2.0)
White blood cell counts increased	5 (2.3)	7	2	1	8 (1.5)
C-reactive protein increased	5 (2.3)	0	0	0	5 (0.9)

Table 100 Haematology parameters -Worst Grade On-study in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population

	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Parameter Name (Units):					
Subjects with Any Post-Baseline Measurement	214 (100)	215 (100)	282 (99.6)	47 (97.9)	543 (99.6)
Worst Post-Baseline Grade On-Study[a]					
Haemoglobin (g/L) – Anaemia					
Normal	129 (60.3)	151 (70.2)	138 (48.9)	29 (61.7)	296 (54.5)
Grade 1	59 (27.6)	48 (22.3)	104 (36.9)	14 (29.8)	177 (32.6)
Grade 2	20 (9.3)	16 (7.4)	37 (13.1)	4 (8.5)	61 (11.2)
Grade 3	6 (2.8)	0	3 (1.1)	0	9 (1.7)
Grade 4	0	0	0	0	0
Leukocytes (10^9/L) – White Blood Cell Decreased					
Normal	150 (70.1)	181 (84.2)	193 (68.4)	36 (76.6)	379 (69.8)
Grade 1	36 (16.8)	18 (8.4)	61 (21.6)	7 (14.9)	104 (19.2)

	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Grade 2	22 (10.3)	15 (7.0)	27 (9.6)	3 (6.4)	52 (9.6)
Grade 3	6 (2.8)	1 (0.5)	1 (0.4)	1 (2.1)	8 (1.5)
Grade 4	0	0	0	0	0
Platelets (10^9/L) – Platelet Count Decreased					
Normal	140 (65.4)	189 (87.9)	207 (73.4)	36 (76.6)	383 (70.5)
Grade 1	60 (28.0)	21 (9.8)	64 (22.7)	8 (17.0)	132 (24.3)
Grade 2	9 (4.2)	3 (1.4)	9 (3.2)	2 (4.3)	20 (3.7)
Grade 3	5 (2.3)	1 (0.5)	1 (0.4)	1 (2.1)	7 (1.3)
Grade 4	0	1 (0.5)	1 (0.4)	0	1 (0.2)

The denominator is the number of subjects with any post-baseline measurement.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib.

Overall, the incidence of clinically significant hematologic abnormalities was 55.1% in the aumolertinib arm and 37.2% in the gefitinib arm through the 06 August 2021 data cut-off date whereas clinically significant clinical biochemistry laboratory test results were 80.8% in the aumolertinib arm and 87.9% in the gefitinib arm. In both groups, these abnormalities chiefly included increases in ALT, AST, CPK, potassium, bilirubin, or albumin.

Clinically significant elevations in AST, ALT, and bilirubin occurred in 34.6%, 31.8%, and 8.9% of subjects in the aumolertinib arm compared to 62.8%, 63.7%, and 20.9% of subjects in the gefitinib arm, respectively. In comparison, the incidence of laboratory elevations in AST was 40.4% and the incidence of laboratory elevations in ALT was 33.0%.

Aumolertinib affects liver function, with up to grade 3 events observed (AST/ALT/bilirubin/phosphatase alkaline increase) in patients with normal baseline liver function. DILI cases have been described, as well as one case meeting Hy's law criteria. See section 2.6.8.3. about hepatotoxicity.

Collectively, Grade 1 and 2 increases in creatinine was observed in almost all subjects treated with aumolertinib. Grade ≥ 3 creatinine increase was rare with two events (0.9%).

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Age: In pooled safety population, ~ 67% of patients are < 65 years, and the median age is 61 years. The occurrence of many AEs is comparable across age groups. However, patients with higher age are more prone to experience ≥ grade 3 adverse events (45.9 % vs 33.2 %) and serious adverse events (34.8 % vs 15.9 %).

Table 101: Summary of Adverse Events of Each Age Subgroup

MedDRA Terms	Age < 65 (N = 364) n (%)	Age 65–74 (N = 145) n (%)	Age 75–84 (N = 33) n (%)	Age 85+ (N = 3) n (%)
Total AEs	347 (95.3)	141 (97.2)	33 (100)	3 (100)
Serious AEs —– Total	58 (15.9)	45 (31.0)	15 (45.5)	3 (100)
Fatal	8 (2.2)	2 (1.4)	1 (3.0)	0
Hospitalization/prolonged existing hospitalization	51 (14.0)	41 (28.3)	14 (42.4)	3 (100)
Life-threatening	3 (0.8)	2 (1.4)	2 (6.1)	0
Disability/incapacity	0	3 (2.1)	0	0
Other (medically significant)	4 (1.1)	3 (2.1)	0	1 (33.3)
AEs leading to drop-out	12 (3.3)	8 (5.5)	3 (9.1)	0
Psychiatric disorders	32 (8.8)	16 (11.0)	3 (9.1)	0
Nervous system disorders	63 (17.3)	29 (20.0)	7 (21.2)	0
Adverse events of clinical interest (AECI)				
Blood creatine phosphokinase increased	153 (42.0)	60 (41.4)	10 (30.3)	0
Cardiac failure	2 (0.5)	2 (1.4)	0	0
Diarrhoea	43 (11.8)	25 (17.2)	2 (6.1)	2 (66.7)
Hepatotoxicity	146 (40.1)	50 (34.5)	8 (24.2)	0
Interstitial lung disease	12 (3.3)	3 (2.1)	1 (3.0)	0
Ocular toxicity	30 (8.2)	22 (15.2)	5 (15.2)	2 (66.7)
QT interval prolongation/Torsades	34 (9.3)	18 (12.4)	6 (18.2)	0
Skin and subcutaneous tissue disorders	125 (34.3)	48 (33.1)	13 (39.4)	1 (33.3)
Thromboembolic events	33 (9.1)	24 (16.6)	8 (24.2)	1 (33.3)
Accidents and injuries	16 (4.4)	14 (9.7)	2 (6.1)	2 (66.7)
Cardiac disorders	72 (19.8)	35 (24.1)	10 (30.3)	1 (33.3)
Vascular disorders	43 (11.8)	29 (20.0)	3 (9.1)	2 (66.7)
Cerebrovascular disorders	0	0	0	0
Infections and infestations	168 (46.2)	65 (44.8)	19 (57.6)	3 (100.0)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [a]	26 (7.1)	11 (7.6)	5 (15.2)	1 (33.3)
Other AE appearing more frequently in older subjects				
Blood and lymphatic system disorders	75 (20.6)	49 (33.8)	8 (24.2)	1 (33.3)
Ear and Labyrinth disorders	6 (1.6)	5 (3.4)	1 (3.0)	1 (33.3)
Eye disorders	30 (8.2)	23 (15.9)	5 (15.2)	2 (66.7)
Gastrointestinal disorders	157 (43.1)	75 (51.7)	11 (33.3)	2 (66.7)
General disorders and administration site conditions	90 (24.7)	38 (26.2)	15 (45.5)	2 (66.7)
Metabolism and nutrition disorders	122 (33.5)	57 (39.3)	15 (45.5)	1 (33.3)

MedDRA Terms	Age < 65 (N = 364) n (%)	Age 65–74 (N = 145) n (%)	Age 75–84 (N = 33) n (%)	Age 85+ (N = 3) n (%)
Musculoskeletal and connective tissue disorders	98 (26.9)	32 (22.1)	7 (21.2)	2 (66.7)
Renal and urinary disorders	65 (17.9)	27 (18.6)	10 (30.3)	1 (33.3)
Respiratory, thoracic, and mediastinal disorders	99 (27.2)	43 (29.9)	12 (36.4)	1 (33.3)

[a] Includes dizziness, fractures, radius fracture, fall, femoral neck fracture, pathological fracture, rib fracture, wrist fracture, foot fracture, orthostatic hypotension, presyncope, spinal compression fracture, and syncope.
MedDRA Version 24.0. Data cutoff of HS-10296-12-01: August 1, 2021; Data cutoff of HS-10296-03-01: August 6, 2021.

Table 102: Study 301 - Summary of Adverse Events of Each Age Subgroup in study 1301

MedDRA Terms	Age <65 n (%)		Age 65-74 n (%)		Age 75-84 n (%)	
	Aumo N= 155	Gefi N=139	Aumo N=54	Gefi N=64	Aumo N=5	Gefi N= 12
Total AEs	153 (98.7)	139 (100)	53 (98.1)	63 (98.4)	5 (100)	12 (100)
Serious AEs – Total	32 (20.6)	29 (20.9)	20 (37.0)	18 (28.1)	3 (60.0)	2 (16.7)
- Fatal	3 (1.9)	0	2 (3.7)	3 (4.7)	0	0
- Hospitalization/prolong existing hospitalization	29 (18.7)	29 (20.9)	17 (31.5)	13 (20.3)	3 (60.0)	2 (16.7)
- Life-threatening	2 (1.3)	2 (1.4)	1 (1.9)	1 (1.6)	1 (20.0)	0
- Disability/incapacity	0	0	2 (3.7)	1 (1.6)	0	0
- Other (medically significant)	1 (0.6)	0	2 (3.7)	2 (3.1)	0	0
AE leading to drop-out	5 (3.2)	5 (3.6)	2 (3.7)	5 (7.8)	1 (20.0)	2 (16.7)
Adverse events of clinical interest						
Blood creatine phosphokinase increased	76 (49.0)	31 (22.3)	29 (53.7)	11 (17.2)	5 (100)	3 (25.0)
Cardiac failure	0	0	1 (1.9)	1 (1.6)	0	0
Diarrhoea	27 (17.4)	43 (30.9)	10 (18.5)	27 (42.2)	0	7 (58.3)
Hepatotoxicity	89 (57.4)	108 (77.7)	19 (35.2)	43 (67.2)	1 (20.0)	7 (58.3)
Interstitial lung disease	9 (5.8)	9 (6.5)	2 (3.7)	2 (3.1)	0	1 (8.3)
Ocular toxicity	11 (7.1)	9 (6.5)	3 (5.6)	7 (10.9)	0	1 (8.3)
QT interval prolongation/Torsades	19 (12.3)	11 (7.9)	10 (18.5)	8 (12.5)	1 (20.0)	1 (8.3)
Skin and subcutaneous tissue disorders	61 (39.4)	88 (63.3)	16 (29.6)	34 (53.1)	0	7 (58.3)
Thromboembolic events	18 (11.6)	6 (4.3)	10 (18.5)	5 (7.8)	3 (60.0)	0
Quality of life decreased						
Accidents and injuries	2 (1.3)	5 (3.6)	5 (9.3)	3 (4.7)	0	1 (8.3)
TEAEs by System Organ Class						
Blood and lymphatic system disorders	32 (20.6)	11 (7.9)	17 (31.5)	12 (18.8)	2 (40.0)	1 (8.3)
Cardiac disorders	41 (26.5)	28 (20.1)	14 (25.9)	14 (21.9)	1 (20.0)	6 (50.0)
Ear and labyrinth disorders	4 (2.6)	2 (1.4)	0	2 (3.1)	0	0
Endocrine disorders	1 (0.6)	0	2 (3.7)	1 (1.6)	0	0
Eye disorders	11 (7.1)	9 (6.5)	4 (7.4)	7 (10.9)	0	1 (8.3)

MedDRA Terms	Age <65 n (%)		Age 65-74 n (%)		Age 75-84 n (%)	
	Aumo N= 155	Gefi N=139	Aumo N=54	Gefi N=64	Aumo N=5	Gefi N= 12
Gastrointestinal disorders	75 (48.4)	72 (51.8)	30 (55.6)	38 (59.4)	2 (40.0)	10 (83.3)
General disorders and administration site conditions	35 (22.6)	37 (26.6)	10 (18.5)	21 (32.8)	2 (40.0)	2 (16.7)
Hepatobiliary disorders	15 (9.7)	27 (19.4)	2 (3.7)	8 (12.5)	0	1 (8.3)
Immune system disorders	3 (1.9)	3 (2.2)	1 (1.9)	1 (1.6)	0	0
Infections and infestations	86 (55.5)	60 (43.2)	24 (44.4)	33 (51.6)	2 (40.0)	7 (58.3)
Injury, poisoning and procedural complications	4 (2.6)	6 (4.3)	5 (9.3)	4 (6.3)	0	1 (8.3)
Metabolism and nutrition disorders	65 (41.9)	47 (33.8)	25 (46.3)	32 (50.0)	5 (100)	9 (75.0)
Musculoskeletal and connective tissue disorders	40 (25.8)	16 (11.5)	9 (16.7)	6 (9.4)	1 (20.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.9)	1 (0.7)	0	0	0	0
Nervous system disorders	30 (19.4)	22 (15.8)	12 (22.2)	10 (15.6)	1 (20.0)	1 (8.3)
Psychiatric disorders	13 (8.4)	11 (7.9)	6 (11.1)	6 (9.4)	0	0
Renal and urinary disorders	22 (14.2)	22 (15.8)	8 (14.8)	17 (26.6)	1 (20.0)	3 (25.0)
Reproductive system and breast disorders	3 (1.9)	8 (5.8)	0	1 (1.6)	0	0
Respiratory, thoracic and mediastinal disorders	38 (24.5)	34 (24.5)	14 (25.9)	12 (18.8)	0	3 (25.0)
Skin and subcutaneous tissue disorders	61 (39.4)	88 (63.3)	16 (29.6)	34 (53.1)	0	7 (58.3)
Vascular disorders	20 (12.9)	8 (5.8)	13 (24.1)	9 (14.1)	2 (40.0)	1 (8.3)

Note: No subject of Age 85+ in Study 301.

Sex: The following PTs were more common in women than men with more than absolute 5% difference: WBC decreased (23.2% vs 11.5%), neutrophil count decreased (13.4% vs 7.7%), ECG QT prolonged (11.9% vs 5.5%), vomiting (13.4% vs 6.5%), nausea (13.1% vs. 5.1%), urinary tract infection (22.6% vs. 8.3%), haematuria 7.9% vs. 2.8%). Men had more proteinuria than women; 13.8% vs. 7.3%.

Race: The safety of aumolertinib has not been evaluated in subjects with advanced NSCLC from different racial groups due to the small numbers of non-Chinese subjects included in the pivotal studies. Study HS-10296-12-01 was conducted in China, Taiwan and the US but included only 5 non-Chinese subjects (3 White, 1 Black, and 1 other), which was too small a number to compare the safety with that observed in Chinese subjects. These non-Chinese subjects also received different doses of aumolertinib (55, 220 and 260 mg) which would confound safety comparisons. Study HS-10296-03-01 was conducted in China.

Hepatic Impairment: Compared with the matched healthy subjects, aumolertinib AUC∞ and Cmax were increased by 39% and 9%, respectively, in subjects with mild hepatic impairment. The AUC∞ of the metabolite HAS-719 increased by approximately 7% and Cmax decreased by approximately 11%.

The following patient subgroups were not included in the pivotal studies: patients with hepatic, renal or cardiac impairment (included prolonged QT syndrome) were not eligible for the studies.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

See section 2.6.2.1.

2.6.8.9. Discontinuation due to adverse events

Table 103: Adverse Events Leading to Permanent Treatment Discontinuation in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population by System Organ Class and Preferred Terms

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Number of subjects with at least 1 TEAE leading to discontinuation of treatment	8 (3.7)	12 (5.6)	15 (5.3)	0	23 (4.2)
Respiratory, Thoracic, and Mediastinal Disorders	3 (1.4)	1 (0.5)	1 (0.4)	0	4 (0.7)
Cough	0	0	1 (0.4)	0	1 (0.2)
Interstitial lung disease	2 (0.9)	1 (0.5)	0	0	2 (0.4)
Atelectasis	0	0	1 (0.4)	0	1 (0.2)
Pleural effusion	0	0	1 (0.4)	0	1 (0.2)
Pulmonary embolism	1 (0.5)	0	0	0	1 (0.2)
Investigations	2 (0.9)	7 (3.3)	3 (1.1)	0	5 (0.9)
Alanine aminotransferase increased	0	1 (0.5)	1 (0.4)	0	1 (0.2)
Blood creatine phosphokinase increased	0	0	1 (0.4)	0	1 (0.2)
Gamma-glutamyltransferase increased	1 (0.5)	2 (0.9)	0	0	1 (0.2)
Neutrophil count decreased	1 (0.5)	0	0	0	1 (0.2)
Platelet count deceased	0	0	1 (0.4)	0	1 (0.2)
White blood cell count increased	0	0	1 (0.4)	0	1 (0.2)
Aspartate aminotransferase increased	0	3 (1.4)	0	0	0
Bilirubin conjugated increased	0	2 (0.9)	0	0	0
Electrocardiogram QT prolonged	0	1 (0.5)	0	0	0
Cardiac Disorders	1 (0.5)	1 (0.5)	2 (0.7)	0	3 (0.6)
Acute myocardial infarction	1 (0.5)	0	0	0	1 (0.2)
Arrhythmia	0	0	1 (0.4)	0	1 (0.2)
Pericardial effusion	0	0	1 (0.4)	0	1 (0.2)
Supraventricular extrasystoles	0	1 (0.5)	0	0	0
General Disorders and Administration Site Conditions	0	0	3 (1.1)	0	3 (0.6)
Death	0	0	2 (0.7)	0	2 (0.4)
Pain	0	0	1 (0.4)	0	1 (0.2)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	0	0	2 (0.7)	0	2 (0.4)
Breast cancer	0	0	1 (0.4)	0	1 (0.2)

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Prostate cancer	0	0	1 (0.4)	0	1 (0.2)
Blood and Lymphatic System Disorders	0	0	1 (0.4)	0	1 (0.2)
Anaemia	0	0	1 (0.4)	0	1 (0.2)
Gastrointestinal Disorders	0	0	1 (0.4)	0	1 (0.2)
Nausea	0	0	1 (0.4)	0	1 (0.2)
Vomiting	0	0	1 (0.4)	0	1 (0.2)
Infections and Infestations	0	1 (0.5)	1 (0.4)	0	1 (0.2)
Pneumonia	0	0	1 (0.4)	0	1 (0.2)
Schistosomiasis liver	0	1 (0.5)	0	0	0
Metabolism and Nutrition Disorders	1 (0.5)	0	1 (0.4)	0	2 (0.4)
Decreased appetite	0	0	1 (0.4)	0	1 (0.2)
Hyponatraemia	1 (0.5)	0	0	0	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (0.4)	0	1 (0.2)
Pain in extremity	0	0	1 (0.4)	0	1 (0.2)
Nervous System Disorders	1 (0.5)	0	1 (0.4)	0	2 (0.4)
Cerebral infarction	1 (0.5)	0	0	0	1 (0.2)
Spinal cord compression	0	0	1 (0.4)	0	1 (0.2)
Psychiatric Disorders	0	0	1 (0.4)	0	1 (0.2)
Major depression	0	0	1 (0.4)	0	1 (0.2)
Vascular Disorders	0	0	1 (0.4)	0	1 (0.2)
Embolism	0	0	1 (0.4)	0	1 (0.2)
Hepatobiliary disorders	0	2 (0.9)	0	0	0
Drug-induced liver injury	0	1 (0.5)	0	0	0
Hepatic function abnormal	0	1 (0.5)	0	0	0

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA= Medical Dictionary for Regulatory Activities; QT = interval, time from the start of the Q wave to the end of the T wave; TEAE = treatment-emergent adverse event.

Dose interruption/reduction due to adverse effects

Table 104: Adverse Events Leading to Dose Interruption in the Pivotal Studies and Pooled (Aumolertinib 110 mg) Safety Population by System Organ Class and Preferred Terms

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Number of subjects with at least 1 TEAE leading to dose interruption	41 (19.2)	54 (25.1)	42 (14.8)	6 (12.5)	89 (16.3)

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Investigations	24 (11.2)	38 (17.7)	23 (8.1)	6 (12.5)	53 (9.7)
Blood creatine phosphokinase increased	12 (5.6)	1 (0.5)	16 (5.7)	5 (10.4)	33 (6.1)
Alanine aminotransferase increased	6 (2.8)	25 (11.6)	3 (1.1)	1 (2.1)	10 (1.8)
Aspartate aminotransferase increased	3 (1.4)	22 (10.2)	1 (0.4)	0	4 (0.7)
Neutrophil count decreased	2 (0.9)	0	2 (0.7)	0	4 (0.7)
Electrocardiogram QT prolonged	2 (0.9)	5 (2.3)	0	0	2 (0.4)
White blood cell count decreased	2 (0.9)	0	0	0	2 (0.4)
Infections and Infestations	3 (1.4)	3 (1.4)	7 (2.5)	0	10 (1.8)
Pneumonia	1 (0.5)	2 (0.9)	4 (1.4)	0	5 (0.9)
General Disorders and Administration Site Conditions	0	1 (0.5)	3 (1.1)	0	3 (0.6)
Chest discomfort	0	0	2 (0.7)	0	2 (0.4)
Hepatobiliary Disorders	3 (1.4)	10 (4.7)	2 (0.7)	0	5 (0.9)
Hepatic function abnormal	2 (0.9)	10 (4.7)	0	0	2 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	3 (1.4)	0	3 (1.1)	0	6 (1.1)
Pulmonary embolism	2 (0.9)	0	0	0	2 (0.4)
Vascular Disorders	1 (0.5)	0	4 (1.4)	0	5 (0.9)
Hypertension	1 (0.5)	0	1 (0.4)	0	2 (0.4)

MedDRA version 24.0.
Only AEs leading to dose interruption which occurred in ≥ 2 subjects in any of the groups (by preferred term) are shown.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MedDRA = Medical Dictionary for Regulatory Activities; QT = interval, time from the start of the Q wave to the end of the T wave; TEAE = treatment-emergent adverse event.

Table 105: Treatment-emergent Adverse Events Leading to Dose Reduction in the Pivotal studies and Pooled (Aumolertinib 110 mg) Safety Population by System Organ Class and Preferred Terms

System Organ Class Preferred Term	301 Aumo (N = 214) n (%)	301 Gefi (N = 215) n (%)	1201 110 mg (N = 283) n (%)	301 Crossover (N = 48) n (%)	All Aumo 110 mg (N = 545) n (%)
Number of subjects with at least one TEAE leading to dose reduction	9 (4.2)	10 (4.7)	7 (2.5)	1 (2.1)	17 (3.1)
Investigations	9 (4.2)	6 (2.8)	7 (2.5)	1 (2.1)	17 (3.1)
Blood creatine phosphokinase increased	6 (2.8)	0	4 (1.4)	1 (2.1)	11 (2.0)
Myoglobin blood increased	0	0	1 (0.4)	0	1 (0.2)
White blood cell count decreased	2 (0.9)	0	0	0	2 (0.4)
Alanine aminotransferase increased	0	5 (2.3)	1 (0.4)	0	1 (0.2)
Aspartate aminotransferase increased	0	4 (1.9)	0	0	0
Blood creatine phosphokinase MB increased	1 (0.5)	0	0	0	1 (0.2)
Neutrophil count decreased	1 (0.5)	0	1 (0.4)	0	2 (0.4)
Electrocardiogram QT prolonged	1 (0.5)	1 (0.5)	0	0	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (0.4)	0	1 (0.2)
Myalgia	0	0	1 (0.4)	0	1 (0.2)

MedDRA version 24.0.
A subject with multiple conditions within a category (preferred term) is counted only once within that category.
The percentages are calculated based on the number of safety population.
Data cutoff of HS-10296-12-01: 01 Aug 2021; Data cutoff of HS-10296-03-01: 06 Aug 2021.
Aumo = aumolertinib; Gefi = gefitinib; MB = myocardial band; MedDRA = medical dictionary for regulatory activities; QT = interval, time from the start of the Q wave to the end of the T wave; TEAE = treatment-emergent adverse event.

2.6.8.10. Post marketing experience

Aumolertinib (Ameile®) was approved for marketing by the NMPA on 17 Mar 2020 for the treatment of subjects with EGFR T790M mutation-positive NSCLC who have progressed during or following treatment with other EGFR TKIs (second-line setting). The indication was extended to the first-line treatment of subjects with locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) replacement mutations, on 14 Dec 2021.

In the reporting period from March 2020 to March 2022, it is estimated that around 107,489 patients might have received aumolertinib in the second-line setting (for an average of around 21 weeks) based on the following assumptions:

- A dose of 110 mg/day
- An average treatment duration of 21 weeks for patients treated in the second-line setting (based on the HS-10296-1201 experience during the Phase II extension part of the study)
- 10% of drug is stocked in hospital pharmacies but not yet dispensed to patients.

The post-marketing reports per event received between 17 Mar 2020 and 16 Mar 2022 (a 24-month period). A total of 162 post-marketing reports (344 events) were received between 17 Mar 2020 and 16 Mar 2022 (a 24-month period). The majority of the reported events (225/344, 65.4%) were not serious. The most frequent events (by PT) were rash (37), pruritus (29), diarrhoea (19), vomiting (13), mouth ulceration (11), decreased appetite (10), interstitial lung disease (9), and abnormal hepatic function (8).

The most frequent serious events (by PT) were interstitial lung disease (9), rash (6), drug-induced liver injury (5), abnormal hepatic function (5), pruritus (4), decreased appetite (3), mouth ulceration (3), myelosuppression (3), platelet count decreased (3), renal impairment (3), vomiting (3), asthenia (2), blood CPK increased (2), death (2), diarrhoea (2), dyspnoea (2), hypersensitivity (2), malignant neoplasm progression (2), metastases to central nervous system (2), muscular weakness (2), myalgia (2), peripheral oedema (2), nausea (2), as well as one report of facial paralysis.

Overall, the frequency and type of events reported are consistent with observations in the aumolertinib clinical studies. However, some events were not reported in the clinical studies, notably facial paralysis (1 post-marketing report). For marketed medicinal products, spontaneously reported AEs usually imply at least a suspicion of causality by the reporter. Nevertheless, some of the events reported are likely to be related to the underlying disease (e.g., metastases to the CNS are a frequent occurrence in patients with advanced NSCLC).

For marketed medicinal products, spontaneously reported AEs usually imply at least a suspicion of causality by the reporter. From post marketing data, some risks that are subject to other concern - Request for supplementary information are also in the line listing: drug-induced liver injury (n=5), potential clinical manifestations of CPK increase (i.e. myalgia n=4, myositis n=1, pain in extremity n=2), thrombosis (n=1), insomnia (n=2), paronychia (n=1). In addition, other potential adverse drug reactions are identified in the listing: hypersensitivity (n=2) and renal impairment (n=3). The Applicant reviewed all cases of hypersensitivity (N=545) and cases of renal impairment (N=544) in the pooled safety population and updated the SmPC and PIL based on these cases.

The applicant also mention that some events were not reported in the clinical studies, notably facial paralysis (1 post-marketing report). The Applicant considers the event of "facial paralysis" to be most likely related to the underlying disease and not to aumolertinib treatment. The Applicant does not consider this event as a potential ADR.

The applicant assumes that roughly 107500 subjects have received treatment with aumolertinib over a two-year period. In the light of that number of subjects, post marketing reported adverse events seem rather low. When looking at the internal distribution of reported events the pattern was somewhat comparable with the pivotal studies. Out of a total of 344 reports the most frequent events were rash (37 events (11%)), pruritus (29 (8.4%)), Musculoskeletal and Connective Tissue Disorders (24 (7.0%)), diarrhoea (19 (5.5%)), vomiting (13 (3.8%)).

Notably, 9 reports of serious interstitial lung disease were reported which underlines the importance of vigilance for this adverse effect that has an established relation with EGFR TKIs.

There were 15 reports of hepatobiliary disorders of which 12 were serious covering different PTs: Hepatic function abnormal, Drug-induced liver injury, Acute hepatic failure, Liver injury.

There were 5 reports of elevated blood CPK of which 2 were serious. There were 3 reports of serious renal impairment. Taken together with 24 reports of Musculoskeletal and Connective Tissue Disorders this supports the concern of clinically relevant myositis or rhabdomyolysis that was also noted in the assessment of the pivotal studies.

One event of the rare disease or complication of thrombocytopenic thrombotic purpura was reported. This event was reported as non-serious which must be an error as this disease is an acute life-threatening disease that requires prompt evaluation and treatment to avoid potentially fatal bleeding and thrombosis. The Applicant has requested to discuss this risk and the conclusions are endorsed.

There were 2 reports of death and one report of accidental death with no further details disclosed.

Overall, the post marketing experience is in line with the adverse event profile observed in the pivotal trials and underlines the importance of monitoring for particularly ILD, rhabdomyolysis (elevated blood CPK, myalgia and renal impairment) and liver toxicity.

2.6.9. Discussion on clinical safety

The majority of the clinical studies of aumolertinib were conducted in China except for the pharmacokinetic study (EQ143-101) conducted in New Zealand and US in healthy participants from different racial and ethnic populations.

The need to demonstrate that the results obtained in the study are relevant for EU patients and medical practice was discussed in the context of a scientific advice. However, non-Chinese patients represent less than 5% (4.6%, n=37) of the population treated in the clinical development and no patient was included in the EU (see "Extrapolation of safety data to non-Chinese population").

Safety data base

The integrated safety database supporting the MAA of aumolertinib in the claimed indications is comprised of 545 subjects with advanced NSCLC (including 48 subjects who initially received gefitinib before receiving aumolertinib as crossover treatment) who received the recommended dose of 110 mg QD of Aumolertinib in 2 pivotal studies: Study HS-10296-12-01 (a Phase 1/2 study in previously treated subjects, for which closeout is now ongoing) and Study HS-10296-03-01 (an ongoing Phase 3 study in the first-line setting). Safety data from these clinical studies based on their respective data cut-off dates (i.e., August 01, 2021 and August 06, 2021, respectively) have been pooled to improve sensitivity and precision.

Exposure

Very high treatment compliance rates were observed across all aumolertinib groups with means ranging from 95.5-99.6%. This was a lot higher than expected for EGFR TKIs in NSCLC patients as this drug class is known for causing AEs that can impair quality of life for patients and lead to discontinuations on account of AEs.

Dose reductions and in particular dose interruptions were less frequent in the gefitinib group of HS-10296-03-01 compared to the aumolertinib group and were also common in HS-10296-12-01 and the crossover group of HS-10296-03-01 (Table 86). Although the safety profile was comparable between gefitinib and aumolertinib in the 1L study (HS-10296-03-01), in terms of severity, seriousness and types of AEs, these data may indicate a lower tolerance with aumolertinib. Overall dose interruptions were more common in female and older subjects. The higher frequency of dose interruptions described

in section 2.6.8.1. versus section 2.6.8.9. were explained by the fact that in section 2.6.8.1. the number of missed doses was derived from the absence of data in the exposure CRF ("0" or "missing") whatever the reason (including AE), whereas in section 2.6.8.9. the number of events were driven from "Treatment interrupted" as one of the "Actions taken with the study drug".

In the pooled safety population, the median duration of exposure to aumolertinib population was 13.3 months (57.7 weeks) and 289 (53%) patients had a duration of exposure of over 12 months which is deemed suitable from a safety assessment perspective.

Demographic and other characteristics of safety population

Baseline demographic characteristics were very similar across the 2 studies. As would be expected for EGFR-mutated NSCLC, the study population includes more females than males (60.2% vs 39.8%), more non-smokers than smokers (71.6% vs 28.4%), 99% of subjects had adenocarcinomas and the majority (66.8%, n= 364) of subjects were < 65 years of age). As previously noted, almost all the subjects in the pivotal studies were Han Chinese, recruited in China or Taiwan.

As a result of exclusion criteria, there were no patients identified as having hepatic, renal or cardiac impairment (included prolonged QT syndrome) at baseline. There were also limited numbers of patients over 75 years of age (6.6%, n=36).

In the controlled study, baseline demographic and disease characteristics were well-balanced across the 2 arms, but there was slight imbalance in median age: 62.0 years (range 25 years to 81 years) in gefitinib arm vs. 59.0 (range 32 years to 78) in aumolertinib arm and the gefitinib arm includes more patients ≥ 65 years old than the aumolertinib arm (35.4% of patients versus 27.5%, i.e. a difference of 7.9%).

Treatment discontinuation - Dose reductions and/or interruptions

In the pooled safety population, a low frequency of dose interruptions, dose reductions and treatment discontinuations with aumolertinib 110 mg due to AEs was observed in 16.3%, 3.1%, and 4.2% of patients, respectively.

In the controlled study, the frequency of dose interruptions, dose reductions and treatment discontinuations due to AEs is lower in patients treated with aumolertinib (16.3%, 3.1% and 4.2%, respectively) than in patients treated with gefitinib (19.1%, 4.2%, and 5.6% respectively).

During the assessment, several instances of serious protocol violations were reviewed, in which treating physicians did not follow protocol guidance to interrupt treatment or perform workup for suspected adverse reactions, despite observed QTc prolongation, rhabdomyolysis, or symptoms of or verified ILD/pneumonitis. It can be expected that the need for treatment interruptions or discontinuations due to adverse events will be higher in the clinical practice than reported in the clinical studies, and the frequencies reported in section 2.6.8.1. might be more reliable, as discussed above. In patients treated with aumolertinib, the most common reasons for permanent discontinuation of treatment are related to the respiratory system, being interstitial lung disease and pulmonary embolism. In patients treated with gefitinib, the most common reasons for permanent discontinuation of treatment are related to investigation SOC, being as expected elevations in liver functions tests (AST, ALT, GGT and Bilirubin).

The most common reasons for dose interruptions and dose reductions of treatment are related to the investigations SOC for both aumolertinib and gefitinib, Blood CPK increased and liver enzyme elevation respectively.

The frequency of dose interruptions, dose reductions and treatment discontinuations due to AEs is lower in patients treated with aumolertinib (16.3%, 3.1% and 4.2%, respectively) than in patients

treated with gefitinib (19.1%, 4.2%, and 3.7% respectively) generally indicating a high adherence to treatment and tolerability. However, nine protocol deviations were retrospectively discovered where aumolertinib dose should have been interrupted or reduced due to blood CPK elevations, but was not. It cannot be ruled out that additional cases of lacking dose modifications due to other reasons than CPK could have gone undetected. Additionally, instances of patients with verified ILD who did not discontinue aumolertinib were noted. This means that the observed frequencies of dose modifications in the aumolertinib are likely underestimates.

Safety findings

Adverse events

In the pooled analysis of the studies comprising 545 patients, AEs were reported for almost all, 96.1% (causally related to aumolertinib in 85.7%) of the patients. A total of 37,4% of AEs (causally related in 23.3%) were CTCAE grade 3 or higher. The incidence of patients with Grade ≥3 AEs was slightly higher in the aumolertinib treatment group (40.7%) compared with the gefitinib treatment group (35.8%). The SOCs in which AEs were most frequently reported were Investigations, Gastrointestinal disorders Skin and subcutaneous Tissue disorders, Blood and Lymphatic System Disorders and Respiratory, Thoracic and Mediastinal Disorders, which is as expected. The most common PTs (frequency of ≥10%) were elevated blood CPK (31.7%), elevated AST (21.7%), elevated ALT (20.2%), rash (19.3%), reduced WBC count (18.5%), upper respiratory tract infection (18.5%), anaemia (18.0%), urinary tract infection (16.9%), reduced platelet count (14.7%), cough (13.6%), diarrhoea (13.2%), constipation (11.6%), reduced neutrophil count (11.0%), vomiting (10.6%), and pruritus (10.5%).

The most common SOCs with reported AEs of CTCAE Grade ≥3 were Investigations, Infections and Infestations, Vascular Disorders, Metabolism and Nutrition Disorders, Blood and Lymphatic System Disorders and Thoracic and Mediastinal Disorders.

Within the AEs grade 3 or higher, elevated blood CPK, ALT elevation, pulmonary embolism and hypertension were the only AEs reported in more than 2% of patients (7.5%, 2.4%, 2.8% and 2.8%% respectively).

In the controlled study, the majority of patients in both arms reported an AE with the vast majority being adjudicated as treatment related. Elevation of blood CPK observed at a consistently higher incidence rate among aumolertinib-treated subjects (41.1%) than gefitinib-treated subjects (9.8%). While the elevated AST, elevated ALT, rash and diarrhoea are observed at lower incidence rates among aumolertinib-treated subjects (30.8%, 30.4%, 24.3% and 17.3 %, respectively) than gefitinib-treated subjects (54.0%, 55.8%, 41.9%, and 35.8%, respectively).

Deaths

In the overall population, at the time of data cut-off (August 2021), death occurred in 225 (41.3%) patients.

The majority of deaths (167/225; 74%) were attributed by the Investigator to disease progression, ~22% (48/225) to "other" and ~4% (10/225) were attributed to AEs.

Ten (10) subjects experienced AEs leading to death: 7 in the aumolertinib and 3 in the gefitinib arm. Fatal TEAEs were mostly thromboembolic events. Venous thromboembolism (i.e. pulmonary embolism and deep vein thrombosis) is listed as important identified risk in the Risk management plan and further detailed below.

Serious adverse events

Overall, 22.2% (n=121) of subjects treated with aumolertinib 110 mg experienced an SAE and only 8.8% were adjudicated as treatment-related by the Investigator. The most commonly reported SAEs were pneumonia (2.6%; 14/545) and pulmonary embolism (2.4%; 13/545).

A similar proportion of patients experienced SAEs in the aumolertinib and gefitinib treatment arms (22.0% vs 21.4%). SAEs reported in ≥ 3 subjects in both arms were Pneumonia (n=6, 2.8% in aumolertinib arm versus n=8, 3.7% in gefitinib arm).

Venous thromboembolism (VTE)
The following AEs were reported only in patients treated with aumolertinib 110 mg: pulmonary embolism (2.4%, n=13) including 1 patient in the crossover population, deep vein thrombosis (1.1%, n= 6) and venous thrombosis limb (1.1%, n= 6). These AEs described above are not described with the other EGFR-TKIs (gefitinib, afatinib, osimertinib), except for the combination of lazertinib and amivantamab (EGFR TKI and monoclonal antibody targeting EGFR)

The Applicant has provided a detailed analysis of thromboembolic events (TEEs), including analysis of risk factors, time-to-onset, grade ≥ 3 events, associated with TEE in patients treated with aumolertinib in the safety analysis set. In addition to "Pulmonary embolism", "venous thrombosis limb" and "deep vein thrombosis" PTs retained by the Applicant to investigate this risk, Cerebral infarction (1.9% vs 0.9% in the AU and GEFI groups, respectively) was also found higher in the aumolertinib group compared with the gefitinib group. The PT Cerebral thrombosis was also reported in the aumolertinib group (≥1) compared with the gefitinib group (0). Cerebral infarction or thrombosis are rare and serious disorders that necessitate prompt medical intervention. As no event of this type was reported in the control group, and considering that thromboembolic events are considered as an identified risk with aumolertinib, this information was also reflected as a warning in SmPC section 4.4 and relevant details presented in section 4.8.

Venous thromboembolism (i.e. pulmonary embolism and deep vein thrombosis) is now considered as an important identified risk in the Risk management plan.

Increased/positive risk of pulmonary embolism was observed in both 1L and 2L studies, and for patients with crossover (gefitinib > aumolertinib – TEAEs n=1/48, 2.1%). These data indicate a higher risk of baseline pulmonary embolism with aumolertinib compared with gefitinib.

AEs of special interest (AESI)

The applicant has identified the following as AESIs: Hepatotoxicity, Elevated blood CPK, Interstitial lung disease, Cardiac failure, QT prolongation, Ocular toxicity and Diarrhoea.

In the overall safety population, AESIs reported in ≥10% of patients were: Elevated blood CPK (40.9%), hepatotoxicity (37.4%), Diarrhoea (13.2%) and QT prolongation (10.6%).

In controlled study, AESIs which occurred with at least ≥10% difference of frequency on the aumolertinib arm compared to the gefitinib arm were: Elevated blood CPK (51.44.9% vs.20.9%), hepatotoxicity (50.9%vs.73.5%), Diarrhoea (17.3%vs.35.8%) and QT prolongation (14.4% vs.9.3%).

Elevated blood creatinine phosphokinase (CPK) and rhabdomyolysis

CPK elevation is associated with aumolertinib, and cases of clinically significant rhabdomyolysis with muscle symptoms and renal impairment were observed. The lack of routine monitoring of blood CPK levels for the first 16 months of the trial is almost certain to have affected the reporting of the adverse events of blood CPK increased and rhabdomyolysis. Routine monitoring of kidney function was performed throughout the entire trial, meaning that overt cases of rhabdomyolysis leading to acute kidney injury have likely been adequately captured, but the frequencies of less severe cases of blood CPK increased and rhabdomyolysis are almost certainly underreported. Hypocalcaemia was reported in

20 (9.3%) in the 301 Aumo group further suggesting that rhabdomyolysis is a frequent event in subjects treated with aumolertinib. Aumolertinib treatment is considered to be associated with rhabdomyolysis and "CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage" is listed as an important identified risk in the RMP. To prevent renal complication related with rhabdomyolysis, in addition to CPK increase monitoring, kidney function should be measured before initiating aumolertinib and periodically during treatment regardless of symptoms**.** Routine monitoring of blood CPK and renal function were added as recommendation in section 4.4 of the SmPC, together with a warning on the risk of rhabdomyolysis, and therefore this risk is considered adequately addressed.

Interstitial lung disease

ILD was reported in 2.9% of the safety pool, but in several cases, it was noted that patients with respiratory symptoms suggestive of ILD did not undergo the appropriate diagnostic workup, and therefore the actual risk of ILD may be higher than reported. Importantly, it is expected that the potential underreporting of ILD will only have affected relatively mild cases of ILD, since all the respiratory symptoms in the discussed cases were of low grade (1-2), and since serious or fatal cases of ILD are all expected to have been detected through the review of SAES, grade ≥ 3 AEs, and fatal adverse events. The risk of ILD was added as an important identified risk in the RMP and is described in sections 4.4 and 4.8 of the SmPC, with recommendations to withhold aumolertinib during investigation for ILD and to permanently discontinue treatment if ILD is verified. Therefore, the risk of ILD is considered appropriately addressed in the SmPC.

Hepatic dysfunction

Aumolertinib is commonly associated with hepatic disorders, mainly liver enzyme elevation. Hepatic enzyme elevations (ALT and AST) were reported by 37.4% (204/545) patients in the pooled safety population, which for the majority were of mild degree [3.7%, experienced as ≥Grade 3 and no SAE] and did not generally lead to dose reduction of aumolertinib. No case of severe liver toxicity has been described in the aumolertinib clinical program. All grade and grade ≥3 hepatotoxicity were higher in subjects treated with gefitinib compared to aumolertinib.

A warning was included in SmPC section 4.4 to highlight that liver function should be monitored prior to initiating treatment, and periodically during treatment. Increases in transaminases and bilirubin are reported for several EGFR-TKIs. Warnings related to hepatotoxicity/transaminases increased are included in SmPC section 4.4 for other EGFR-TKIs e.g., dacomitinib and gefitinib.

Considering that events of hepatic injury have been described with aumolertinib, this risk needs to be further monitored. "Severe hepatic disorders (including DILI, liver injury and hepatitis)" have been added in the RMP as an important potential risk to investigate further clinical consequences, severity and seriousness of hepatic disorders identified with Aumolertinib. The observed incidence of hepatotoxicity is comparable in both the subgroups of participants - with and without liver metastasis (data not shown), aumolertinib does not elevate the risk of hepatic toxicity among participants who have liver metastasis.

Diarrhoea

Diarrhoea was common, as also seen with other EGFR inhibitors. The instances of diarrhoea (13.2%) with aumolertinib were generally Grades 1 to 2 in severity and manageable without dose reduction or interruption. SAEs of diarrhoea were rare with 3 occurrences (0.6%). No fatal diarrhoea AEs were reported.

The severity of diarrhoea seen in clinical trials reflects the margin of selectivity against wild-type EGFR displayed by aumolertinib when compared to other EGFR TKIs.

Aumolertinib-treated subjects experienced a lower incidence of diarrhoea event than gefitinib-treated subjects (17.3% versus 35.8%). However, the rate of grade ≥ 3 and SAE were comparable and between the aumolertinib and gefitinib groups and overall low.

Hence, diarrhoea appears manageable for most patients with no medical intervention to prevent the development of complications such as dehydration or electrolyte disturbance. Details on diarrhoea were included in the subsection Description of selected adverse reactions of section 4.8 of the SmPC.

QT prolongation

Of the EGFR TKIs indicated for NSCLC (afatinib, dacomitinib, osimertinib and erlotinib) only osimertinib include a warning on cardiac toxicity. Compared to osimertinib (0.8 %), the incidence of QTc interval prolongation is higher with aumolertinib.

In the safety analysis populations, QTc interval prolongation is reported by 10.6% (58/545) patients, which is considered high. No case of Torsade de Pointes was reported. However, in 4 of the 8 cases, the Grade ≥ 3 AEs were symptomatic events (cardiac arrest, cardio-respiratory arrest, sudden cardiac death, and syncope) rather than an asymptomatic ECG change. Two (0.4%) subjects in HS-10296-03-01 Study with QT prolongation died, one due to sudden cardiac death and one due to cardio-respiratory arrest.

Arrhythmic events are expected to be rare, hence, it may not have been statistically possible to detect them at this stage, despite the existence of an inherent risk for such events. The risk of QTc prolongation leading to torsade de pointes and cardiac arrest was therefore listed as an important identified risk in the RMP.

As patients with clinically important cardiac abnormalities in rhythm and conduction were excluded from the pivotal studies, the effect of aumolertinib on the patients with these baseline risk factors is not known. Therefore, a careful selection and close monitoring of patients may avert the development of QT prolongation. Considering the frequency and the seriousness of QT prolongation and complications, the use of aumolertinib in patients with baseline cardiovascular risk factors of confirmed QT prolongation should be contraindicated, notably in (i) patients with long QT syndrome, (ii) patients with familial history of sudden death or polymorphic ventricular arrhythmia, (iii) patients with QT/QTc interval > 500 msec, (regardless of the correction method). This contraindication is reflected in section 4.3 of the SmPC. In addition, a requirement to have an electrocardiogram (ECG) performed prior to treatment initiation, at least once during the first 3 weeks of therapy, and periodically thereafter as clinically indicated was included in section 4.2 of the SmPC.

Information on time-to-onset and time to resolution for the QTc interval were added to sections 4.4 and 4.8 of the SmPC.

Ocular effects

Ocular effects were experienced by about 8% of patients and there is no need of dedicated dose interruption and reductions guidance. None were Grade ≥ 3. Ocular effects generally manifested as conjunctivitis (3.1% of patients) followed by dry eye (2.6%) and vision blurred (2.2%). Comparable levels of ocular toxicity were observed in the gefitinib group (8.8%).

Considering that an association between the use of EGFR TKIs and the occurrence of ophthalmic adverse events has been observed and aumolertinib non-clinical findings suggested a signal for the occurrence of corneal epithelial ulceration/erosion, a causal relationship between the medicinal product and the adverse event was considered at least a reasonable possibility and included in section 4.8 of the SmPC.

Skin disorders

Skin disorders are important class effects of TKIs and could be important for the patient's well-being as well as tolerability of the treatment. A review of skin and subcutaneous tissue disorders is reflected in section 4.8 of the SmPC. Moreover, the possible risk of Stevens Johnson Syndrome was reviewed based on 1 post marketing case received. The case, initially reported as severe erythema multiforme by the reporter, lacking signs of cutaneous detachment (Nikolsky sign), details regarding the percentage of skin body surface area (BSA) detached, or biopsy results. The evidence was considered insufficient for a confirmation of the risk of SJS and it was deemed more appropriate not to list SJS in the SmPC at this stage, but to list "Severe Cutaneous Adverse Reaction (SCARs): including SJS and erythema multiforme" as a potential risk in the RMP with dedicated routine pharmacovigilance activities (use of a targeted follow-up questionnaire for SCAR and EM). Otherwise, the proposed list of ADRs is accepted: paronychia, dry skin, dermatitis, erythema and palmar-planar erythrodysaesthesia syndrome.

Changes in laboratory parameters: Most of the changes in laboratory parameters were grade 1-2.

The most relevant laboratory findings were related to hepatotoxicity and CPK increase and described above.

Safety in special populations:

A higher incidence of SAEs, and AEs leading to treatment discontinuation was observed in the elderly population and was driven by increased hospitalisation. Safety data in patients 75 years or older are limited but were not supportive of an upfront dose adjustment.

Extrapolation of safety data to non-Chinese population

The majority of the clinical studies of aumolertinib were conducted in China except for the pharmacokinetic study (EQ143-101) conducted in New Zealand and US in healthy participants from different racial and ethnic populations and non-Chinese patients represent less than 5% (4.6%, n=37) of the population treated in the clinical development with no patient included in EU.

Somatic EGFR mutations are observed in 40% of Asian populations and in about 10% of NSCLC in Caucasian populations.

The characterisation of the safety profile of aumolertinib at the recommended dose of 110 mg once daily in the non-Chinese and in particular Caucasian population was therefore primarily based on extrapolation.

The PK study HS-10296-108 was initiated in Dec 2024 and designed as a Phase 1, Open-label, Multiple-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Aumolertinib in European Participants with Locally Advanced or Metastatic, EGFR-mutated NSCLC. Its primary objective was to study the pharmacokinetics of aumolertinib in European patients. The study enrolled 19 participants and was conducted in Southeast Europe (sites in Serbia, Bosnia-Herzegovina, Moldova, and Bulgaria). The median exposure of 66 days and the small number of patients were considered too limited to draw direct conclusions on the safety profile of aumolertinib in the European population. However, it was considered acceptable to extrapolate the safety data collected during the development in the Asian population to the European patients based on the documented equivalence of PK from the HS-10296-108 study, and was further supported by the fact that efficacy and safety of osimertinib was shown to be similar across different ethnicities in the analyses of ethnicity subsets within the FLAURA trial (see Tagrisso variation EMEA/H/C/004124/II/0019).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The risks associated with aumolertinib treatment are considered differentiated from other agents in its class. Some specific risks identified with aumolertinib were significant, such as venous thromboembolic events, rhabdomyolysis, and high frequency of QT interval prolongation. However, these risks are manageable with standard risk mitigation strategies that are effective in clinical practice (monitoring of liver enzyme, CPK and renal function, guidelines for dose adjustments, and patient education about early signs of pneumonitis to facilitate prompt intervention). Therefore, based on updated data, the observed safety profile of aumolertinib is acceptable in the context of a life-threatening disease.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 106 Summary of safety concerns

Summary of safety concerns	
Important identified risks	QTc prolongation leading to torsade de pointes and cardiac arrest CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage Interstitial lung disease Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)
Important potential risks	Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme Drug-induced liver injury (DILI) and hepatitis
Missing information	None

2.7.2. Pharmacovigilance plan

Table 107 On-going 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 authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
Not applicable				

2.7.3. Risk minimisation measures

Table 108 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
QTc prolongation leading to torsade de pointes and cardiac arrest	Routine risk communication: *SmPC sections 4.2, 4.3, 4.4, and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Recommendation for ECG monitoring and dose modification is included in the SmPC section 4.2.* *Contraindications are included in the SmPC section 4.3.* *Recommendations on regular ECG and electrolyte monitoring, dose modification, or permanent discontinuation are included in the SmPC section 4.4.* *Description of drugs that should be avoided during treatment with this product is included in the SmPC sections 4.2, 4.4 and 4.5.* *PIL section 2 advises patients to not take Aumseqa and talk to their doctor if they have or had a heart rhythm disorder, such as abnormally fast or irregular heartbeat or a condition called "QT prolongation" or blood-related family members who have had abnormally fast or irregular heart rhythm or died suddenly from heart problems.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have or had any rapid or irregular heartbeats, dizziness, light-headedness, chest discomfort, shortness of breath or fainting.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	help if they experience side effects such as very fast or irregular heartbeat causing fainting, dizziness, light headedness, chest discomfort, or shortness of breath. Additional risk minimization measures: None	
CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage	Routine risk communication: *SmPC sections 4.2, 4.4, and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Recommendation for dose modification is included in the SmPC section 4.2.* *Section 4.4 of the SmPC instructs to advise patients to report any unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.* *Section 4.4 of the SmPC instructs to withhold aumolertinib and initiate treatment for rhabdomyolysis if rhabdomyolysis occurs.* *Recommendations on monitoring of renal function is included in the SmPC section 4.4.* *Description of drugs that should be avoided during treatment with this product in the SmPC sections 4.2, 4.4 and 4.5.* *PIL section 2 advises patients to talk to their doctor if they have unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.* Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Interstitial lung disease	Routine risk communication: *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Pulmonary symptoms that warrant further investigation are included in the SmPC section 4.4.* *Instructions for treatment interruption, discontinuation, and initiation of appropriate treatment for ILD are included in the SmPC section 4.4.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have suffered from inflammation on their lungs.* *PIL section 2 advises patients to talk to their doctor if they have sudden difficulty in breathing together with a cough or fever.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience sudden difficulty in breathing together with a cough or fever, shortness of breath at rest or made worse by exertion, or dry cough that will not go away.* Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)	Routine risk communication: *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Section 4.4 of the SmPC instructs to promptly evaluate patients if symptoms*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	of thromboembolic events occur or are suspected. *Section 4.4 of the SmPC instructs to withhold aumolertinib and stabilize the patient before resuming therapy.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have had a blood clot (thrombus) in a blood vessel.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience any of the following symptoms: shortness of breath, chest pain, cough with blood, rapid or irregular heartbeat, light headedness, excessive sweating, fever, leg pain or swelling, clammy skin.* Additional risk minimization measures: None	
Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme Additional pharmacovigilance activities: None
Drug-induced liver injury (DILI) and hepatitis	Routine risk communication: *SmPC sections 4.4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Section 4.4 of the SmPC instructs about monitoring of liver function.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17.03.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Aumseqa (Aumolertinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The finally agreed indications are:

Aumseqa as monotherapy is indicated for:

- the first line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations
- the treatment of adult patients with advanced EGFR T790M mutation positive NSCLC

The aim of new treatments is to prolong progression-free survival and overall-survival whilst minimising toxicity.

3.1.2. Available therapies and unmet medical need

For the treatment of locally advanced or metastatic NSCLC with EGFR TKI-sensitizing mutations, the standard of care is the EGFR TKIs. The first-generation EGFR TKIs, gefitinib and erlotinib, are reversible inhibitors that have activity against both mutated and WT EGFR. The second-generation, small-molecular mass EGFR TKIs, afatinib and dacomitinib, are distinct from the first-generation inhibitors, as these agents are irreversible inhibitors and also have activity towards other EGFR family members.

The frequency of T790M mutation as the mechanism of acquired resistance after treatment with first- and second-generation EGFR TKIs prompted the development of novels EGFR TKIs which are active towards both EGFR T790M and EGFR TKI-sensitizing mutations in exons 19 or 21. Osimertinib is currently the only EGFR TKI approved for the treatment of EGFR-mutant NSCLC patients with the acquired resistance T790M mutation. As per ESMO guideline, osimertinib is the preferred option in first-line treatment of metastatic NSCLC harbouring sensitizing EGFR mutations.

Despite the progress in treating lung cancer patients with activating mutations in the EGF-receptor, there is a remaining need for expanding the treatment armamentarium.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a Phase III controlled, double-Blind, multicenter study to assess the efficacy and safety of HS-10296 versus gefitinib as first-line treatment in patients with EGFR mutation positive, locally advanced or metastatic NSCLC and a Phase 1/2 open-label, multicenter, single-arm clinical study to evaluate the safety, tolerability, PK, and efficacy of oral QD administration of aumolertinib in subjects with locally advanced or metastatic NSCLC that have progressed after previous treatment with EGFR TKIs.

3.2. Favourable effects

First-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR mutation

- In the primary analysis (DCO 15 January 2021) in study HS-10269-03-01 the primary endpoint PFS by Investigator was met with median PFS of 19.12 months in the aumolertinib arm and 9.72 months in the gefitinib arm (HR=0.460 ; 95%CI 0.358, 0.591; p<0.0001). In the updated analysis (DCO 06 August 2021) the median PFS by Investigator was 19.81 months in the aumolertinib arm and 9.72 months in the gefitinib arm (HR=0.450 ; 95%CI 0.354, 0.572).
- The ORR (secondary endpoint) was 74.8% (95%CI 68.4, 80.4) in the aumolertinib arm and 72.1% (95%CI 65.6, 78.0) in the gefitinib arm in the updated analysis (DCO 06 August 2021).
- In the updated analysis, the median DoR by Investigator was 19.19 months in the aumolertinib arm vs 8.28 months in the gefitinib arm (HR=0.378; 95%CI 0.285, 0.503).
- As of 30 Sept 2022, the median OS was numerically higher in the aumolertinib arm than in the gefitinib arm (39.16 months and 31.15 months, respectively), the OS HR was 0.816 (95% CI: 0.631, 1.056).

Treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC

- At DCO date of 01 August 2021, the confirmed ORR by ICR was 68.9% (95%CI 62.6, 74.6) in the FAS in the Phase 1/2 study HS-10296-12-01.
- The median DoR by ICR was 15.1 (95%CI 12.9, 16.6) months in the FAS as of DCO date of 01 August 2021.

Both indications

- CNS analyses from both pivotal studies HS-10296-03-01 and -12-01 demonstrated better outcomes of aumolertinib on brain metastasis compared to gefitinib.

3.3. Uncertainties and limitations about favourable effects

First-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR mutation

- Despite a numerically higher median OS in the aumolertinib arm than in the gefitinib arm; there was no statistically significant difference on OS between the two treatments as of the DCO of 30 Sept 2022. The OS comparison is confounded by the possible cross over from gefitinib to aumolertinib upon progression and confirmation of the presence of T790M mutation.

Treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC

- Study HS-10296-12-01 is a phase 1 / 2 single arm, open-label study, the non-comparative nature of the study design leads to uncertainties, notably hampering the interpretation of time to event endpoints. Nevertheless, the magnitude of effect was considered likely to translate into a clinical benefit, especially when taking into consideration the availability of an earlier-line randomised controlled trial (RCT) HS-10296-03-01, where a benefit in terms of PFS was observed.

3.4. Unfavourable effects

- In the pooled analysis of the studies comprising 545 patients, AEs were reported for almost all, 96.1% of the patients. A total of 37, 4% AEs were CTCAE grade 3 or higher.
- According to the pooled data from the safety data analysis, the administration of Aumolertinib is mainly characterised by the following **AEs** (frequency of ≥10%) : elevated blood CPK (31.7%), elevated AST (21.7%), elevated ALT (20.2%), rash (19.3%), reduced WBC count (18.5%), upper respiratory tract infection (18.5%), anaemia (18.0%), urinary tract infection (16.9%), reduced platelet count (14.7%), cough (13.6%), diarrhoea (13.2%), constipation (11.6%), reduced neutrophil count (11.0%), vomiting (10.6%), and pruritus (10.5%).
- Elevated blood CPK (7.5%), ALT elevation (2, 4%), pulmonary embolism (2, 8%) and hypertension (2, 8%) were the most common **high-grade (≥G3) AEs** reported in more than 2% of patients.
- Serious adverse events (**SAEs**) were reported in 22.2% (n=121/545) subjects treated with aumolertinib 110 mg. The most commonly reported SAEs were pneumonia (2.6. %; 14/545) and pulmonary embolism (2.4. %; 13/545).

- The following AEs were reported only in patients treated with aumolertinib 110 mg: pulmonary embolism (2.4%, n=13), deep vein thrombosis (1.1%, n= 6) and venous thrombosis limb (1.1%, n= 6) and not with most of the other EGFR-TKIs (gefitinib, afatinib, osimertinib).
- Overall, 6 (~ 3%) **deaths** attributed to AEs were reported during the studies.
- Among the **AEs of special interest**, it should be noted the ILDs, the QT Interval Prolongation and the CPK elevation. The former was reported by 10.6% (58/545) patients, which is considered high. No case of Torsade de Pointes was reported. However, 4 of the 8 Grade ≥ 3 AEs cases were symptomatic events (cardiac arrest, cardio-respiratory arrest, sudden cardiac death, and syncope) rather than an asymptomatic ECG change, contra-indication to patients with clinically important cardiac abnormalities in rhythm and conduction and recommendation for ECG monitoring were implemented to mitigate that risk. Regarding the CPK elevation, it was reported by 40.9% (223/545) patients in the pooled safety population, which for the majority were of mild degree [7.7%, experienced as ≥Grade 3 and no SAE] and did not generally lead to discontinuation of aumolertinib. ILD appears to be reported more frequently with aumolertinib than certain other EGFR-TKIs. Compared to TKIs dacomitinib (1.2%) and afatinib (0.7%), the incidence of ILD is higher with aumolertinib (2.9%), but comparable to osimertinib (3.7 %).

3.5. Uncertainties and limitations about unfavourable effects

- Severe skin reactions (Stevens-Johnson syndrome and Toxic Epidermal Necrolysis)have been reported post marketing for medicinal products of the same class. One potential case of SJS was reported with aumolertinib, but the limitations of the safety database prevent definitive conclusions. SCARs will be subject to specific follow up as important potential risk listed in the RMP.

3.6. Effects Table

Table 109 Effects Table for Aumseqa in 1L treatment of EGFR-mutated advanced NSCLC and T790M mutation-positive advanced NSCLC (data cut-off: 15 Jan 2021 for HS-10296-03-01, 01 August 2021 for HS-10296-12-01).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
First-line treatment of EGFR mutated advanced NSCLC						
Progression-free survival by Investigator	Median PFS	Months	19.12	9.72	Superiority trial Gefetinib is an active comparator but no longer the SoC in the sought indication 62% of events	Phase 3 study HS-10296-03-01 (CSR)
	Hasard ratio (95% CI) p-value		0.460 (0.358, 0.591) p<0.0001			
Overall survival	Median OS	Months	39.16	31.15	DCO= 30 Sept 2022 54.8% of events	
	Hasard ratio (95% CI)		0.816 (0.631, 1.056)			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
ORR	Objective response rate Odds ratio (95%CI):	%	73.8 1.092 (0.704, 1.693)	72.1		
T790M mutation-positive advanced NSCLC						
ORR	Objective response rate by ICR (95%CI)	%	68.9 (62.6, 74.6)	NA	Single arm trial	Phase 1/2 HS-10296-12-01 (CSR)
Median DoR	Duration of response by ICR (95%CI)	Months	15.1 (12.9, 16.6)	NA		
Unfavourable Effects in the total safety dataset, N=545						
AEs grade ≥3	Adverse events grade 3-4 regardless causality	%	37%	35.8%	Pooled data from 2 pivotal studies : phase 2 single arm open label and Phase 3 controlled vs. gefitinib 73.5%	Safety section of ARs
SAEs	Serious AEs regardless causality	%	22.2%	22.8%		
AEs leading to death		%	2%	1.4%		
AEs leading to discontinuation		%	4.2%	5.6%		
AEs leading to reductions or interruptions		%	16.9%	25.6%		
ILD	AE of special interest	%	2.9%	5.6%		
QT prolongation	AE of special interest	%	10.6%	9.3%		
CPK elevation	AE of special interest	%	40.9%	20.9%		

Abbreviations: CSR=Clinical study report, HR=Hazard ratio, NA=not applicable, ORR=Objective response rate, OS=Overall survival, PFS=Progression-free survival,

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the Phase 3 study HS-10296-03-01 supporting the claimed indication in first-line treatment in patients with advanced NSCLC with activating EGFR mutations, aumolertinib has demonstrated a clinically relevant and statistically significant improvement of PFS compared to gefitinib (9.4 months).

The claimed indication of aumolertinib is the treatment of patients with advanced EGFR T790M mutation-positive NSCLC was based on data of Phase 1/2 study HS-10296-12-01, a single-arm trial. Despite the single arm trial design, it is acknowledged that the totality of the data provides comprehensive data in the presence of the availability of an earlier-line randomized controlled trial. A high and durable ORR was reported with aumolertinib indicating a convincing antitumor activity.

Therefore, based on updated data, the observed safety profile of aumolertinib is acceptable in the context of a life-threatening disease.

The reported safety profile of aumolertinib is mainly in line with the known safety profile of the other EGFR-TKIs. The safety profile appeared to be manageable with a reported frequency of treatment discontinuations of 4.2%, and a number of deaths due to AEs of 3%. The present application has revealed new severe safety issues that have not been previously described for this class, such as venous thromboembolic events, rhabdomyolysis, and high frequency of QT interval prolongation. However, these risks are manageable with standard risk mitigation strategies that are effective in clinical practice (monitoring of liver enzyme, CPK and renal function, ECG at treatment initiation and guidelines for dose adjustments).

The pivotal studies pertaining to both indications were conducted in China. The extrapolation of the clinical data to non-Chinese population was considered acceptable based on the principle laid out in ICH guideline E5 R1 (Ethnic factors in the acceptability of foreign clinical data - CPMP/ICH/289/95), including the representativeness of the study population and the fact that the additional data from the HS-10296-108, where PK parameters in non-Asian patients were comparable to Asian patients in the pivotal HS-10296-12-01 trial with 15.3% higher Cmax of aumolertinib in European patients. Differences of other PK parameters were smaller and differences are not considered clinically relevant.

3.7.2. Balance of benefits and risks

The 9.4-month improvement in median PFS observed in first-line treatment in patients with locally advanced or metastatic NSCLC with activating EGFR mutations was considered to be clinically relevant. In addition, the clinical data of aumolertinib for the indication in treatment of T790M mutation-positive NSCLC patients demonstrated a convincing ORR. The observed safety profile of aumolertinib is acceptable in this therapeutic context. The benefit-risk balance is considered positive.

3.8. Conclusions

The overall benefit/risk balance of Aumseqa is positive.

4. Recommendations

Outcome

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

Aumseqa as monotherapy for:

- the first line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (for biomarker based patient selection, see section 4.2).
- the treatment of adult patients with advanced EGFR T790M mutation positive NSCLC (for biomarker based patient selection, see section 4.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product

Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Aumolertinib is to be qualified as a new active substance in itself as it is a constituent of a medicinal product previously authorised within the European Union.