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Approved

Protocol Title:

A Phase 3, single-arm, open-label, multicentre study to assess the efficacy and safety of deep subcutaneous injections of lanreotide Autogel® 120 mg administered every 28 days in Chinese participants with unresectable, locally advanced or metastatic Grade 1 or 2 gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

Protocol Number: D-CN-52030-411

Compound: lanreotide Autogel® [lanreotide (INN) acetate] (IPN52030)

Brief Title: An open-label phase 3 study to assess the efficacy and safety of lanreotide Autogel® in Chinese participants with GEP-NETs

Study Phase: 3

Acronym: **PALACE**

Sponsor Name: Ipsen Pharma

Legal Registered Address:
65, Quai Georges Gorse
92100 Boulogne Billancourt, France
Tel: PPD

Date: 17 May 2021
Version number: 2.0
Amendment number: 1

Sponsor Signatory:

PPD

Date

Medical Monitor Name and Contact Information:

PPD
Ipsen (Shanghai) Pharmaceutical Science and Development Company, Ltd.
No. 2306 International Capital Plaza
No. 1318 North Sichuan Road
Shanghai 200080, China
Tel: PPD

Principal Investigator Signature Page

I have read and agree to Protocol D-CN-52030-411 entitled 'a phase 3, single-arm, open-label, multicentre study to assess the efficacy and safety of deep subcutaneous injections of lanreotide Autogel® 120 mg administered every 28 days in Chinese participants with unresectable, locally advanced or metastatic Grade 1 or 2 gastroenteropancreatic neuroendocrine tumours (GEP-NETs)' with Amendment 1. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: [ ]
TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
[ ]
[ ]
[ ]
[ ]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 – Protocol Version 2.0	17 May 2021
Original Protocol Version 1.0	02 October 2020

Amendment 1 (Protocol Version 2.0, 17 May 2021)

Overall Rationale for the Amendment: The main reason for this protocol amendment is to address comments from Center for Drug Evaluation (CDE) and include clarifications.

Summary Change Table from Previous Version of the Protocol

Changes related to the same topic are presented together where possible. New or amended text in the protocol is indicated in bold. Deletions are marked in strikeout text. Minor formatting and editing are not included.

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
Sponsor signatory	PPD	PPD	Change of medical monitor
1.1 and 2.1	A previous lanreotide formulation (lanreotide prolonged release (PR) ~~30 mg~~) has been registered in China (since 2002) and more than 15 other countries for the treatment of clinical symptoms of NETs and for the treatment of acromegaly.	A previous lanreotide formulation (lanreotide prolonged release (PR)) has been registered in China (since 2002) and more than 15 other countries for the treatment of clinical symptoms of NETs and for the treatment of acromegaly.	The dose has been deleted to avoid confusions (PR 40 mg in China and PR 30 mg in the other countries). The 40 mg dose of lanreotide filled in the lanreotide PR vial is equivalent to the 30 mg dose marketed in the European Union since not all the syringe contents are injected; therefore, the actual dose injected from the vial is in fact only 30 mg.
1.3 (Table 1)		*Foot-notes i, m and n updated* *Foot-note q added to biomarkers, antibody and lab tests*	Specification of flexibility for the concerned assessments *See modification in Table 1 changes below*
4.1	After the end of study assessments, participants will enter a remote post-intervention survival follow-up period and ~~will be contacted by~~ telephone to collect survival status and subsequent therapies.	After the end of study assessments, participants will enter a remote post-intervention survival follow-up period and **a** telephone **call will be used** to collect survival status and subsequent therapies.	Update for clarification as participant's relative could also be contacted
8.1.6	After the end of study assessments, ~~participants will be contacted by~~ telephone to collect survival status (date of contact, alive/dead, date of death, whether death is related to NET if known) and subsequent therapies (dose, unit, frequency, start and stop date) started since the previous contact.	After the end of study assessments, **a** telephone **call will be used** to collect survival status (date of contact, alive/dead, date of death, whether death is related to NET if known) and subsequent therapies (dose, unit, frequency, start and stop date) started since the previous contact.	

<table>
<tr><th>Section</th><th>WAS (02 OCTOBER 2020, V1.0)</th><th>IS (17 MAY 2021, V2.0)</th><th>Rationale</th></tr>
<tr><td>5.1</td><td>(7) Has a ~~WHO~~ performance status lower or equal to 2
~~https://www.nice.org.uk/guidance/ta121/chapter/Appendix-C-WHO-performance-status-classification~~</td><td>(7) Has an Eastern Cooperative Oncology Group (ECOG) performance status lower or equal to 2 (Appendix 10.9)</td><td>ECOG performance status is widely used in oncology and clinical physicians are familiar with it.</td></tr>
<tr><td>10.9</td><td colspan="2">Appendix 9: Eastern Cooperative Oncology Group (ECOG) Performance Status
Table 10 Eastern Cooperative Oncology Group (ECOG) Performance Status
<table>
<tr><th>Grade</th><th>Description</th></tr>
<tr><td>0</td><td>Fully active, able to carry on all pre-disease performance without restriction</td></tr>
<tr><td>1</td><td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td></tr>
<tr><td>2</td><td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td></tr>
<tr><td>3</td><td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td></tr>
<tr><td>4</td><td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td></tr>
<tr><td>5</td><td>Dead</td></tr>
</table>
As published by [Oken 1982]. Eastern Cooperative Oncology Group.</td><td></td></tr>
<tr><td>11</td><td></td><td>Oken M, Creech R, Tormey D et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55</td><td></td></tr>
<tr><td>8 and 1.3 (Table 1)</td><td>• The following will be recorded at screening:
- ~~WHO~~ performance status</td><td>• The following will be recorded at screening:
- ECOG performance status
See also changes in Table 1 below this table</td><td></td></tr>
<tr><td>5.2</td><td>(11) ~~No~~ other concurrent malignancy than neuroendocrine tumours.</td><td>(11a) Has other concurrent malignancy than neuroendocrine tumours.</td><td>Typo correction</td></tr>
</table>

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
6.1 (Table 3)	Route of administration Subcutaneous injection	Route of administration **Deep** subcutaneous injection	Harmonisation with the IMP label
8 and 1.3 (Table 1)	• The following will be recorded at screening: - Other prior and concomitant medications (see Section 6.8).	• The following will be recorded at screening: - Other prior **(within 3 months before screening)** and concomitant medications (see Section 6.8). *Table 1 below: Foot-note has been updated accordingly*	Time period has been added to collect meaningful data. A 3-month period was considered sufficient to assess the exclusion criteria.
8.1.1	Diagnostic imaging will be performed at screening (baseline), W24, and W48. … At W24 and W48 (and W72, if applicable) the following should be performed:	Diagnostic imaging will be performed at screening (baseline), **W12**, W24, **W36** and W48. … At **W12,** W24, **W36** and W48 (and W72, if applicable) the following should be performed:	Correction for consistency with Table 1

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
8.1.1	At W12, W24, W36 and W48 (and W72, if applicable) the following should be performed: • Diagnostic imaging test (CT or MRI) of the head. If the screening test reveals a lesion in the brain or pituitary gland, the same diagnostic imaging test should be repeated. • Diagnostic imaging test (CT or MRI) of the neck, chest, abdomen and pelvis. • Diagnostic imaging test of bone lesions (bone scintigraphy or FDG-PET, CT or MRI). If the screening test revealed a bone lesion, assessment should be performed using the same method.	At W12, W24, W36 and W48 (and W72, if applicable) the following should be performed: • Diagnostic imaging test (CT or MRI) of the head. If the screening test reveals a lesion in the brain or pituitary gland **or if clinically indicated**, the same diagnostic imaging test should be repeated. • Diagnostic imaging test (CT or MRI) of the neck, chest, abdomen and pelvis. • Diagnostic imaging test of bone lesions (bone scintigraphy or FDG-PET, CT or MRI). If the screening test revealed a bone lesion **or if clinically indicated**, assessment should be performed using the same method.	Update for clarification
8.1.3	The presence or absence endocrine symptoms of NETs (e.g. ~~skin symptoms, digestive symptoms, neurological symptoms, systemic symptoms~~) will be assessed at screening. In participants with symptoms, a baseline assessment of the symptoms experienced in the last 4 weeks will be performed by questioning before study intervention administration at Day 1. ~~Participants will then record their symptoms,~~ and any medications taken to treat these symptoms, during the intervention period (and the	The presence or absence **of** endocrine symptoms of NETs (e.g. **flushing, diarrhoea, abdominal pain, weakness, heartburn, nausea, vomit, sweating, tremor, palpitation, or erythema**) will be assessed **by the investigator** at screening. In participants with symptoms **of NETs at screening**, a baseline assessment of the symptoms experienced in the last 4 weeks will be performed by questioning before study intervention administration at Day 1. **These symptoms will be recorded in the CRF**.	Clarification on how the NET symptoms will be collected

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
	independent injection period, if applicable) ~~using a diary. The first diary will be issued at the Day 1 visit. The participant will be instructed to bring the diary to each visit to the study site.~~ At each visit, the diary will be reviewed and collected, and a new diary ~~issued.~~ ~~Following review of the diary with the participant, the investigator, will enter information determined to be associated with NET symptoms into the CRF (e.g. symptoms appeared/disappeared, frequency of symptoms and severity~~).	**For participants with diarrhoea and/or flushing at baseline, a diary will be dispensed at Day 1 and the participants will be instructed to record the number of diarrhoea and/or flushing episodes per day and** any medications taken to treat these symptoms, during the intervention period (and the independent injection period, if applicable). At each visit, the diary will be reviewed and collected **by the investigator,** and a new diary will be dispensed. **The investigator will enter information of diarrhoea and/or flushing determined to be associated with NETs in the CRF (the frequency of diarrhoea and/or flushing, the severity graded upon CTCAE 5.0 and the use of any rescue medication).** **For participants with other symptoms at baseline, these symptoms will be assessed by the investigator by questioning at each visit during the intervention period (and the independent injection period, if applicable). The investigator will enter the information of the symptoms determined to be associated with NETs in the CRF (disappeared, reappeared, improved, aggravated or no change, severity graded upon CTCAE 5.0 and the use of any rescue medication).**	
1.3 (Table 1)	*See changes in Table 1 below this table*	*NET clinical symptoms assessment at screening has been added for consistency with Section 8.1.3; foot-note updated.*	

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
8.2.1 and 1.3 (Table 1)	A complete physical examination will be carried out by the investigator or medically qualified designee at screening, baseline (Day 1) and ~~each~~ subsequent visit to the study site in the intervention period (and independent injection period if applicable).	A complete physical examination will be carried out by the investigator or medically qualified designee at screening, baseline (Day 1) and subsequent visits to the study site in the intervention period (and independent injection period if applicable) **as per Table 1**.	Update for clarification and update of Table 1 below for consistency
8.2.2 and 1.3 (Table 1)	Vital signs will be measured at screening, baseline (Day 1) and ~~each~~ subsequent visit to the study site in the intervention period (and independent injection period if applicable)	Vital signs will be measured at screening, baseline (Day 1) and subsequent visits to the study site in the intervention period (and independent injection period if applicable) **as per Table 1**.	Update for clarification and update of Table 1 below for consistency
	• Vital signs are to be taken before blood collection ~~for laboratory tests~~.	• Vital signs are to be taken before blood collection **if performed the same day**.	
8.2.6 and 1.3 (Table 1)	Refer to Inclusion Criterion (8) in Section 5.1 for pregnancy testing entry criteria.	Refer to Inclusion Criterion (8) in Section 5.1 for pregnancy testing entry criteria **and Table 1**. *Pregnancy test missing visits have been added in Table 1 for consistency with the visits for clinical safety laboratory tests.*	Update for clarification
8.3	Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).	Adverse events **(including injection site-related reactions)** will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).	Update for clarification. Observing injection local reaction was required by CDE.

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
8.6 and 1.3 (Table 1)	- A ~~15~~ mL sample ~~will~~ be taken to assess other biomarkers (e.g. ~~pancreatic polypeptide~~, gastrin, ~~vasoactive intestinal peptide,~~ glucagon, ~~somatostatin~~, insulin ~~and neurotensin~~).	- A **5** mL sample **might** be taken to assess other biomarkers (e.g. gastrin, glucagon and insulin, **if applicable**).	According to the clinical practice in China, most of patients have nonfunctioning NETs and these tests are not performed regularly; gastrin, glucagon, and insulin may be tested per clinical symptoms because the most common functioning NETs are gastrinoma and insulinoma in China. See also changes in Table 1 below
8.8	• Indirect costs will be assessed using a bespoke questionnaire:	• Indirect costs will be assessed using a bespoke questionnaire **(see Appendix 10.7)**:	Appendix 7 added in Section 10.7 for clarity
10.7	**Appendix 7: Impact of Treatment Administration Setting on Costs** **This section of the survey will ask you questions about the costs, including travel time and personal time, associated with your lanreotide Autogel® treatment at home and in hospital.** ***Thinking about hospital visits you attended to receive your lanreotide Autogel® injection in hospital, prior to switching to the independent injection:*** **(at visit W48)** **1. If you normally travelled to the hospital, how many kilometers did you travel one-way from your house to the hospital? Please write the estimated number of kilometers as below. If you do not know the exact number kilometers, please provide your best estimate.** **___ (Estimated kilometers)** **2. When you visited the hospital to receive your lanreotide Autogel® injection, how did you normally travel? Please select the option that best describes how you normally travelled from your home to the hospital If you normally used more than one form of transport, please select the form of transport used for the main (longest in terms of distance) part of your journey.** **a. Car (by myself)**		

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
	b. Car (accompanied by someone else) c. Train d. Bus e. Taxi f. Walking g. Bicycle h. Other 3. If you used public transport, and were accompanied by a friend or family member, how much did they spend on the cost of their journey? Please write the estimated cost as below. Put zero if you did not normally pay a fare. Total cost of return fare (CNY) ___ (Yuan) 4. If you normally travelled to the hospital or clinic by public transport (i.e. bus or train), what was the approximate cost of the journey (there and back)? Please write the estimated cost as below. Put zero if you did not normally pay a fare. Total cost of return fare (CNY) ___ (Yuan) 5. If you normally travelled to the hospital or clinic by taxi what was the approximate cost of the journey (there and back)? Please write the estimated cost in the box below. Put zero if you did not normally pay a fare. Total cost of return fare (CNY) ___ (Yuan) 6. If you normally travelled to the hospital by car and had to pay parking and/or toll fees, how much did these fees amount to? Please write the estimated cost in the box below. Put zero if you did not normally pay a fee. Parking/toll fees (CNY) ___ (Yuan) 7. When you visited the hospital to receive your lanreotide Autogel® injection, how long did it normally take one-way to travel there from your home? Please write the approximate number of hours and/or minutes as below. - (Hrs-Mins)		

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
	8. When you visited the hospital to receive your lanreotide Autogel® injection, how long did you normally spend there? Please write the approximate number of hours and/or minutes as below. **__-__ (Hrs-Mins)** **9. What would you have normally been doing as your usual daily activities if you had not gone to the hospital to receive your lanreotide Autogel® injection? Please select the option that best describes what you would normally be doing as your main activity.** **a. Housework** **b. Childcare** **c. Leisure activities** **d. Attending school/university** **e. Paid work** **f. Volunteering** **g. On sick leave** **h. Seeking work** **i. Other** ***Thinking about Impact of switch in administration setting on main daily activities:*** **(at visit W72)** **10. How much has your ability to do your usual daily activities changed since switching from hospital to the independent administration of lanreotide Autogel®?** **a. Overall ability to do my main activity has improved** **b. Overall ability to do my main activity has not changed** **c. Overall ability to do my main activity has worsened**		

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
8.8	• In addition, the impact of switch in administration setting on overall ability to work will be assessed using a bespoke questionnaire.	• In addition, the impact of switch in administration setting on overall ability to work will be assessed using a bespoke questionnaire **(Appendix 10.8)**.	Appendix 8 added in Section 10.8 for clarity
10.8	**Appendix 8: The Impact of Switch in Administration Setting on Overall Ability to Work** **Question: (at visit W72)** ***Thinking about your overall experience of switch in lanreotide Autogel® injection administration setting:*** (1) **Do you think switching from hospital to independent administration of lanreotide Autogel® injection has had a positive or negative effect on your overall ability to work?** (a) **Positive effect** (b) **No effect** (c) **Negative effect**		
9.3 (Table 5)	Safety set All participants who receive at least one dose of study intervention ~~and have safety evaluation data after administration~~.	Safety set All participants who receive at least one dose of study intervention.	Standard definition of safety set
9.4.3	• Point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated for the following: ~~- Proportion of participants who are alive and without tumour progression at W24 and W48~~ - CBR at W48	• **Proportion of participants who are alive and without tumour progression at W24 and W48 and their 95% CI will be calculated by the Kaplan-Meier method** • Point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated for the following: - CBR at W48	Correction of the methodology used for the analysis

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
10.1.3		• **A specific ICF for pregnant partner must be used before collecting details on the pregnancy and its outcome (see Section 8.3.6).**	Addition for clarity
10.3.4	**SAE Reporting to the sponsor-via ~~an Electronic Data Collection Tool~~** • ~~The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.~~ • ~~If the electronic system is unavailable, then~~ the study site will use the paper SAE data collection tool ~~(see next section)~~ to report the event within 24 hours of awareness of the event. • The study site will ~~enter~~ the SAE data into the ~~electronic system as soon as it becomes available~~. • ~~After the study is completed at a given study site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data~~. • ~~If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off line, then the site can report this information on a paper SAE form~~	**SAE Reporting to the sponsor via paper** • The study site will use the paper SAE data collection tool to report the event within 24 hours of awareness of the event. • The study site will **email** the SAE **form or fax the cover sheet and SAE form to the sponsor. The same will apply to any SAE follow up form**. • Contacts for SAE reporting can be found on the SAE form and the cover sheet.	SAEs are collected via paper only

Section	WAS (02 OCTOBER 2020, V1.0)	IS (17 MAY 2021, V2.0)	Rationale
	~~(see next section).~~ • Contacts for SAE reporting can be found on the SAE form and the cover sheet. **SAE Reporting to sponsor via Paper** ~~• The study site will email the SAE form or fax the cover sheet and SAE form to the sponsor if the electronic data collection tool is unavailable. It must be retrospectively recorded as soon as the electronic data collection tool becomes available.~~ ~~• Contacts for SAE reporting can be found on the SAE form and the cover sheet.~~		

Table 1 Schedule of Activities (only changes, in bold and underlined or strikeout)

	Screen (W-4)	Main Intervention Period									Independent Injection Period (~5 participants only)				Remote Post Intervention Follow-up Period[a]
		D1	W4/W8	W12	W16/ W20	W24	W28/ W32	W36	W40/ W44	W48 [b]	W48 [b]	W52/ W56 [c]	W60 W64/ W68 [c]	W72 [d]	
Visit Schedule	**D-28**	**D1**	**D29/ D57**	**D85**	**D113/ D141**	**D169**	**D197/ D225**	**D253**	**D281/ D309**	**D337**	**D337**	**D365/ D393**	**D421/D449 /D477**	**D505**	**Within 4 weeks after last W48, ~~or~~ W72 or ED**
Visit Window (Days)	**-28 to 0**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Visit	V1	V2	V3/4	V5	V6/7	V8	V9/10	V11	V12/13	EOSI Visit/ED	V14	(V15/16)	(V17-19)	EOSI Visit/ED	
Prior medications/therapies **(p)**	X														
Pregnancy test (WOCBP only)	X	**X**				**X**				**X**	**X**			**X**	
~~WHO~~ **ECOG** performance score	X														
NET clinical symptoms[j]	**X**	X	X	X	X	X	X	X	X	X	X	(X)		X	
Biomarkers [q]:															
Anti-lanreotide antibodies **[q]**		X				X				X	X				
Physical examination	X	X	**X**	X	**X**	X	**X**	X	**X**	X	X	(X)	**(X)**	X	
Vital signs	X[m]	X [m]	**X**	X	**X**	X[m]	**X**	X	**X**	X[m]	X	(X)	**(X)**	X[m]	
Clinical safety laboratory tests **[q]**	X	X				X				X	X			X	

Abbreviations: AE=adverse event; CgA=chromogranin A; CT=computed tomography; D=day; ECG=electrocardiogram; **ECOG= Eastern Cooperative Oncology Group;** ED=early discontinuation; EOSI=end of study intervention; FDG-PET=fluorodeoxyglucose-positron emission tomography; FSH=follicle stimulating hormone; h=hour; HCP=healthcare professional;

5-HIAA=5-hydroxyindoleacetic acid; MRI=magnetic resonance imaging; NET=neuroendocrine tumour; QoL=quality of life; WOCBP=woman of childbearing potential; W=week ~~; WHO=World Health Organisation~~

i CT and/or MRI based on the tumour lesion**; can be performed at the visit or up to 7 days before the visit.** ~~When bone metastasis is suspected, bone scintigraphy or FDG-PET will also be performed~~. **See Section 8.1.1 for details**

j **Presence or absence endocrine symptoms of NETs will be assessed at screening.** Participants with ~~endocrine symptoms of NETs~~ **diarrhoea and/or flushing related to NETs** will be provided with a diary to record their daily symptoms and any medications taken to treat these symptoms. The first diary will be ~~issued~~ **dispensed** at the Day 1 visit. ~~The participant will be instructed to bring the diary to each visit to the study site. At each visit, the diary will be reviewed and collected, and a new diary issued.~~ **See Section 8.1.3 for details**

k ~~Pancreatic polypeptide, gastrin, vasoactive intestinal peptide~~ **Gastrin,** glucagon, ~~somatostatin~~ **and** insulin ~~and neurotensin~~**, if applicable**.

m Vital signs are to be taken before blood collection ~~for laboratory tests~~ **if performed the same day**.

n Not performed in participants with a documented cholecystectomy. Performed at any time if symptoms are thought to be related to gallbladder lithiasis. **It can be performed at the visit or up to 7 days before the visit.**

p Any medications/therapies related to NETs prior to Screening visit; other medications/therapies within 3 months prior to Screening visit

q Biomarker, antibody and lab test samples can be collected at the visit or up to 3 days before the visit.

Other action required

Case report form (CRF) update	Yes ☒	No ☐
Informed consent form update	Yes ☒	No ☐
Database update	Yes ☒	No ☐
Statistical analysis plan (SAP) update	Yes ☒	No ☐

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BICR	Blinded independent central review
ECG	Electrocardiogram
CBR	Clinical benefit rate
CgA	Chromogranin A
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
DCR	Disease control rate
DILI	Drug-induced liver injury
D	Day
DNA	Deoxyribonucleic acid
DRE	Disease related event
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
ECLA	ElectroChemiLuminescent Assay
EEA	European Economic Area
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients
EOSI	End of study intervention
FAS	Full analysis set
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GEP-NEC	Gastroenteropancreatic neuroendocrine carcinoma

ABBREVIATION	Wording Definition
GEP-NEN	Gastroenteropancreatic neuroendocrine neoplasm
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
GH	Growth hormone
GI-NETs	Neuroendocrine tumours originating in the gastrointestinal tract
hCG	Human chorionic gonadotrophin
HCP	Healthcare professional
5-HIAA	5-hydroxyindoleacetic acid
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
ITT	Intention-to-treat
IVRS/IWRS	Interactive voice/web response system
LAR	Long-acting release
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MTK	Multi-target tyrosine kinase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT	Identification number for ClinicalTrials.gov
NET	Neuroendocrine tumour
ORR	Overall response rate
OS	Overall survival
Pan-NETs	Neuroendocrine tumours originating in the pancreas
PFS	Progression free survival
PPS	Per-protocol set
PR	Prolonged release
PRRT	Peptide receptor radionucleotide therapy
PSUR	Periodic safety update report

ABBREVIATION	Wording Definition
QoL	Quality of life
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTL	Quality tolerance limit
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SoA	Schedule of activities
SSTRs	Somatostatin receptors
SUSAR	Suspected unexpected serious adverse reaction
TACE	Transcatheter arterial chemoembolisation
TAE	Transcatheter arterial embolisation
TEAE	Treatment emergent adverse event
TTP	Time to progression
ULN	Upper limit of normal
US(A)	United States (of America)
W	Week
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

LIST OF DEFINITIONS

TERM	Definition
Clinical benefit rate (CBR)	The proportion of participants with a best overall response of confirmed CR, confirmed PR or continued SD until the time of assessment
Disease control rate (DCR)	The proportion of participants with a best overall response of confirmed CR, confirmed PR or SD
Main intervention period	Participants will receive deep subcutaneous injection of lanreotide Autogel 120 mg every 28 days (i.e. 4 weeks; a total of 12 injections). Visits for study assessments will be performed one screening visit, 13 visits one, every 4 weeks (Day 1, W4 to W48); with end of study assessments at W48 (EOSI).
Independent injection period/cohort	Only for independent injection period: participants will receive deep subcutaneous injection of lanreotide Autogel 120 mg every 28 days by independent (self/partner) injection. For this period there will be up to six additional visits from W52 to W68 and W72 (EOSI)
Post-intervention survival follow-up	Follow up of the participants survival status (alive or not) within 4 weeks after the last participant enrolled in the main study reaches W48 or until the day of discontinuation. In the independent injection period: follow up on participants survival status (alive or not) within 4 weeks until the last participant enrolled in this cohort reaches W72 or until the day of discontinuation.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 3, single-arm, open-label, multicentre study to assess the efficacy and safety of deep subcutaneous injections of lanreotide Autogel® 120 mg administered every 28 days in Chinese participants with unresectable, locally advanced or metastatic Grade 1 or 2 gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

Brief Title:

An open-label phase 3 study to assess the efficacy and safety of lanreotide Autogel® in Chinese participants with GEP-NETs

Rationale:

Lanreotide Autogel® formulation (60, 90 and 120 mg) has been approved in more than 70 countries worldwide for the treatment of acromegaly and for the treatment of symptoms of neuroendocrine tumours (NETs) since 2001. In addition, since 2014, lanreotide Autogel 120 mg has been approved for controlling tumour growth in patients affected by GEP-NETs. In December 2019, lanreotide Autogel 60, 90 and 120 mg was approved in China for the treatment of acromegaly. A previous lanreotide formulation (lanreotide prolonged release (PR) has been registered in China (since 2002) and more than 15 other countries for the treatment of clinical symptoms of NETs and for the treatment of acromegaly. This bridging study will be conducted to support the registration of the lanreotide Autogel 120 mg formulation in China for the treatment of GEP-NETs and treatment of clinical symptoms of NETs.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of repeated deep s.c. injection of lanreotide Autogel 120 mg every 28 days for 24 weeks in Chinese participants with unresectable, locally advanced or metastatic GEP-NETs	• CBR of tumour response assessed using RECIST (Version 1.1) and confirmed by BICR at W24: *CBR is defined as the proportion of participants with a best overall response of confirmed CR, confirmed PR, or continued SD until the time of assessment.*
Secondary	
• To evaluate the efficacy of lanreotide Autogel® 120 mg administered every 28 days for 48 weeks	• PFS within 24 and 48 weeks after first administration of study intervention: *PFS is defined as the time from the first administration of study intervention to the date of the first documented PD measured using RECIST (Version 1.1) and confirmed by BICR, or death from any cause, whichever comes first.* • OS at the end of the main study: *OS is defined as the time from the first administration of study intervention to the date of death from any cause.*

Objectives	Endpoints
Secondary	
	• TTP within 48 weeks after first administration of study intervention: *TTP is defined as the time from the first administration of study intervention to the date of the first documented PD, or clinical progression confirmed by the investigator.* • Proportion of participants alive and without tumour progressive at W24 and W48 • CBR at W48 • ORR at W24 and W48: *ORR is the proportion of participants with a best overall response of confirmed CR or confirmed PR.* • DCR at W24 and W48: *DCR is the proportion of participants with a best overall response of confirmed CR, confirmed PR or SD.* • Change from baseline in NET-related clinical symptoms at W24 and W48 • Change from baseline in plasma CgA, 5-HIAA and other biomarkers in the circulation at W12, W24, W36 and W48 • Change from baseline in QoL assessment at each visit
• To evaluate safety of lanreotide Autogel 120 mg administered every 28 days for 48 weeks	• AEs throughout the study • Change from baseline in clinical safety laboratory tests: (haematology, chemistry and urinalysis) at W24 and W48 • Change from baseline in physical examination at W12, W24, W36, W48 • Change from baseline in vital signs at W12, W24, W36, W48 • Change from baseline in 12-lead ECG at W24 and W48 • Change from baseline in gallbladder echography at W24 and W48 • Change from baseline in putative anti-lanreotide antibody at W24 and W48
Exploratory	
• To evaluate independent injection of lanreotide Autogel 120 mg administered every 28 days for maximum 24 weeks during the independent injection period (independent injection cohort)	• Proportion of participants preferring independent injection over HCP injections at W72 • Participant-reported indirect costs (e.g. transport costs) at W48 and W72 • Participant-reported work productivity at W48 and W72 • Safety: AEs throughout the independent injection period; change from baseline in physical examination and vital signs at W52, W56, W72; change from baseline in clinical safety laboratory tests, 12-lead ECG and gallbladder echography at W72 • Antitumour effect (assessed by imaging) at W72, change from baseline in NET-related clinical symptom control at W72 (if applicable), change from baseline in QoL at W72 or change from baseline in biomarkers in the circulation (if applicable) at W72

Abbreviations: AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CgA=chromogranin A; CR=complete response; DCR=disease control rate; ECG=electrocardiogram; GEP-NET=gastroenteropancreatic neuroendocrine tumour; HCP=healthcare professional; 5-HIAA=5-hydroxyindoleacetic acid; NET=neuroendocrine tumour; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression free survival; PR=partial response; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumours; s.c.=subcutaneous(ly); SD=stable disease; TTP=time to progression; W=week

Overall Design:

This is a prospective, multicentre, single-arm, nonrandomised, open-label, interventional, phase 3 study in Chinese adult participants with unresectable, well differentiated locally advanced or metastatic GEP-NETs (gastric, pancreas, midgut, hindgut), Grade 1 or 2, nonfunctioning and functioning.

The main study will include a screening period of up to 4 weeks followed by a 48-week intervention period. During the intervention period, 43 participants will receive deep subcutaneous injection of lanreotide Autogel 120 mg every 28 days (i.e. 4 weeks; a total of 12 injections). The main study will include 14 visits (one screening visit, 13 visits, one every 4 weeks (Day 1, W4 to W48 (EOSI)) during the 48-week intervention period.

After completion of the main study period, approximately five participants (assuming 10 to 25% eligible participants after 48 weeks of intervention) will continue in an independent injection period with lanreotide Autogel 120 mg every 28 days for 24 weeks (a total of six independent injections). To be eligible, the participant must provide additional informed consent to continue, have a positive benefit/risk ratio of continuing study intervention (no disease progression at W48 and good tolerability during the main study period) and be a suitable candidate for independent injection (considered able to independently administer lanreotide following training and likely to benefit from independent administration e.g. reducing the burden of frequent hospital visits), in the opinion of the investigator. For the independent injection period there will be up to six additional visits (W52 to W68 (optional) and W72 (EOSI)). Visits for study assessments will be performed at W48, W52 (optional) and W56 (optional); with end of study intervention assessments at W72. At the W48 visit, the first injection will be performed by the participant or their partner at the study site (under medical supervision) for training purposes. At W52 and W56, the second and third injections may also be performed at the study site for training purposes or may be performed at home if no further training is needed, in the opinion of the investigator. At W60, W64 and W68, the fourth, fifth and sixth injections will be performed at home or at the study site. Participants will be contacted by telephone at W52, W56, W60, W64 and W68 (if no study site visit is performed) for safety purposes.

The primary efficacy endpoint is clinical benefit rate (CBR) of tumour response assessed using Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 and confirmed by blinded independent central review (BICR) after 24 weeks of study intervention. Secondary efficacy endpoints will be assessed during the intervention period, including progression free survival (PFS), overall survival (OS), time to progression (TTP), proportion of participants alive and without progressive tumour, CBR after 48 weeks of intervention, overall response rate (ORR), disease control rate (DCR), NET-related clinical symptoms, circulating chromogranin A (CgA), 5-hydroxyindoleacetic acid (5-HIAA) and other biomarkers and quality of life (QoL). Safety data including adverse events (AEs), clinical safety laboratory tests, electrocardiograms (ECG), physical examination, vital signs and gallbladder echography will also be evaluated. Exploratory endpoints will be assessed in the five participants continuing in the independent injection period (proportion of participants preferring independent injection over HCP injections, participant-reported indirect costs and work productivity, plus tumour response, NET-related clinical symptoms, QoL, biomarkers and safety).

The post-intervention survival follow-up will be performed for all participants (not entering independent injection period) within 4 weeks after the last participant enrolled in the study reaches W48 or until the day of discontinuation. When the last participant W48/EOSI/ED visit has occurred, all further post-intervention survival follow-up will stop for these participants. This post-intervention survival follow-up will be performed also for all participants in the

independent injection period within 4 weeks after the last participant enrolled in the independent injection study reaches W72 or until the day of discontinuation. When the last participant W72/EOSI/ED visit has occurred, all further post-intervention survival follow-up will stop for these participants

Condition/Disease: GEP-NETs

Study Hypothesis:

The study hypothesis is that lanreotide Autogel 120 mg is efficacious in Chinese participants with unresectable, well differentiated, locally advanced or metastatic Grade 1 or 2 GEP-NETs at W24.

Study Duration:

The maximum duration of the study is approximately 24 months (main study: approximately 18 months).

The maximum duration of the study per participant:

- Screening period: up to 4 weeks
- Main study period: 48 weeks
- Independent injection period for independent injection cohort only: additional 24 weeks

Visit Frequency:

- Main study: 14 visits (one screening visit, 13 visits, one every 4 weeks (Day 1, Week (W) 4 to W48) during the 48-week intervention period
- Independent injection period (only for independent injection cohort): Up to six additional on-site visits (W52 to W68 (optional), W72).

Number of Participants:

Approximately 51 participants will be enrolled to achieve 43 receiving study intervention and 36 participants evaluable for CBR at W24. Approximately five participants are expected to be enrolled in the independent injection period.

Note: "Enrolled" means a participant's, or their legally authorised representative's, agreement to participate in a clinical study following completion of the informed consent process.

Intervention Groups and Duration:

The main study will include a screening period of up to 4 weeks followed by a fixed-dose intervention period of 48 weeks with deep subcutaneous injections of lanreotide Autogel® 120 mg every 28 days in the buttocks (12 injections in total). In addition, participants who had clinical benefit (complete response, partial response or stable disease) at the end of the 48-week intervention period in the main study will be included in the independent injection period at the discretion of the investigator and with participant's consent. The independent injection duration will be maximum 24 weeks (total six injections).

Data Monitoring/Other Committee:

Not applicable. There will be no oversight committees in the study.

Statistical Methods:

Sample size calculation was based on the primary endpoint. The expected CBR at W24 was set to 64% referring to the results of Japanese Study ITM-014N-001 and global pivotal Study 2-55-52030-726 (CLARINET; NCT00353496). The threshold CBR at W24 was defined as 40% based on Japanese study ITM-014N-001 and medical expert's opinions. When a statistical test was performed for a null hypothesis with one sided type I error of 2.5%, a minimum sample size required to yield a power of at least 80% would be 36 participants. Considering 15% drop-off rate, 43 participants would be necessary for the primary efficacy evaluation CBR at W24.

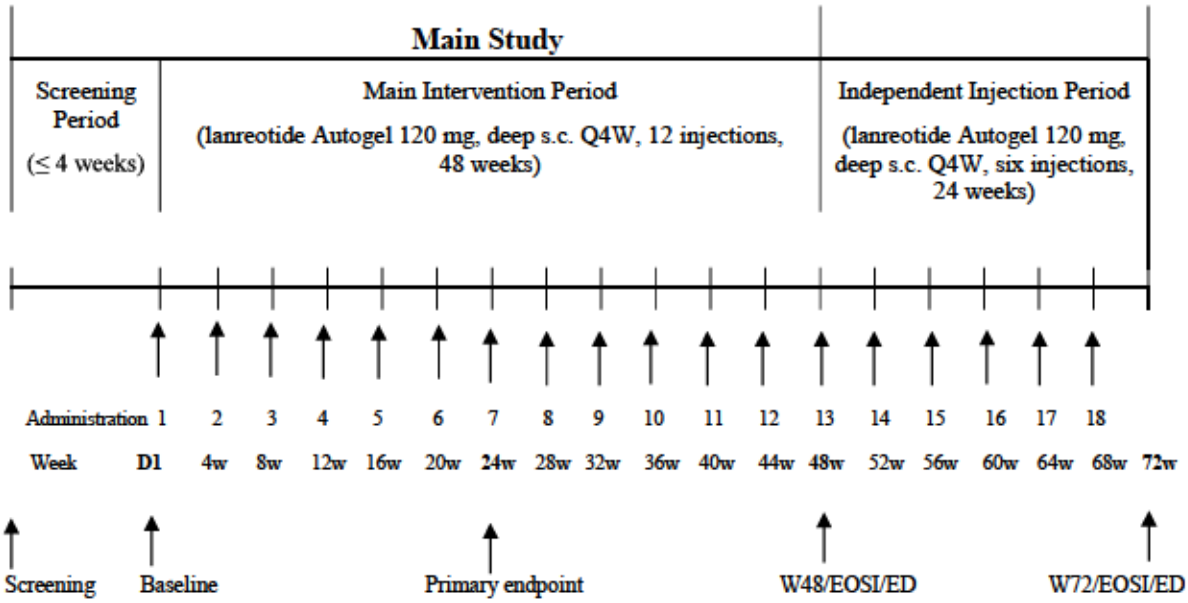
Point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated for a CBR at W24, and other secondary endpoints, if applicable.

Time-dependent parameters (PFS, TTP and OS), Kaplan-Meier curves and life tables will be generated, and median with 95% CIs will be calculated. Other data will be analysed using descriptive statistics and frequency tables.

1.2 Schema

The study schema is shown in Figure 1.

Figure 1 Study Schema



Abbreviations: D=day; ED=early discontinuation; EOSI=end of study intervention; Q4W=every 28 days; s.c.=subcutaneous(ly); w=week

Note: W48/EOSI=end of main study (after 48 weeks of intervention period) for all participants; W72/EOSI=end of independent injection period only for independent injection period

After finishing the intervention in the main study period or the independent injection period, the investigator will record overall survival status within 4 weeks after the last participant last visit in either period reaches W48 or W72, respectively, or the day of discontinuation, irrespective of subsequent therapy

1.3 Schedule of Activities (SoA)

The SoA is provided in Table 1.

If the COVID-19 pandemic prevents participants from coming to the site, participants can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the participant's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the investigator in a separate document. Such document will be filed in the trial master file. Institutional review boards (IRBs)/independent ethics committees (IECs)/ will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Table 1 Schedule of Activities

	Screen (W-4)	Main Intervention Period									Independent Injection Period (~5 participants only)				Remote Post Intervention Follow-up Period[a]
		D1	W4/W8	W12	W16/ W20	W24	W28/ W32	W36	W40/ W44	W48 [b]	W48 [b]	W52/ W56 [c]	W60 W64/ W68 [c]	W72 [d]	
Visit Schedule	**D-28**	**D1**	**D29/ D57**	**D85**	**D113/ D141**	**D169**	**D197/ D225**	**D253**	**D281/ D309**	**D337**	**D337**	**D365/ D393**	**D421/D449 /D477**	**D505**	**Within 4 weeks after last W48, W72 or ED**
Visit Window (Days)	**-28 to 0**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Visit	V1	V2	V3/4	V5	V6/7	V8	V9/10	V11	V12/13	EOSI Visit/ED	V14	(V15/16)	(V17-19)	EOSI Visit/ED	
Eligibility assessments:															
Informed consent	X										X				
Demography (including height)	X														
Medical/disease history[e]	X														
Prior medications/therapies [p]	X														
Pregnancy test (WOCBP only)	X	X				X				X	X			X	
FSH test (if required)	X														

	Screen (W-4)	Main Intervention Period									Independent Injection Period (~5 participants only)				Remote Post Intervention Follow-up Period[a]
		D1	W4/W8	W12	W16/ W20	W24	W28/ W32	W36	W40/ W44	W48 [b]	W48 [b]	W52/ W56 [c]	W60 W64/ W68 [c]	W72 [d]	Within 4 weeks after last W48, W72 or ED
Visit Schedule	D-28	D1	D29/ D57	D85	D113/ D141	D169	D197/ D225	D253	D281/ D309	D337	D337	D365/ D393	D421/D449 /D477	D505	
Visit Window (Days)	-28 to 0		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit	V1	V2	V3/4	V5	V6/7	V8	V9/10	V11	V12/13	EOSI Visit/ED	V14	(V15/16)	(V17-19)	EOSI Visit/ED	
ECOG performance score	X														
Inclusion/exclusion criteria	X	(X) [f]									X[g]				
Study intervention:															
Lanreotide Autogel® injection		X	X	X	X	X	X	X	X		X[h]	X[h]	X[h]		
Efficacy assessments:															
CT/MRI/tumour assessment[i]	X			X		X		X		X	X			X	
QoL - EORTC QLQ-C30		X		X		X		X		X	X			X	
Survival status			X												
NET clinical symptoms[j]	X	X	X	X	X	X	X	X	X	X	X	(X)		X	
HCP vs independent injection														X	
Biomarkers [q]:															
Serum/plasma CgA		X		X		X		X		X	X			X	
5-HIAA (24h urine collection)		X		X		X		X		X	X			X	
Other biomarkers[k]		X		X		X		X		X	X			X	
Immunogenicity assessment:															
Anti-lanreotide antibodies [q]		X				X				X	X				
Health economics[l]											X			X	
Safety Assessments:															
Physical examination	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)	X	

	Screen (W-4)	Main Intervention Period									Independent Injection Period (~5 participants only)				Remote Post Intervention Follow-up Period[a]
		D1	W4/W8	W12	W16/ W20	W24	W28/ W32	W36	W40/ W44	W48 [b]	W48 [b]	W52/ W56 [c]	W60 W64/ W68 [c]	W72 [d]	Within 4 weeks after last W48, W72 or ED
Visit Schedule	D-28	D1	D29/ D57	D85	D113/ D141	D169	D197/ D225	D253	D281/ D309	D337	D337	D365/ D393	D421/D449 /D477	D505	
Visit Window (Days)	-28 to 0		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit	V1	V2	V3/4	V5	V6/7	V8	V9/10	V11	V12/13	EOSI Visit/ED	V14	(V15/16)	(V17-19)	EOSI Visit/ED	
Vital signs	X[m]	X [m]	X	X	X	X[m]	X	X	X	X[m]	X	(X)	(X)	X[m]	
12-lead ECG	X					X				X	X			X	
Gallbladder echography[n]	X[o]					X				X	X			X	
Clinical safety laboratory tests [q]	X	X				X				X	X			X	
AEs	Record continuously														
Concomitant medications/nondrug therapy		Record continuously													
Subsequent therapies															X

Abbreviations: AE=adverse event; CgA=chromogranin A; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ED=early discontinuation; EOSI=end of study intervention; FDG-PET=fluorodeoxyglucose-positron emission tomography; FSH=follicle stimulating hormone; h=hour; HCP=healthcare professional; 5-HIAA=5-hydroxyindoleacetic acid; MRI=magnetic resonance imaging; NET=neuroendocrine tumour; QoL=quality of life; WOCBP=woman of childbearing potential; W=week
(X)=only if a study site visit is performed

Note: On days of study intervention administration, all assessments are performed prior to lanreotide injection

a The remote post-intervention survival follow-up will be performed for all participants (not entering independent injection period) within 4 weeks after the last participant enrolled in the study reaches W48 or until the day of discontinuation. This post-intervention survival follow-up also will be performed for all participants in the independent injection period within 4 weeks after the last participant enrolled in the independent injection study reaches W72 or until the day of discontinuation.

b For participants not continuing in the independent injection period, the procedures in the W48/EOSI/ED column will be performed. For participants continuing in the independent injection period, the procedures in the W48 column will be performed.

c May be a study site visit or remotely by telephone call to the participant

d EOSI/ED visit for participants continuing in the independent injection period

e Including drugs, alcohol, tobacco

f Recheck clinical status/eligibility before first dose of study intervention

g For details see Section 5.1 criteria 10

h Participants will perform six independent injections. At W48, the first injection will be performed by the participant or their partner at the study site under medical supervision for training purposes. At W52 and W56, the second and third injections may also be performed at the study site under medical supervision for training purposes or may be performed at home if no further training is needed, in the opinion of the investigator. At W60, W64 and W68, the fourth, fifth and sixth injections will be performed at home or at the study site.

i CT and/or MRI based on the tumour lesion; can be performed at the visit or up to 7 days before the visit. See Section 8.1.1 for details

	Screen (W-4)	Main Intervention Period									Independent Injection Period (~5 participants only)				Remote Post Intervention Follow-up Period[a]
		D1	W4/W8	W12	W16/ W20	W24	W28/ W32	W36	W40/ W44	W48 [b]	W48 [b]	W52/ W56 [c]	W60 W64/ W68 [c]	W72 [d]	
Visit Schedule	**D-28**	**D1**	**D29/ D57**	**D85**	**D113/ D141**	**D169**	**D197/ D225**	**D253**	**D281/ D309**	**D337**	**D337**	**D365/ D393**	**D421/D449 /D477**	**D505**	**Within 4 weeks after last W48, W72 or ED**
Visit Window (Days)	**-28 to 0**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Visit	V1	V2	V3/4	V5	V6/7	V8	V9/10	V11	V12/13	EOSI Visit/ED	V14	(V15/16)	(V17-19)	EOSI Visit/ED	

j Presence or absence endocrine symptoms of NETs will be assessed at screening. Participants with diarrhoea and/or flushing related to NETs will be provided with a diary to record their daily symptoms and any medications taken to treat these symptoms. The first diary will be dispensed at the Day 1 visit. See Section 8.1.3 for details

k Gastrin, glucagon, and insulin, if applicable

l The following questionnaires will be performed: Impact of treatment administration setting on costs, Work Productivity and Activity Questionnaire: General Health (WPAI:GH) and the impact of switch in administration setting on overall ability to work.

m Vital signs are to be taken before blood collection if performed the same day.

n Not performed in participants with a documented cholecystectomy. Performed at any time if symptoms are thought to be related to gallbladder lithiasis. It can be performed at the visit or up to 7 days before the visit.

o Not necessary if performed within 24 weeks prior to Visit 2

p Any medications/therapies related to NETs prior to Screening visit; other medications/therapies within 3 months prior to Screening visit

q Biomarker, antibody and lab test samples can be collected at the visit or up to 3 days before the visit.

1.4 Brief Summary

The purpose of this study is to determine the efficacy and safety of lanreotide Autogel 120 mg administered by deep subcutaneous injection in Chinese participants with unresectable, well differentiated, locally advanced or metastatic Grade 1 or 2 gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Study details include:

Study duration: Approximately 24 months (main study: approximately 18 months)

Treatment duration: Every 28 days for 48 weeks (main intervention period) and an additional 24 weeks (independent injection period only)

Visit frequency: Every 4 weeks (main intervention and independent injection periods), for a maximum of 48 weeks (main intervention period) and for an additional 24 weeks (independent injection period)

Hypothesis: The study hypothesis is that lanreotide Autogel 120 mg is efficacious in Chinese participants with unresectable, well differentiated, locally advanced or metastatic Grade 1 or 2 GEP-NETs at Week 24.

Main observation: The proportion of participants with a tumour response on imaging assessment according to the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1

2 INTRODUCTION

2.1 Study Rationale

This bridging study will be conducted to support the registration of the lanreotide Autogel 120 mg formulation in China for the treatment of GEP-NETs and treatment of clinical symptoms of NETs.

Neuroendocrine tumours are a heterogeneous group of slow growing neoplasms that arise from diffuse neuroendocrine cells. In China, the incidence is around 2.03 per 100000 persons/year. Somatostatin analogues are the treatment of choice for hormone-related syndromes and lanreotide is a well-established peptide analogue of the natural hormone somatostatin, in which the biochemical stability of the peptide has been increased by incorporation of modified amino acids.

Lanreotide Autogel® formulation (60, 90 and 120 mg) has been approved in more than 70 countries worldwide for the treatment of acromegaly and for the treatment of symptoms of neuroendocrine tumours (NETs) since 2001. In addition, since 2014, lanreotide Autogel 120 mg has been approved for controlling tumour growth in patients affected by gastroenteropancreatic neuroendocrine tumours (GEP-NETs). In December 2019, lanreotide Autogel 60, 90 and 120 mg was approved in China for the treatment of acromegaly. A previous lanreotide formulation (lanreotide prolonged release (PR)) has been registered in China (since 2002) and more than 15 other countries for the treatment of clinical symptoms of NETs and for the treatment of acromegaly.

The efficacy of lanreotide Autogel 120 mg in treating the symptoms associated with "functioning" GEP-NETs has been demonstrated in Study 2-55-52030-730 (ELECT) and the antiproliferative effect in "nonfunctioning" GEP-NETs in Study 2-55-52030-726 (CLARINET). Results from Study ITM-014N-001 and extension study support the efficacy of lanreotide Autogel in Japanese participants with NETs. In addition, published literature [Ito 2017, Kang 2019] suggests that Asian patients respond well to SSA treatment with no specific safety signals detected, and the results reported with lanreotide Autogel 120 mg were consistent with those in the pivotal Study 726. The sponsor will conduct a bridging study in participants with GEP-NETs for further confirmation in China. Scientific rational of study design is provided in Section 4.2.

Lanreotide Autogel is presented as ready to use, prefilled syringes, with a recommended dose of 120 mg administered every 28 days for the treatment of GEP-NETs and treatment of clinical symptoms associated with NETs. In the countries where lanreotide Autogel is approved, this presentation enables patients or their caregivers to independently administer lanreotide Autogel injections in a place and at a time of their choosing, after appropriate training from a healthcare professional (HCP), rather than having to travel to healthcare practitioners, with no notable loss of efficacy. This could potentially lead to an improvement in the Chinese patient's care and quality of life (QoL) and be less of a burden on them financially and on the health service in China. The dosing regimen of one deep s.c. injection every 28 days is also more convenient and may result in fewer injection site reactions compared to the existing lanreotide formulation (administered i.m. every 10 or 14 days for the treatment of clinical symptoms of NETs associated with carcinoid tumours).

2.2 Background

Neuroendocrine tumours are a heterogeneous group of slow growing neoplasms that arise from diffuse neuroendocrine cells. The majority of NETs originate in the gastrointestinal tract (GI-NETs) and in the pancreas (pan-NETs) and are therefore collectively referred to as GEP-NETs. In China, the incidence is around 2.03 per 100,000/year [Guo 2016].

The term gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) encompasses two main subtypes; GEP-NETs which are well-differentiated and gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) which are poorly differentiated. In a hospital-based, nationwide multicentre 10-year (2001 to 2010) retrospective study which collected 2010 GEP-NEN patients' information in tertiary referral hospitals, the most common primary sites for GEP-NENs were the pancreas (31.5%) and rectum (29.6%), followed by the gastric body (15.4%) and gastric cardia (11.6%) of the stomach. Small intestinal (5.6%) and colonic (3.0%) NENs took up a relatively small proportion of all patients [Fan 2017].

Based on the ability to secrete bioactive substances, and whether these substances result in a clinical syndrome (symptoms associated with hormonal hypersecretion of NETs) or not, GEP-NETs have been described as "functioning" or "nonfunctioning".

Initial treatment consists of surgical removal of the tumour (when possible) and treatment of hormonal syndrome (when present). Once the tumour enters in a progressive phase, treatment usually includes hepatic artery embolisation, chemotherapy, radiolabelled somatostatin analogues and/ or interferon. The response rate of these treatments depends on tumour type and are often associated with frequent and severe side effects. In the European Neuroendocrine Tumor Society (ENETS) consensus guidelines [ENETS 2020], SSA is recommended for the inhibition of tumour growth in both intestinal and pancreatic NET and the treatment of clinical symptoms of NETs.

Natural somatostatin inhibits the secretion of a broad range of hormones and acts by binding to membrane bound somatostatin receptors (SSTRs) (comprising SSTRs 1 to 5) expressed on most NETs. Approximately 80 to 90% of NETs express somatostatin receptors on their cell surface that bind with high affinity to lanreotide. Lanreotide is a well-established octapeptide analogue of the natural hormone somatostatin in which the biochemical stability of the peptide has been increased by incorporation of modified amino acids. It binds with higher affinity to SSRT2 and SSTR5 and once bound, lanreotide inhibits the signal transmission pathways mediated by somatostatin receptors, causing a reduction in hormone and biogenic amine secretion that may improve tumour related symptoms and stabilise tumour growth. [Modlin 2010].

Lanreotide Autogel (Somatuline® Autogel®) formulation is administered via a deep subcutaneous injection into the external quadrant of the buttock by a healthcare professional (HCP). Alternatively, in Europe, and in most other countries where the product is registered, the patient or the patient's carer/partner can be trained by the HCP to administer the medication, and in the case of independent injection the solution is administered by deep subcutaneous injection into the upper outer thigh.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of lanreotide Autogel may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

The sponsor believes that the overall risk of differences in the safety and efficacy profile of lanreotide Autogel due to ethnicity differences is low and race will likely not be a factor significantly affecting exposure and trough concentration.

Important identified risks with lanreotide include gastrointestinal effects, cholelithiasis, pancreatitis, effects on glycoregulation, effects on thyroid function, bradycardia, injection site reactions and allergic reactions. Participants with cholelithiasis may require periodic monitoring.

Important potential risks with lanreotide include effects on bioavailability of concomitant medications and hepatic dysfunction.

Further information on these risks can be found in Section 6 (summary of data and guidance for the investigator) of the Investigator's Brochure. At the start and during the study, there will be appropriate monitoring of the participant, exclusion criteria and criteria for temporary and/or permanent discontinuation of study intervention.

There are potential risks associated with tumour assessments. Participants who receive computed tomography (CT) scans will receive an intravenous injection of an iodine-based dye (contrast media) which may cause allergic reactions. Magnetic resonance imaging (MRI) scans are generally not advised for participants with epilepsy. Investigators/site staff are required to cross check the participant's medical history prior to the assessment to determine their suitability for either procedure.

2.3.2 Benefit Assessment

Clinical studies and published experience support the efficacy of lanreotide. The main potential benefit for participants is receipt of treatment that has been demonstrated to prolong progression free survival (PFS) and control tumour growth. Lanreotide is also associated with a reduction of bothersome NET-related symptoms (e.g. diarrhoea and flushing) and improvement in quality of life (QoL) (see Section 4.2).

The lanreotide Autogel formulation offers further benefits in terms of convenience for the participant and HCP. The currently approved lanreotide PR formulation is administered by intramuscular injection. Lanreotide Autogel formulation will be administered by a deep subcutaneous injection, allowing the potential for independent injection. As this formulation is associated with a more sustained release, the frequency of injections can be decreased to every 28 days, compared to every 10 or 14 days with lanreotide PR intramuscular injection and possible associated local injection site reactions could potentially be reduced. This could result in an improvement in the participant's care and QoL and therefore greater acceptance. As there are no other independently administered therapies available in China indicated to treat patients with GEP-NETs, the strain on the health service in China could also be reduced.

2.3.3 Overall Benefit/Risk Conclusion

Based on the most recent periodic safety update report (PSUR) for lanreotide (data lock point May 2019), review of the available safety data (primarily from postmarketing experience but also from clinical studies) has not changed the benefit/risk profile of lanreotide, which remains favourable when used in its approved indications and in accordance with the approved prescribing information. In addition, a cumulative review of the spontaneous individual case safety reports originating from China and Taiwan combined (using the same data lock point as the PSUR) has shown that the pattern of adverse reactions grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class is generally consistent with the reports from the rest of the world.

Taking into account the measures outlined in Section 2.3.1 to minimise risk to study participants, the potential risks identified in association with lanreotide Autogel are justified by the anticipated benefits that may be afforded to participants with GEP-NETs.

The overall benefit/risk profile of lanreotide Autogel therefore remains favourable with no signal or indication that Chinese or Asian patients tolerate the therapy any differently to any Western or Caucasian populations.

3 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are correlated in Table 2.

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of repeated deep s.c. injection of lanreotide Autogel 120 mg every 28 days for 24 weeks in Chinese participants with unresectable, locally advanced or metastatic GEP-NETs	• CBR of tumour response assessed using RECIST (Version 1.1) and confirmed by BICR at W24: *CBR is defined as the proportion of participants with a best overall response of confirmed CR, confirmed PR, or continued SD until the time of assessment.*
Secondary	
• To evaluate the efficacy of lanreotide Autogel 120 mg administered every 28 days for 48 weeks	• PFS within 24 and 48 weeks after the first administration of study intervention: *PFS is defined as the time from the first administration of study intervention to the date of the first documented PD measured using RECIST (Version 1.1) and confirmed by BICR, or death from any cause, whichever comes first.* • OS at the end of the main study: *OS is defined as the time from the first administration of study intervention to the date of death from any cause.* • TTP within 48 weeks after the first administration of study intervention: *TTP is defined as the time from the first administration of study intervention to the date of the first documented PD, or clinical progression confirmed by the investigator.* • Proportion of participants alive and without tumour progressive at W24 and W48 • CBR at W48 • ORR at W24 and W48: *ORR is the proportion of participants with a best overall response of confirmed CR or confirmed PR.* • DCR at W24 and W48: *DCR is the proportion of participants with a best overall response of confirmed CR, confirmed PR or SD.* • Change from baseline in NET-related clinical symptoms at W24 and W48 • Change from baseline in plasma CgA, 5-HIAA and other biomarkers in the circulation at W12, W24, W36 and W48 • Change from baseline in QoL assessment at each visit
• To evaluate the safety of lanreotide Autogel 120 mg administered every 28 days for 48 weeks	• AEs throughout the study • Change from baseline in clinical safety laboratory tests: (haematology, chemistry and urinalysis) at W24 and W48 • Change from baseline in physical examination at W12, W24, W36, W48 • Change from baseline in vital signs at W12, W24, W36, W48 • Change from baseline in 12-lead ECG at W24 and W48 • Change from baseline in gallbladder echography at W24 and W48 • Change from baseline in putative anti-lanreotide antibody at W24 and W48

Exploratory	
• To evaluate of independent injection of lanreotide Autogel 120 mg administered every 28 days for 24 weeks during the independent injection period (independent injection cohort)	• Proportion of participants preferring independent injection over HCP injections at W72 • Participant-reported indirect costs (e.g. transport costs) at W48 and W72 • Participant-reported work productivity (where relevant) at W48 and W72 • Safety: AEs throughout the independent injection period; change from baseline in physical examination and vital signs at W52, W56, W72; change from baseline in clinical safety laboratory tests, 12-lead ECG and gallbladder echography at W72 • Antitumour effect (assessed by imaging) at W72, change from baseline in NET-related clinical symptom control at W72 (if applicable), change from baseline in QoL at W72 or change from baseline in tumour biomarkers in the circulation (if applicable) at W72

Abbreviations: AE=adverse event ; BICR=blinded independent central review; CBR=clinical benefit rate; CgA=chromogranin A; CR=complete response; DCR=disease control rate; ECG=electrocardiogram; GEP-NET=gastroenteropancreatic neuroendocrine tumour; HCP=healthcare progression; 5-HIAA=5-hydroxyindoleacetic acid; NET=neuroendocrine tumour; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression free survival; PR=partial response; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumours; s.c.=subcutaneous(ly); SD=stable disease; TTP=time to progression; W=week

The study population, study intervention and prohibited medications are described in Section 5, Section 6 and Section 6.8, respectively. Analysis sets are defined in Section 9.3 and other estimands are described in further detail in Section 9.4.

4 STUDY DESIGN

4.1 Overall Design

This is a prospective, multicentre, single-arm, nonrandomised, open-label, interventional, phase 3 study in Chinese adult participants with unresectable, well differentiated locally advanced or metastatic GEP-NETs (gastric, pancreas, midgut, hindgut), Grade 1 or 2, nonfunctioning and functioning. The study design is illustrated in Figure 1.

The main study will include a screening period of up to 4 weeks followed by a 48-week intervention period. During the intervention period, 43 participants will receive deep subcutaneous injection of lanreotide Autogel 120 mg every 28 days (i.e. 4 weeks; a total of 12 injections). The main study will include 14 visits (one screening visit, 13 visits, one every 4 weeks (Day 1, W4 to W48 (EOSI)) during the 48-week intervention period.

After completion of the main study period, approximately five participants (assuming 10 to 25% eligible participants after 48 weeks of intervention in the main study) will enter an independent injection period with lanreotide Autogel 120 mg every 28 days for 24 weeks (a total of six independent injections). To be eligible, the participant must provide additional informed consent to continue, have a positive benefit/risk ratio of continuing study intervention (no disease progression at W48 and good tolerability during the main study period) and be a suitable candidate for independent injection (considered able to independently administer lanreotide following training and likely to benefit from independent administration e.g. reducing the burden of frequent hospital visits) in the opinion of the investigator. For the independent injection period there will be up to six additional visits (W52 to W68 (optional) and W72 (EOSI)). Visits for study assessments will be performed at W48, W52 (optional) and W56 (optional); with EOSI assessments at W72. At the W48 visit, the first injection will be performed independently at the study site (under medical supervision) for training purposes. At W52 and W56, the second and third injections may also be performed at the study site for training purposes or may be performed at home if no further training is needed, in the opinion of the investigator. At W60, W64 and W68, the fourth, fifth and sixth injections will be performed at home or at the study site. Participants will be contacted by telephone at W52, W56, W60, W64 and W68 (if no study site visit is performed) for safety purposes.

The primary efficacy endpoint is clinical benefit rate (CBR) of tumour response assessed using Response Evaluation Criteria in Solid Tumours RECIST Version 1.1 [Eisenhauer 2009] and confirmed by blinded independent central review (BICR) after 24 weeks of study intervention. Secondary efficacy endpoints will be assessed during the intervention period, including PFS, overall survival (OS), time to progression (TTP), proportion of participants alive and without progressive tumour, CBR after 48 weeks of intervention, overall response rate (ORR), disease control rate (DCR), NET-related clinical symptoms, circulating chromogranin A (CgA), 5-hydroxyindoleacetic acid (5-HIAA) and other biomarkers and QoL. Safety data including AEs, clinical safety laboratory tests, electrocardiograms (ECG), physical examination, vital signs and gallbladder echography will also be evaluated. Exploratory endpoints will be assessed in the five participants continuing in the independent injection period (proportion of participants preferring independent injection over HCP injections, participant-reported indirect costs and work productivity, plus tumour response, NET-related clinical symptoms, QoL, biomarkers and safety).

The maximum duration of the study is approximately 24 months (main study: approximately 18 months).

Maximum duration of the study per participant:

- Screening period: up to 4 weeks
- Main study period: 48 weeks
- Independent injection period for the independent injection cohort only: additional 24 weeks

After the end of study assessments, participants will enter a remote post-intervention survival follow-up period and a telephone call will be used to collect survival status and subsequent therapies. This follow-up will be performed for all participants (irrespective of whether they participate in the independent injection period or not) within 4 weeks after the last participant enrolled in the study reaches W48 or W72 (for independent injection period only) or until the day of discontinuation.

4.2 Scientific Rationale for Study Design

The main effects of lanreotide are reducing symptoms of NETs and/or tumour stabilisation:

- A global pivotal phase 3, randomised placebo-controlled study in participants with enteropancreatic endocrine tumours (Study 2-55-52030-726 (CLARINET; NCT00353496)) demonstrated that treatment with lanreotide Autogel 120 mg every 28 days for 96 weeks reduced the risk of progression or death by 53% (hazard ratio=0.47, 95% confidence interval (CI): 0.30, 0.73) [Caplin 2014].
- A single-arm, open-label phase 2 study in Japanese participants with unresectable, metastatic or locally advanced NETs (Study ITM-014N-001) demonstrated that lanreotide Autogel 120 mg every 28 days for 12 months was associated with a CBR (defined as the proportion of participants with a complete response, partial response or stable disease in accordance with RECIST Version 1.1) at 24 weeks of 64.3% (95% CI, 44.1-81.4) [Ito 2017].
- A phase 3, randomised placebo-controlled study in participants with a history of carcinoid syndrome (Study 2-55-52030-730 (ELECT; NCT00774930)) demonstrated the efficacy of treatment with lanreotide Autogel 120 mg every 28 days for 16 weeks in controlling symptoms of NETs. There was a statistically significant difference in the number of days in which subcutaneous octreotide was used as rescue medication between the lanreotide and placebo groups, representing a difference of –14.8% (95% CI: –26.8, –2.8; p=0.017). The odds ratio of full/partial treatment success (≤3 days octreotide use in W12 to W15) was significantly greater with lanreotide than placebo (2.4; 95% CI: 1.1, 5.3; p=0.036) [Vinik 2016].

The present study to demonstrate the efficacy and safety of lanreotide Autogel 120 mg in Chinese participants with NETs will be conducted with a multicentre, single-arm, nonrandomised, open-label design for the following reasons:

- This study design is similar to Study ITM-014N-001 in Japanese participants [Ito 2017] to facilitate the collection of bridging data. Disease epidemiology in the Chinese population is similar to that of the Japanese population and no ethnic differences are expected in Chinese versus Japanese participants.
- As NETs are a rare, a single arm study allows collection of as much data as possible on administration of the active treatment.
- Since NETs are a serious disease that could progress with a high mortality rate depending on primary location and metastases, the use of a single arm design is considered ethical due to treatment being available for GEP-NETs in China. Placebo administration for the sake of participation in the study is assumed to be difficult.

The primary endpoint is to assess the CBR at W24:

- CBR is a confirmed objective efficacy endpoint for antitumour effect on the basis of the pharmacological actions of somatostatin analogues and the results of overseas clinical studies.
- The same primary endpoint was used in Study ITM-014N-001 in Japanese participants [Ito 2017]. As the primary antitumour effect of lanreotide Autogel is assumed to be stabilisation of tumours, CBR (which includes complete response, partial response or continued stable disease) was considered as an indicator which enables evaluation of participants confirmed as having persistent stable disease. Partially because this study is a single arm-study, CBR at W24 has been selected as the primary endpoint which enables examination of antitumour effects.

The key secondary endpoints in this study are to assess efficacy and safety in participants with GEP NETs at W48:

- Grade 1 or 2 GEP-NETs according to World Health Organisation (WHO) 2019 classification [Nagtegaal 2019] are usually slow-growing tumours associated with a relatively long survival. The parameter CBR will therefore be also assessed at the W48 timepoint.
- Symptom episodes, PFS and changes in circulating biomarkers.
- Standard safety parameters which are generally recognised as reliable, accurate and relevant.

The sample size justification is provided in Section 9.1.

4.3 Justification for Dose

In a phase 1 study (Study E-28-52030-717) investigating the effect of race and ethnicity, an overlay of the 90% prediction interval of the pharmacokinetic time course of the Caucasian population model with the observed concentrations from the 11 available Asian participants was performed. Most of the serum lanreotide concentrations in these Asian participants laid within the 90% prediction interval. Therefore, no significant effect of race on the pharmacokinetics of lanreotide Autogel® was observed in participants with GEP-NETs. Overall, no significant effect of race on the exposure and C_{trough} of lanreotide is expected. This is consistent with what has been demonstrated for lanreotide Autogel in participants with acromegaly (please refer to the Investigator's Brochure).

Lanreotide Autogel 120 mg was administered by subcutaneous injection every 28 days as a double-blind treatment for 96 weeks in Study 2-55-52030-726 (CLARINET) (with continuing open-label treatment in an extension study up to ~8 years), as an open-label treatment for 12 months in Study ITM-014N-001 and as a double-blind treatment for 16 weeks in Study 2-55-52030-730 (ELECT) (with further open label treatment for an initial 32 weeks and then in an extension study for at least 2 years) (see Section 4.2).

The same dose and dose frequency will therefore be investigated in this study to obtain efficacy and safety bridging data in Chinese participants with GEP-NETs.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

For each individual participant, their participation in the main study intervention period is considered to be completed if they finish 48 weeks of study intervention. After finishing the intervention in the main study period, the investigator will record overall survival status within

4 weeks after the last participant last visit in the main study reaches W48 or the day of discontinuation, irrespective of subsequent therapy.

A participant who continues into the independent injection period will be considered to have completed the study if he/she finishes the additional 24 weeks of study intervention in the independent injection period.

After finishing the intervention in this independent injection period, the investigator will record overall survival status within 4 weeks after the last participant last visit in the independent injection period reaches W72 or the day of discontinuation, irrespective of subsequent therapy.

Criteria for study intervention discontinuation and participant discontinuation/withdrawal from the study are described in Section 7.1 and Section 7.2, respectively. Lost to follow-up is described in Section 7.3.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

(1) Capable of giving signed informed consent as described in Appendix 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

(2) Male or female of 18 years of age or older when informed consent is obtained.

(3) Has a histologically proven Grade 1 or 2 GEP-NET according to WHO classification [Nagtegaal 2019].

(4) Has an unresectable (or if the participant refuses surgery) metastatic or locally advanced NET.

(5) Has a measurable tumour according to RECIST Version 1.1.

(6) Has a nonfunctioning or functioning GEP-NET of a known primary localisation (gastric, pancreas, midgut, hindgut).

(7) Has an Eastern Cooperative Oncology Group (ECOG) performance status lower or equal to 2 (Appendix 10.9)

(8) A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of nonchildbearing potential (see Appendix 10.4.1), or
- Is a woman of childbearing potential (WOCBP) and using an acceptable contraceptive method (see Appendix 10.4.1 and Appendix 10.4.2) during the study intervention period (at a minimum until 90 days after the last dose of study intervention). The investigator should evaluate the potential for contraceptive method failure (e.g. noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations; sensitive to 25 IU β-human chorionic gonadotropin (hCG)) within 4 weeks before the first dose of study intervention, if a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

(9) Male participants must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception. The participants must agree to use the contraception during the whole period of the study and for 90 days after the last dose of study intervention.

(10) For the independent injection period enrolment, the participant:

- Must provide additional written informed consent prior to study related procedures in the independent injection period

- The participant has been receiving the intervention with lanreotide Autogel at a stable dose and frequency for 44 weeks, shows no disease progression at W48 and good tolerability during the main study period
- Must be considered a suitable candidate for independent injection (considered able to independently administer lanreotide following training and likely to benefit from an independent administration) in the opinion of the investigator.
- The suitable candidate should be considered able to understand the injection technique, as judged by the investigator

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

(1) Participants with poorly differentiated GEP-NEC, high-grade GEP-NEC and goblet cell carcinoid.

(2) Has been treated with octreotide acetate long-acting release (LAR) or lanreotide acetate Autogel formulation within 8 weeks prior to screening tests or lanreotide PR 40 mg within 4 weeks prior to screening tests.

(3) Has been treated with subcutaneous or intravenous octreotide acetate within 1 week prior to screening tests.

(4) Has been treated with mammalian target of rapamycin (mTOR) inhibitors or multi-target tyrosine kinase (MTK) inhibitors within 4 weeks prior to screening tests.

(5) Has been treated with peptide receptor radionucleotide therapy (PRRT) at any time prior to screening tests.

(6) Has been treated with radiotherapy within 4 weeks prior to screening tests.

(7) Has been treated with chemotherapy, radiofrequency ablation or cryoablation within 8 weeks prior to screening tests.

(8) Has been treated with interferon, transcatheter arterial embolisation (TAE) or transcatheter arterial chemoembolisation (TACE) within 24 weeks prior to screening tests.

(9) Has had a major surgery related to neuroendocrine tumours within 12 weeks prior to screening tests.

(10) Has been treated with other investigational drugs or unlicensed drugs within 8 weeks prior to screening tests.

(11a) Has other concurrent malignancy than neuroendocrine tumours.

(12) Cancer history of any malignancies, other than a neuroendocrine tumour (except for basocellular carcinoma of the skin or in-situ carcinoma of the cervix), unless the participant has been in complete remission for ≥5 years (and with no relapse) after curative cancer treatment.

(13) Participants with medical history of hypersensitivity to somatostatin analogues.

(14) Participants with symptomatic cholelithiasis.

(15) Alanine transaminase (ALT) (or aspartate transaminase (AST) >2×upper limit of normal (ULN); ALT or AST ≥5×ULN if hepatic impairment is resulting from metastasis of NET.

(16) Total bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).

(17) Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.

Note: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B) is acceptable if the participant otherwise meets entry criteria.

(18) Participants with second degree or higher atrioventricular block, arrhythmia that requires treatment, or other severe heart disease.

(19) QTc >450 msec for male participants or QTc >470 msec for female participants or QTc >480 msec in participants with bundle branch block.

Note A: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.

Note B: The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the study.

(20) Participants who have to receive prohibited drugs or therapies stipulated by the study protocol from the date that informed consent was obtained to the observation for 48 weeks after the first administration (or withdrawal).

(21) Participants suffering from alcoholism or drug abuse, or participants who have a history of it.

(22) Any other medical condition that could jeopardise the safety of the participant or the assessment of efficacy during the study, as assessed by the investigators or sub-investigators.

5.3 Lifestyle Considerations

Due to the potential interference with the assay for 5-HIAA, participants will be instructed not to eat bananas, pineapple, plums, walnuts, eggplant, tomatoes, chocolate or avocado during the urine collection period and the 72 hours prior to urine collection at Day 1, W12, W24, W36, W48 (and W72 for participants continuing in the independent injection period) (see Section 8.6).

Participants will be required to fast for at least 6 hours before all clinical laboratory safety tests.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, reason for screen failure, eligibility criteria and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened; the exception being if they have symptomatic cholelithiasis (according to exclusion criterion (14) that has been successfully operated on after screening. Rescreened participants should be assigned a new participant number. A participant who is rescreened is

required to sign another ICF if the rescreening occurs more than 4 weeks from the previous ICF signature date. The informed consent process is described in Appendix 10.1.3.

5.5 Criteria for Temporarily Delaying Enrolment/Study Intervention Administration

Not applicable. There are no criteria for temporarily delaying enrolment or study intervention administration.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention Administered

All participants will receive a fixed dose of lanreotide Autogel 120 mg by deep subcutaneous injection every 28 days during the study. There is an allowed window of ±3 days for each injection. Details of study intervention are provided in Table 3.

Table 3 Study Intervention Administered during the Study

Intervention name	Lanreotide Autogel
Type	Drug
Description	White to yellowish white semi solid (gel)
Dose formulation	Sustained-release injection
Unit dose strength	120 mg lanreotide (equivalent to 0.246 mg/mg of lanreotide concentration)
Dosage level	120 mg every 28 days
Route of administration	Deep subcutaneous injection
Use	Experimental
IMP and AMP/NIMP	IMP
Sourcing	Provided centrally by the sponsor (Ipsen PharmSciences, 17-20 rue Ethe Virton, 28100 Dreux, France).
Packaging and labelling	Study intervention will be provided in a prefilled syringe product with needle in a laminated package. Each package will be labelled for clinical study use as specified in the pharmacy manual. The label will include, at a minimum: a unique identifier (study intervention number), lot number, content, dose, storage conditions and name & address of sponsor.
Storage requirements	2 to 8°C, in the original airtight packaging, avoiding thawing. The laminated package should be taken out from the refrigerator approximately 30 minutes before administration. It must not be opened until immediately before administration.

Abbreviations: AMP=auxiliary medicinal product; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product

In the main study period, participants will receive 48 weeks of intervention with lanreotide Autogel (12 injections; Day 1 to W44). Injections will be made in the superior external quadrant of the buttocks by the investigator or designee.

Approximately five participants will continue in the independent injection period. A further 24 weeks of intervention with lanreotide Autogel (six injections) will be independently administered. The first injection at W48 will be performed at the study site (under medical supervision) for training purposes. At W52 and W56, the second and third injections may also be performed at the study site for training purposes or may be performed at home, if no further training is needed in the opinion of the investigator. At W60, W64 and W68, the fourth, fifth and sixth injections will be performed at home or at the study site. Independent injections will be made in the upper outer thigh.

The injection site should be alternated between the right and left side between injections. The injection site should be carefully examined to avoid repeated injection at the same site.

Immediately before administration, the prefilled syringe should be taken out from the laminated package. The prefilled syringe should be removed from its tray, the cap of the needle removed, and study intervention injected.

The syringe and laminated package of the used study intervention should be discarded according to the study site's standard procedure for discarding medical waste.

6.2 Preparation, Handling, Storage and Accountability

Further guidance and information for the receipt, preparation, management and disposal/return of the study intervention are provided in the "Investigational Medicinal Product Handling Manual".

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants screened in the study and who meet the eligibility criteria may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, disposal and record maintenance (i.e. receipt, reconciliation and final disposition records).
- At each dispensation (at scheduled and unscheduled visits, if applicable), study intervention number(s) will be assigned by the Interactive Voice/Web Response System (IVRS/IWRS). The IVRS/IWRS will also manage all logistical aspects of the study intervention (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the investigator, study site coordinators and project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IVRS/IWRS reference manual provided to each study site. In case of technical or dispensation queries, a 24-hour helpline is available. If a participant discontinues the study before any intake of study intervention, his/her assigned study intervention number(s) will not be reused.
- In addition to the information provided in the IVRS/IWRS, study intervention accountability paper records will be maintained by the investigator.
- The sponsor will provide guidance on the destruction of unused study intervention. If destruction is authorised to take place at the investigational site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented.

6.3 Measures to Minimize Bias: Randomisation and Blinding

6.3.1 Randomisation

This is a nonrandomised study. All participants who fulfil the inclusion/exclusion criteria will receive lanreotide Autogel 120 mg.

6.3.2 Maintenance of Blinding

This is an open-label study therefore no procedures for blinding are applicable. All participants will receive the same study intervention. Note: only the independent central reviewers making tumour assessments will be blinded to certain participant baseline and response information (see Section 8.1.1).

6.4 Study Intervention Compliance

6.4.1 Main Intervention Period

In the main study period, participants will receive all doses of study intervention at the study site directly from the investigator or designee. The date and time of each dose and the injection site (right/left) will be recorded in the source documents and case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.4.2 Independent Injection Period

Participants continuing into the independent injection period will receive a further six doses of study intervention. The first will be independently administered at the study site under medical supervision. The second and third doses will either be independently administered at the study site under medical supervision or at home. The remaining three doses will be independently administered at home. Independent administration may be performed by the participant or their partner.

- For injections performed at the study site, the date and time of each dose and the injection site (right/left) will be recorded in the source documents and CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff.
- For injections performed at home, the date and time of each dose and the injection site (right/left) will be recorded in the participant diary. Compliance with study intervention independent administration will be assessed at W72/EOSI by review of the diary and direct questioning and documented in the source documents and CRF.

A record of the quantity of lanreotide Autogel prefilled syringes dispensed and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates and any deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

6.5 Dose Modification

Not applicable. No dose modifications are to be performed in the study.

6.6 Continued Access to lanreotide Autogel 120 mg after the End of the Study

The participants will not receive any additional study intervention following the end of the study. Based on GEP-NET clinical management guideline, there are subsequent therapy options for GEP-NET in routine clinical practice. Participants will be treated according to investigator's judgment.

6.7 Treatment of Overdose

For this study, any dose of study intervention greater than that specified in the protocol (120 mg per deep subcutaneous injection) will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose. Appropriate treatment of overdose of study intervention will be determined by the investigator according to the characteristics of the events and will be recorded in the CRF. An event resulting from an overdose of the study intervention is not considered as serious unless it meets the definition of an SAE.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.

- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be discontinued.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until lanreotide can no longer be detected systemically (at least 28 days).
- Document the quantity of the excess dose as well as the duration of the overdose. See Appendix 10.3.1 for reporting requirements concerning overdose.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements), therapy or procedure that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Prohibited Concomitant Medications, Therapies and Procedures

See Section 5.2 for medications which would result in exclusion from the study.

The concomitant medications, therapies or procedures which are not permitted during this study are:

- Interferon, radionuclide (other than that used for imaging or SSTR scintigraphy), chemotherapy or chemoembolisation, radiofrequency ablation or cryoablation
- Any somatostatin analogues other than study intervention
- GH antagonist
- Cyclosporin
- mTOR inhibitor, MTK inhibitors
- Tumour resection

6.8.2 Rescue Medication

No rescue medications are specified for the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. An early discontinuation visit (W48/EOSI/ED or W72/EOSI/ED depending on whether the study intervention discontinuation occurs in the main intervention period or independent injection period) should be conducted if study intervention is permanently discontinued (see the SoA (Table 1) for data to be collected at the time of study intervention discontinuation).

Participants who discontinue study intervention but have not withdrawn from the study must be followed for survival data (according to the post-intervention survival follow-up schedule in Table 1) until death or within 4 weeks after the last W48 visit of the last participant in the main intervention period or within 4 weeks after the last W72 visit of the last participant in the independent injection period (unless the participant has specifically withdrawn consent for any further contact).

If participants are lost to follow-up, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Participants meeting any of the following criteria should permanently discontinue study intervention:

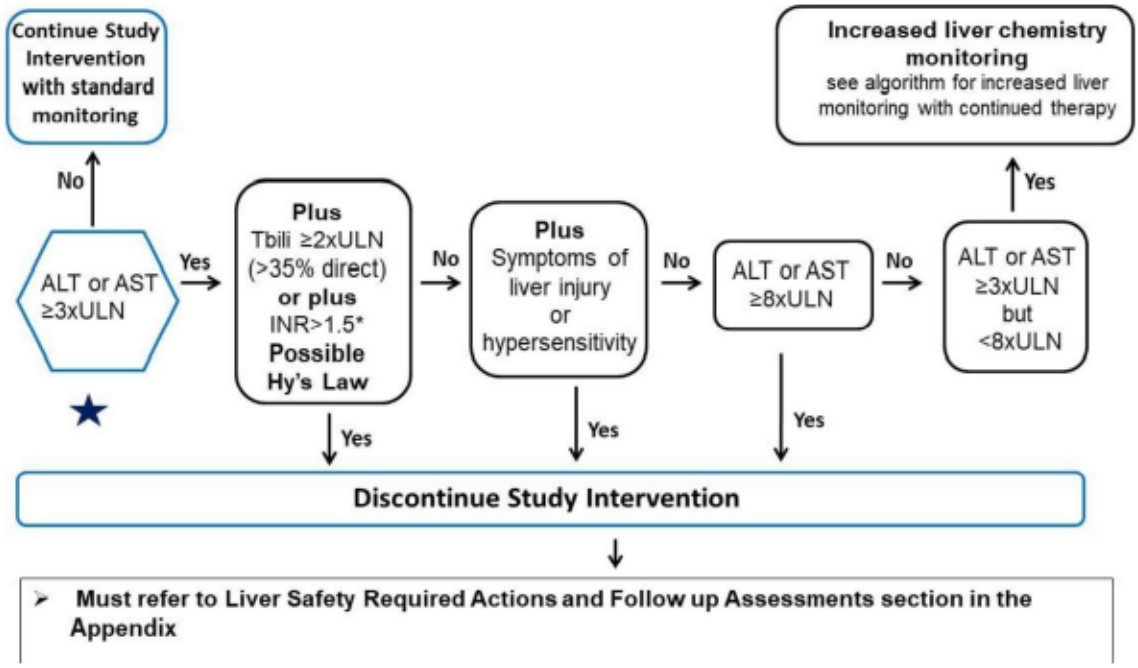
- Death.
- Disease progression.
- Unacceptable toxicity, including liver injury meeting the criteria in Section 7.1.1 (unless rechallenge is considered appropriate, see Section 7.1.4) and cardiac changes meeting the stopping criteria in Section 7.1.2.
- Changes in the condition or intercurrent illness making continuation of study intervention unacceptable in the investigator's opinion.
- Receipt of an alternative anticancer therapy for the study indication.
- Significant protocol deviation or major noncompliance with study procedures making the participant unsuitable for further study intervention administration.
- Is retrospectively found not to have met all eligibility criteria (see Section 5.1 and Section 5.2) and the investigator considers the participant would not derive benefit due to this.
- Pregnancy (see Section 8.3.6).
- Withdrawal of consent for study intervention but still providing consent for follow-up.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the stopping criteria conditions outlined in the algorithm in Figure 2 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in the best interest of the participant. The required follow-up assessments are provided in full in Appendix 10.5.1.

If increased liver chemistry monitoring is required whilst continuing study intervention according to Figure 2, then the algorithm in Figure 3 should be followed. The required follow-up assessments are provided in full in Appendix 10.5.2.

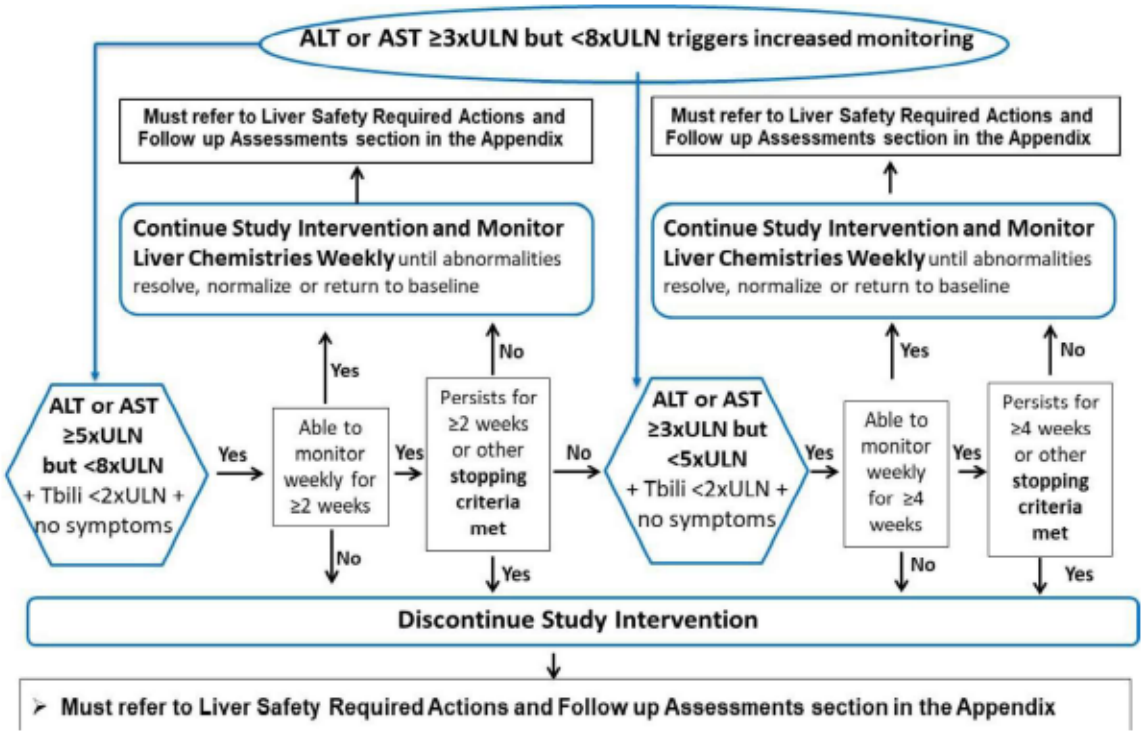
Figure 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase, INR=international normalised ratio; Tbili = Total bilirubin; ULN=upper limit of normal

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 10.5.1

Figure 3 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT or AST ≥3×ULN but <8×ULN



Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase, INR=international normalised ratio; Tbili = Total bilirubin; ULN=upper limit of normal

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 10.5.2

7.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcB or QTcF (as determined prior to initiation of the study)) after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant without underlying bundle branch block who meets either of the following will be withdrawn from study intervention:

- QTc >500 msec
- Change from baseline of QTc >60 msec

Discontinuation criteria for participants with underlying bundle branch block are provided in Table 4.

Table 4 QTc Study Intervention Discontinuation Criteria for Participants with Underlying Bundle Branch Block

Baseline QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
<450 msec	>500 msec
450 to 480 msec	≥530 msec

7.1.3 Criteria for Temporary Discontinuation

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, study intervention administration may be temporarily discontinued depending on the participant clinical presentation. In some cases, the investigator may request that a participant be retested before the intervention administration is resumed.

Study intervention should also be temporarily discontinued in case of:

- Severe unremitting gastrointestinal intolerance: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 diarrhoea (increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living) or vomiting (≥6 episodes (separated by 5 minutes) in 24 hours; tube feeding, total parenteral nutrition or hospitalisation indicated) despite optimal antidiarrheal or antiemetic treatment.
- Poorly controlled diabetes mellitus: NCI CTCAE Grade ≥4 hyperglycaemia (blood glucose >500 mg/dL, >27.8 mmol/L) that does not resolve to CTCAE Grade ≤2 (fasting glucose ≤250 mg/dL, ≤13.9 mmol/L) within 14 consecutive days after starting optimal antidiabetic treatment.
- Pancreatitis: NCI CTCAE Grade ≥3 amylase (>2×ULN) or lipase (>2×ULN) with symptoms, or for >7 consecutive days without symptoms.
- Any other AE or lesser severity of the AEs listed above that, in the opinion of the investigator, could jeopardise the participant's safety.

7.1.4 Restart/Rechallenge

7.1.4.1 Study Intervention Restart or Rechallenge after Liver Stopping Criteria Met

A participant who meets liver chemistry stopping criteria cannot restart study intervention. The participant must permanently discontinue study intervention and may continue in the study for protocol-specified assessments.

7.1.4.2 Study Intervention Restart of Rechallenge after other Criteria for Temporary Discontinuation Met

If any of the criteria for temporary discontinuation of study intervention outlined in Section 7.1.3 are met, the investigator should assess whether restart/rechallenge is appropriate in the event of recovery, considering the assessment of the relationship to study intervention, underlying disease, intercurrent illness or concomitant medications and the overall benefit/risk for the participant. If restart/rechallenge is not assessed to be appropriate, study intervention should be permanently discontinued.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit (W48/EOSI/ED or W72/EOSI/ED as applicable) should be conducted. See the SoA (Table 1) for data to be collected at the time of study discontinuation.
- The reason for discontinuation will be recorded in the CRF.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.

- If the participant withdraws consent, it should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from follow-up. Participant data and biological samples collected up to the date of consent withdrawal will be included in the analyses.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Study site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants who received study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 10.1.9.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (see Table 1). Protocol waivers and exemptions are not allowed. Additional unscheduled visits or procedures may be performed at the discretion of the investigator (e.g. for safety purposes).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.

Screening will be performed in the 4 weeks prior to the first dose of study intervention. No study related procedures will be performed until the participant has provided written informed consent by signing the ICF (see Appendix 10.1.3).

- The following will be recorded at screening:
  - Demographic information.
  - Disease history (date of diagnosis, primary NET site, NET grade (Ki67 index or mitotic counts per 10 HPF (High Power Field; 400×Microscope Magnification per field for NET), presence or absence of SSTR, presence or absence of NET-related symptoms and tumour classification, NET size and presence or absence of progression.
  - History of previous treatment of NET.
  - Complete medical history, including evaluation for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, haematological, immunological, dermatological, ophthalmological, psychiatric, genitourinary, and surgical history and any other diseases or disorders.
  - ECOG performance status.
  - Other prior (within 3 months before screening) and concomitant medications (see Section 6.8).
- The following will be performed at screening:
  - CT/MRI scan and tumour assessment (see Section 8.1.1).
  - Safety assessments: physical examination, vital signs, 12-lead ECG, gallbladder echography and clinical safety laboratory tests (see Section 8.2.1 to Section 8.2.5).
  - Pregnancy test for WOCBP (see Section 8.2.6).
  - Follicle stimulating hormone (FSH) test (if required to determine postmenopausal status; see Appendix 10.4.1).
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (see Table 1).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The procedures and assessments to be performed in the intervention period and independent injection period are described in Section 8.1 (efficacy), Section 8.2 and Section 8.3 (safety),

Section 8.6 (biomarkers) and Section 8.7 (immunogenicity). All assessments should be performed before study intervention administration on study visit days.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 210 mL for the main study (or 260 mL for participants continuing in the independent injection period).
- Repeat or unscheduled samples may be taken for safety reasons or in case of technical issues with the samples.
- Early discontinuation visit procedures should be performed (W48/EOSI/ED or W72/EOSI/ED as applicable) for participants who discontinue the study.

8.1 Efficacy Assessments

8.1.1 Tumour Assessment

Diagnostic imaging will be performed at screening (baseline), W12, W24, W36 and W48. A further scan will be performed at W72 for participants continuing in the independent injection period.

A CT scan is the preferred method of tumour measurement and will be used whenever possible. Magnetic resonance imaging may be used but should be considered as an alternative method. In order to ensure comparability between tumour assessments, the same method of tumour measurement must be used throughout the study for each participant, wherever possible.

At screening (baseline), the following should be performed:

- CT or MRI of the neck, chest, abdomen and pelvis in the 4 weeks before the start of study intervention.
- CT or MRI of the head, bone scintigraphy or fluorodeoxyglucose-positron emission tomography (FDG-PET), CT or MRI of bone lesions before the first dose of study intervention.

At W12, W24, W36 and W48 (and W72, if applicable) the following should be performed:

- Diagnostic imaging test (CT or MRI) of the head.

  If the screening test reveals a lesion in the brain or pituitary gland or if clinically indicated, the same diagnostic imaging test should be repeated.
- Diagnostic imaging test (CT or MRI) of the neck, chest, abdomen and pelvis.
- Diagnostic imaging test of bone lesions (bone scintigraphy or FDG-PET, CT or MRI).

  If the screening test revealed a bone lesion or if clinically indicated, assessment should be performed using the same method.

Tumour response will be assessed according to RECIST Version 1.1 [Eisenhauer 2009].

Data will be reviewed locally by the local radiologist/investigator at the study site and also saved in digital format and sent for BICR according to instructions in the Imaging Manual. In order to prevent the disclosure of personal details, participant information should be anonymised in a manner that individuals cannot be identified when submitting image data. The BICR will be performed as specified in the Independent Review Charter.

The local assessment will be used for the clinical management of the study participant (e.g. whether to discontinue due to disease progression). participant management will be at the investigator's discretion.

8.1.2 Clinical Progression

The investigator will record any clinical/biological signs of tumour progression and, where applicable, additional tumour assessments should be performed to determine radiological progression following the procedure in Section 8.1.1.

8.1.3 Neuroendocrine Tumour Clinical Symptoms

The presence or absence of endocrine symptoms of NETs (e.g. flushing, diarrhoea, abdominal pain, weakness, heartburn, nausea, vomit, sweating, tremor, palpitation, or erythema) will be assessed by the investigator at screening.

In participants with symptoms of NETs at screening, a baseline assessment of the symptoms experienced in the last 4 weeks will be performed by questioning before study intervention administration at Day 1. These symptoms will be recorded in the CRF.

For participants with diarrhoea and/or flushing at baseline, a diary will be dispensed at Day 1 and the participants will be instructed to record the number of diarrhoea and/or flushing episodes per day and any medications taken to treat these symptoms during the intervention period (and the independent injection period, if applicable). At each visit, the diary will be reviewed and collected by the investigator, and a new diary will be dispensed. The investigator will enter information of diarrhoea and/or flushing determined to be associated with NETs in the CRF (the frequency of diarrhoea and/or flushing, the severity graded upon CTCAE 5.0 and the use of any rescue medication).

For participants with other symptoms at baseline, these symptoms will be assessed by the investigator by questioning at each visit during the intervention period (and the independent injection period, if applicable). The investigator will enter the information of the symptoms determined to be associated with NETs in the CRF (disappeared, reappeared, improved, aggravated or no change, severity graded upon CTCAE 5.0 and the use of any rescue medication).

8.1.4 Circulating Biomarkers

Biomarker assessments are described in Section 8.6.

8.1.5 Quality of Life

Participant reported outcomes will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC QLQ-C30) at baseline (Day 1), W12, W24, W36 and W48 (see Appendix 10.6). A further assessment will be performed at W72 for participants continuing in the independent injection period. The questionnaires will be provided in the participant's local language and should be completed under the same conditions throughout the study, wherever possible.

The questionnaire form should be completed before any assessments or procedures, including study intervention administration on the visit day and before any consultation with the investigator in relation to disease status.

Completed questionnaires will be reviewed by the investigator or designated study site personnel. Investigators must not encourage the participants to change any responses.

8.1.6 Survival Status

The date of death or last known to be alive date will be recorded to determine OS. Whether the death was related to NET (if known) will also be recorded. For participants that are lost to follow-up or withdraw consent, attempts to determine survival status should be made by access to public records, as permitted by local law.

After the end of study assessments, a telephone call will be used to collect survival status (date of contact, alive/dead, date of death, whether death is related to NET if known) and subsequent therapies (dose, unit, frequency, start and stop date) started since the previous contact.

The data will be collected within 4 weeks after the last participant in the main study reaches W48 or the day of discontinuation.

The data will be also collected within 4 weeks after the last participant enrolled in the independent injection period reaches W72 or the day of discontinuation.

8.1.7 Healthcare Professional versus Independent injection

Participants continuing in the independent injection period will be asked if they prefer independent injection or HCP injections at the end of the independent injection period (W72).

8.2 Safety Assessments

Adverse event recording and reporting is detailed in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

A complete physical examination will be carried out by the investigator or medically qualified designee at screening, baseline (Day 1) and subsequent visits to the study site in the intervention period (and independent injection period if applicable) as per Table 1.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any clinically significant abnormalities/changes from baseline in accordance with the NCI CTCAE Version 5 [NCI CTCAE 2017] should be recorded as an AE at the discretion of the investigator.

8.2.2 Vital Signs

Vital signs will be measured at screening, baseline (Day 1) and subsequent visits to the study site in the intervention period (and independent injection period if applicable) as per Table 1.

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
  - Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs are to be taken before blood collection if performed the same day.
- Any clinically significant abnormalities/changes from baseline in the opinion of the investigator in accordance with NCI CTCAE Version 5 [NCI CTCAE 2017] should be recorded as an AE at the discretion of the investigator.

8.2.3 Gallbladder Echography

Gallbladder echography will be performed in all participants unless they have a documented cholecystectomy. A gallbladder echography will be carried out by the investigator or medically qualified designee at screening, W24 and W48 (plus W72 for participants continuing in the independent injection period).

The presence of lithiasis and sludge will be assessed and recorded (Yes/No) in the CRF.

Unscheduled assessments should be performed at any time if symptoms are thought to be related to gallbladder lithiasis.

Abnormal test findings that result in study intervention discontinuation or require intervention or diagnostic evaluation to assess the risk to the participant, should be recorded as AEs.

8.2.4 Electrocardiograms

- Single 12-lead ECG will be obtained at screening, W24 and W48 (plus W72 for participants continuing in the independent injection period) according to study site standard procedures. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcB or QTcF intervals should be used. Study intervention discontinuation criteria for QTc and any additional readings that may be necessary are specified in Section 7.1.2.
- Any clinically significant abnormalities/changes from baseline in the opinion of the investigator in accordance with NCI CTCAE Version 5 [NCI CTCAE 2017] should be recorded as an AE at the discretion of the investigator.

8.2.5 Clinical Safety Laboratory Assessments

Clinical laboratory safety tests to be performed will be performed at screening, baseline (Day 1) and W24 and W48 (plus W72 for participants continuing the independent injection period).

- The list of protocol-required clinical safety laboratory tests to be performed is provided in Table 7. All protocol-required laboratory tests must be conducted in accordance with the Laboratory Manual and the SoA (Table 1).
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or period of time after the last dose of study intervention judged reasonable by the investigator should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
- If laboratory values from nonprotocol specified laboratory tests performed at the study site's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.6 Pregnancy Testing

Refer to Inclusion Criterion (7) in Section 5.1 for pregnancy testing entry criteria and Table 1. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy in a participant at any time during the study.

8.3 Adverse Events (AEs) and Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 10.3.1 and Appendix 10.3.2, respectively.

Adverse events (including injection site-related reactions) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected continuously from obtaining informed consent until the EOSI visit (28 days after the last dose of study intervention) as specified in the SoA (Table 1). This includes medical occurrences that begin before the start of study intervention.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Recording and Reporting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports is provided in Appendix 10.3.3.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness of the event, as indicated in Appendix 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.3.

8.3.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.6 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the signing of the ICF and until 90 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate forms (SAE form in the CRF and Drug Exposure Form – paper form) and submit to the sponsor within 24 hours of learning of the pregnancy (female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner)).
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention (see Section 7).

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Disease-related events (DREs) related to NET clinical symptoms (in participants with functional NETs) or disease progression (including metastases) should be recorded as part of the efficacy evaluation (see Section 8.1.1 and Section 8.1.3) and not as AEs/SAEs:

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR
- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8 Adverse Events of Special Interest

Not applicable. No AEs of special interest have been defined for this study.

8.3.9 Reporting of Study Intervention Errors including Misuse/Abuse

- Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a study intervention (medicinal product) while under the control of a healthcare professional, participant or consumer (European Medicines Agency (EMA) definition).
- Misuse refers to situations where the study intervention is intentionally and inappropriately used not in accordance with the protocol.
- Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Study intervention errors and uses outside of what is foreseen in the protocol will be recorded in the CRF irrespective of whether associated with an AE/SAE or not. It will also be documented in the AE section of the CRF if associated with an AE. It will be reported in the safety database only if associated with an SAE.
- Misuse or abuse will be collected and reported in the safety database, whether associated or not with an AE/SAE, within 24 hours of investigator's awareness.

8.4 Pharmacokinetics

Not applicable. Pharmacokinetics are not evaluated in this study.

8.5 Genetics and/or Pharmacogenomics

Not applicable. Genetics are not evaluated in this study.

8.6 Biomarkers

Full details on processes for collection, storage, shipment to the central laboratory and destruction of samples can be found in the Laboratory Manual.

Blood and urine samples will be collected at baseline (Day 1), W12, W24, W36 and W48 (plus W72 for participants continuing in the independent injection period) to measure circulating CgA, 5-HIAA and other biomarkers.

Chromogranin A is expressed in 80 to 90% of all GEP-NETs and hence in participants in this study. Chromogranin A determination is also useful for staging, prognosis and follow up, since the serum concentration correlates to the tumour mass. 5-hydroxyindoleacetic acid, the major metabolite of serotonin, is of value for diagnosis of NETs and correlates with severity of carcinoid syndrome.

- The following blood samples will be taken, and sampling dates and times will be recorded in the CRF:
  - A 5 mL sample will be taken to assess CgA.
  - A 5 mL sample might be taken to assess other biomarkers (e.g. gastrin, glucagon and insulin, if applicable).
- A 24-hour urine collection at home prior to each scheduled visit is required to assess 5-HIAA. Participants will be provided with a receptacle by the study site for this purpose. The collection period will begin once the participant has emptied his/her bladder (not into the collection receptacle) after waking up on the morning of the day prior to the visit. This time should be recorded on the receptacle.

The participant will be instructed to collect all their urine in the receptacle for a period of 24 hours and bring the sample to the scheduled visit. Due to the potential interference with the

assay for 5-HIAA, participants will be instructed not to eat bananas, pineapple, plums, walnuts, eggplant, tomatoes, chocolate or avocado during the urine collection period and the 72 hours prior to each collection. At the study visits the investigator will question the participant about his/her diet over the collection period. At the end of the collection period the participant should empty his/her bladder as fully as possible into the collection receptacle and record the time.

The collected urine will be given to the investigator (or designee), who will measure the volume of urine collected and record this, along with the start and stop times of the collection period, in the CRF. A sample of the total urine will be taken to be sent for analysis.

In addition, urinary creatinine will be analysed in order to assess compliance with the 24-hour collection period.

Samples will be analysed using validated methods.

8.7 Immunogenicity Assessments

Putative antibodies to lanreotide will be evaluated in serum samples collected from all participants at baseline (Day 1), W24 and W48. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

At each timepoint, 5 mL blood samples will be collected, and the sampling data and time recorded in the CRF. Full details on processes for collection, storage, shipment to the central laboratory and destruction of samples can be found in the Laboratory Manual.

The determination of putative anti-lanreotide antibodies will be evaluated using an ElectroChemiLuminescent assay (ECLA) validated method.

8.8 Health Economics or Medical Resource Utilisation and Health Economics

Health economics will be evaluated in the five participants continuing in the independent injection period. Participants will be interviewed at the W48 and W72 visits and the following information collected:

- Indirect costs will be assessed using a bespoke questionnaire (see Appendix 10.7):
  - Travel time to hospital visits.
  - Distance between participant's home and hospital clinic.
  - Mode of transport to hospital/clinic visits (i.e. car, train bus, etc.)
  - Cost of travel to a hospital/clinic visit for treatment - participant and friend/family member, if appropriate.
  - Time spent at hospital.
  - Main activities missed due to attending hospital appointments for treatment (i.e. paid work, childcare, volunteering).
  - Impact of switch in administration setting on main daily activities.
- Work-related productivity (where relevant) will be assessed using the Work Productivity and Activity Questionnaire: General Health (WPAI:GH) (see Appendix 10.6):
  - Hours of work missed due to problems associated with GEP-NETs.
  - Impact of health on work productivity.
  - Impact of health on ability to carry out everyday activities (other than work).
- In addition, the impact of switch in administration setting on overall ability to work will be assessed using a bespoke questionnaire (Appendix 10.8).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The null hypothesis H0: P≤40% versus the alternative hypothesis H1: P>40%, where P is the CBR at the end of 24 weeks of study intervention. The threshold CBR at W24 was defined as 40%.

9.2 Sample Size Determination

Approximately 51 participants will be enrolled to achieve 43 receiving study intervention in the main study period and 36 participants evaluable for CBR at W24. Based on Chinese epidemiology, it is expected to have the relevant representation of all types of GEP-NETs in the Chinese population, including Pan-NET and GI-NET.

Note: "Enrolled" means a participant's, or their legally authorised representative's, agreement to participate in a clinical study following completion of the informed consent process.

The expected CBR at W24 was set to 64% based on the results from Japanese Study ITM-014N-001 and global pivotal Study 2-55-52030-726 (CLARINET; NCT00353496). The threshold CBR at W24 was defined as 40% based on Japanese Study ITM-014N-001 and medical expert's opinions. When a statistical test was performed for a null hypothesis with one-sided type I error of 2.5%, a minimum sample size required to yield a power of at least 80% would be 36 participants. Considering a 15% drop-off rate, 43 participants would be necessary for the primary efficacy evaluation of CBR at W24.

To provide clinical experience of independent injection in Chinese participants, approximately five qualified participants (having a positive benefit/risk ratio) will have independent injection of lanreotide Autogel during the 24 weeks of the independent injection period (assuming 10 to 25% eligible participants after 48 weeks of intervention in the main study will continue to receive independent injection). The aim is to achieve five participants that have been trained to perform independent injections and are considered able to independently administer lanreotide from the investigator.

9.3 Analysis Sets

For the purposes of analysis, the analysis sets in Table 5 are defined:

Table 5 Analysis Set Definitions

Participant Analysis Set	Description
Enrolled set	All participants who sign the ICF
Safety set	All participants who receive at least one dose of study intervention. If there is any doubt whether a participant was treated or not, they will be assumed treated for the purposes of analysis
ITT	All participants who receive at least one dose of study intervention
mITT	All participants in the ITT having at least W24 data recorded for the primary efficacy endpoint
PPS	All participants in the mITT who did not experience any major protocol deviations that may interfere with the efficacy evaluation
Immunogenicity set	All participants in the ITT who have baseline and at least one postbaseline anti-lanreotide antibody result
Independent injection set	All participants who receive the study intervention by independent injection

Abbreviations: ICF=informed consent form; ITT=intention-to-treat; mITT=modified intention-to-treat; PPS=per-protocol set; W=week

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Other endpoints as well as demographic, baseline characteristics and disposition will be detailed in the SAP.

Statistical analyses will be performed using Statistical Analysis System® (SAS®) software (Version 9.4 or higher).

Three analyses are planned according to the following data cut-offs:

(1) The first analysis will be performed when all participants complete the first 24 weeks of the main study period. The cut-off date considered for this analysis is the date of the last W24 visit for the last participant. All available data at the time of this data cut-off date will be included in this analysis. The purpose of this analysis is the final analysis of the primary efficacy endpoint, as well as efficacy and safety analyses of the first 24 weeks of the main study period. This analysis will not be considered as an interim analysis because the first 24 weeks of main study period is of primary interest.

(2) The second analysis will be performed when all participants have had the opportunity to complete the main study (W48). The reporting database will include all main study data for all participants enrolled into the study.

(3) The third and final analysis will be performed when the last participant completes the independent injection period. The reporting database will include all independent injection period study data.

9.4.1 General Considerations

9.4.1.1 Analysis Sets

The primary efficacy evaluation will be performed on the intention-to-treat (ITT) set. Supportive analysis of the primary efficacy evaluation will be based on the modified intention-to-treat (mITT) set and the per protocol set (PPS). Secondary analyses will be performed on the ITT set. Supportive analysis of the secondary efficacy evaluation may be based on the PPS. The immunogenicity evaluation will be performed in the immunogenicity set. Safety analyses will be performed on the safety set. Exploratory analyses will be performed on the independent injection set.

9.4.1.2 Participant Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation types will be described in the Protocol Deviation Document and their impact on inclusion in each analysis set for any participant will be specified. The final list of protocol deviations impacting each analysis set will be reviewed during the data review meeting held prior to database lock.

9.4.1.3 Adjustment of Multiplicity

Multiplicity will not be adjusted.

9.4.1.4 Significance Testing and Estimations

The 95% exact confidence intervals for the primary endpoint will be calculated based on the Clopper-Pearson method.

9.4.1.5 Statistical/Analytical Methods

Continuous data will be summarised with the following items: number of participants, median, range, mean and standard deviation, if relevant. Categorical data will be presented in contingency tables with frequencies and percentages of each modality (including missing data modality). To describe time-dependent parameters (PFS, TTP and OS), Kaplan-Meier curves and life tables will be provided. The 95% CI on the median will be given.

9.4.2 Analysis of Primary Endpoint

Point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated for a CBR at W24 (see Table 2).

9.4.3 Analysis of Secondary Efficacy Endpoints

The following analyses will be performed on the secondary efficacy endpoints (see Table 2):

- For time-dependent parameters (PFS, TTP and OS), Kaplan-Meier curves and life tables will be generated, and median with 95% CIs will be calculated at W24 and W48.

  Censoring rules for the PFS and TTP endpoints are shown in Table 6.

Table 6 Censoring Rules for PFS and TTP Endpoints

Situation	Date of Progression or Censoring	Outcome
No baseline radiological assessments	The day of first administration	Censored
Confirmed (documented) PD during the study	Date of radiological assessment showing PD	Event
No death or confirmed PD	Date of last adequate radiological assessment	Censored
Study intervention discontinuation for clinical (unconfirmed) progression	Date of last adequate radiological assessment	Censored
Study intervention discontinuation for toxicity or reason other than confirmed PD, clinical progression or death	Date of last adequate radiological assessment	Censored
New anticancer treatment for GEP-NET started with no confirmed PD beforehand	Date of last adequate radiological assessment before start of new treatment	Censored
Death during the study before confirmed PD	Date of death (PFS)/Date of last adequate radiological assessment (TTP)	Event (PFS)/Censored (TTP)
Confirmed PD after two or more missed radiological assessments	Date of last adequate radiological assessment before missed assessments	Censored
Study intervention discontinuation for other than confirmed PD or death, and no postbaseline radiological assessments	The day of first administration	Censored

Abbreviations: GEP-NET=gastroenteropancreatic neuroendocrine tumours; PD=progressive disease; PFS=progression free survival; TTP=time to progression

The OS will be assessed once the data from the last participant completing the main study are available. Overall survival is defined as the time from the day of first administration to death due to any cause. Participants who are not known to have died at the time of the analysis will be censored. Where possible, post-intervention survival status will be confirmed for all participants that are alive at the last assessment. Any participant who is confirmed to be alive will be censored at this time. Any participant who could not be contacted at this time will be censored at the time that the participant was last confirmed to be alive.

- Proportion of participants who are alive and without tumour progression at W24 and W48 and their 95% CI will be calculated by the Kaplan-Meier method
- Point estimates and exact 95% CIs based on the Clopper-Pearson method will be calculated for the following:
  - CBR at W48
  - ORR at W24 and W48
  - DCR at W24 and W48
- Descriptive statistics will be used to summarise:
  - Change from baseline in NET-related clinical symptoms at W24 and W48
  - Change from baseline in QoL assessment at evaluation points using the EORTC QLQ-C30
  - Change from baseline in CgA and other biomarker(s) in the circulation at W24 and W48.

9.4.4 Analysis of Exploratory Efficacy Endpoints

Descriptive statistics will be used to summarise the exploratory efficacy endpoints (see Table 2) for participants continuing in the independent injection period:

- Proportion of participants preferring independent injection over HCP injections at W72
- Participant-reported indirect costs (e.g. transport costs) at W48 and W72
- Participant-reported work productivity at W48 and W72
- The antitumour effect (assessed by imaging) at W72
- Change from baseline in NET-related symptoms control at W72 (if applicable)
- Change from baseline in CgA and other biomarkers in the circulation at W72
- Change from baseline in QoL at W72.

9.4.5 Safety Analyses

Adverse events reported by investigators using the NCI CTCAE classification (Version 5) will be coded using MedDRA (latest version).

A Treatment Emergent Adverse Event (TEAE) is defined as any AE that occurs during the active phase of the study if:

- It was not present prior to receiving the first dose of study intervention, or
- It was present prior to receiving the first dose of study intervention but the intensity increased during the active phase of the study.

Summary incidence tables of all TEAEs will be provided by MedDRA system organ class and preferred term. In addition, summary tables will be further presented by worst associated NCI CTCAE Grade and relationship to study intervention. Listings of SAEs and TEAEs leading to withdrawal will be provided.

Summary statistics (mean, median, standard deviation and range as appropriate) will be presented for vital signs, ECG variables and clinical safety laboratory tests at each assessment, with change from baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented for the number and percentage of participants with low, normal or high values and normal or abnormal results.

Haematological and biochemical toxicities will be graded according to the NCI CTCAE criteria, where available. The NCI CTCAE Grade 3 and 4 haematology and biochemistry variables by participant and by cycle will be listed. For white blood cells, neutrophils, platelets and haemoglobin, with associated Grade 3 or 4 toxicities, nadir and day to nadir will be calculated.

9.4.6 Subgroups Analyse(s)

Descriptive subgroup analyses of the primary efficacy variable will be performed on the primary tumour type.

Further details will be provided in the SAP.

9.5 Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate sponsor medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF and any participant recruitment materials, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study site and adherence to applicable local regulations, ICH guidelines and the IRB/IEC requirements/procedures.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

- The ICF(s) and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws and approved prior to use as described in Appendix 10.1.1.
- The investigator or his/her authorised representative will explain to the participant (or their legally authorised representative) the nature and objectives of the study and possible risks associated with the participation. They will answer all questions regarding the study.

- Participants (or their legally authorised representative, when applicable) must be informed that their participation is voluntary.
- The investigator or his/her authorised representative will obtain written informed consent from each participant (or their legally authorised representative, when applicable) before any study-specific procedure is performed. The investigator will retain the original of each participant's signed ICF.
- A copy of the signed ICF(s) must be provided to the participant (or their legally authorised representative).
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- All participants will provide written informed consent for the main study period prior to screening procedures being performed. Participants continuing into the independent injection period will be required to provide further written informed consent for the additional procedures before entering the independent injection period.
- If applicable, participants must be re-consented to the most current version of the ICF during their participation in the study.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 4 weeks from the previous ICF signature date.
- The ICF will contain a separate section that addresses the use of all data for optional future research. These data may only be used for scientific health-related research to find new ways to detect, treat, prevent or cure health problems. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. A specific consent will be required to document a participant's agreement to allow any data to be used for future research.
- A specific ICF for pregnant partner must be used before collecting details on the pregnancy and its outcome (see Section 8.3.6).

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Not applicable. There will be no oversight committees in the study.

10.1.6 Dissemination of Clinical Study Data

- The sponsor seeks to publish the results of its clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.

- Protocol and result summary will be made publicly available on the United States (US) Clinical Trials Registry (ClinicalTrials.gov). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation (chinadrugtrials.org.cn).
- A clinical study report (CSR) will be prepared if at least one participant has signed informed consent and received study intervention, regardless of whether the study is completed or prematurely terminated. The CSR may be disclosed according to regulatory requirements.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded in a CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections, make all documents available for audit and inspection and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined in the integrated oversight plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organisations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH GCP guidelines, local regulations, or as specified in the study agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the study site.
- Data entered in the CRF or that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The investigator must maintain accurate documentation that supports the information entered in the CRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

10.1.9.1 First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

10.1.9.2 Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination:
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or ICH GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Safety Tests

- The tests detailed in Table 7 will be performed by the local laboratory according to the timepoints in the SoA (Table 1).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-Required Clinical Safety Laboratory Tests

Test	Parameters Assessed	
Pregnancy testing	Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential)[a]	
Other screening tests	FSH (as needed in women of non-childbearing potential only)	
Haematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, and differential white blood count (neutrophil, eosinophil basophil, monocyte and lymphocyte)	
Biochemistry	Liver function[b]:	Total protein, albumin, total and direct bilirubin, ALP[c], ALT, AST, GGT
	Renal function:	Blood urea nitrogen, creatinine
	Pancreatic function:	Amylase, lipase
	Lipid profile:	LDL cholesterol, HDL cholesterol, triglyceride
	Electrolytes:	Sodium, potassium, chloride
	Minerals:	Calcium, inorganic phosphate,
	Miscellaneous:	Fasting glucose[d], HbA1c, lactate dehydrogenase
Endocrinology	FT3, FT4, TSH, and prolactin	
Coagulation	aPTT, PT, INR	
Urinalysis[e]	Protein, glucose, urobilinogen and occult blood	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; FSH=follicle stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; HbA1c=glycated haemoglobin; hCG=human chorionic gonadotropin; HDL=high density lipoprotein; INR=international normalised ratio; IRB/IEC=institutional review board/independent ethics committee LDL=low density lipoprotein; PT=prothrombin time; TSH=thyroid stimulating hormone; ULN=upper limit of normal

a Urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC
b Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 and Appendix 5. All events of ALT or AST ≥3×ULN and total bilirubin ≥2×ULN (>35% direct bilirubin) or ALT or AST ≥3×ULN and INR >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to sponsor in an expedited manner
c If alkaline phosphatase is elevated, consider fractionating
d The participant must not have eaten any food for at least 6 hours prior to blood sample being taken
e Local urine dipstick testing will be standard for the protocol unless serum testing is required by local regulation or the IRB/IEC.

Investigators must document their review of each clinical safety laboratory report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse. **A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection** must be reported as serious (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation)).

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required forms.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the NCI CTCAE Version 5 [NCI CTCAE 2017] grading system.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs. • If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via paper
• The study site will use the paper SAE data collection tool to report the event within 24 hours of awareness of the event. • The study site will email the SAE form or fax the cover sheet and SAE form to the sponsor. The same will apply to any SAE follow up form. • Contacts for SAE reporting can be found on the SAE form and the cover sheet.

10.4 Appendix 4: Contraceptive and Barrier Guidance

The following guidance is adapted from the Clinical Trials Facilitation Group [CTFG 2014].

10.4.1 Definitions

Women in the following categories are considered WOCBP (fertile):

(1) Following menarche

(2) From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause:
  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement [insert threshold if required (>40 IU/L or mIU/mL) or remove to allow for flexibility with different local thresholds for defining postmenopausal state] is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonoestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilisation methods (for the purpose of this study) include:
  - Documented hysterectomy.
  - Documented bilateral salpingectomy.
  - Documented bilateral oophorectomy.
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determine eligibility for study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
- Intrauterine device
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*)*

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - Oral
  - Injectable
- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[e]

Abbreviations: CTFG=Clinical Trials Facilitation Group

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly

c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action

d Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception

e Male condom and female condom should not be used together (due to risk of failure from friction)

10.5 Appendix 5: Liver Safety: Suggested Actions, Follow-up Assessments and Study Intervention Rechallenge Guidelines

10.5.1 Stopping Criteria and Follow-up Assessments

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event aetiology. The stopping criteria, actions and follow-up assessments to be performed are shown in Table 8.

Table 8 Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST ≥8×ULN
ALT or AST-increase	ALT or AST ≥5×ULN but <8×ULN persists for ≥2 weeks ALT or AST ≥3×ULN but <5×ULN persists for ≥4 weeks
Bilirubin[a], [b]	ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN (>35% direct bilirubin)
INR[2]	ALT or AST ≥3×ULN **and** INR >1.5
Cannot Monitor	ALT or AST ≥5×ULN but <8×ULN and cannot be monitored weekly for ≥2 weeks ALT or AST ≥3×ULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT or AST ≥3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions, Monitoring, and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study intervention. • Complete SAE CRF as a medically important event[b] • Report the event to the sponsor within **24 hours** • Perform follow-up assessments as described in the Follow up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilise, or return to baseline **MONITORING:** **If ALT or AST ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5:** • Repeat liver chemistry tests (include ALP, ALT, AST, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilise, or return to baseline • A specialist or hepatology consultation is recommended	• Viral hepatitis serology[d] • Obtain serum CPK, LDH, GGT and GLDH, and serum albumin • Fractionate bilirubin, if total bilirubin ≥2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications) • Record alcohol use **If ALT or AST ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5** obtain the following in addition to the assessments listed above [EASL 2019]: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal

If ALT or AST≥3×ULN AND total bilirubin <2×ULN and INR ≤1.5: • Repeat liver chemistry tests (include ALP, ALT, AST, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilises, or return to baseline **RESTART/RECHALLENGE:** • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and sponsor approval is granted • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments	antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James 2009] • Liver imaging (ultrasound, magnetic resonance or CT) to evaluate liver disease • Liver biopsy may be considered and discussed with local specialist if available, for instance: - In participants when serology raises the possibility of autoimmune hepatitis - In participants when suspected drug induced liver injury progresses or fails to resolve on withdrawal of study intervention - In participants with acute or chronic atypical presentation

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; CRF=case report form; CT=computed tomography; DNA=deoxyribonucleic acid; GGT=gamma glutamyl transferase; GLDH=glutamate dehydrogenase; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalised ratio; LDH=lactate dehydrogenase; RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal

a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury

b All events of ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN (>35% direct bilirubin) or ALT or AST ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

c New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

d Includes: Hepatitis A IgM antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive HBsAg) quantitative hepatitis B DNA and hepatitis delta antibody If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of hepatitis D RNA virus (where needed) [Le Gal 2005]

10.5.2 Criteria for Increased Monitoring with Ongoing Study Intervention

Criteria requiring increased monitoring, are shown in Table 9. Study intervention may be continued.

Table 9 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Criteria	Actions
ALT or AST ≥5×ULN and <8×ULN **and** total bilirubin <2×ULN or INR<1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT or AST≥3×ULN and <5×ULN **and** total bilirubin <2×ULN or INR<1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** which can be monitored weekly for 4 weeks.	• Notify the sponsor **within 24 hours** of learning of the abnormality to discuss participant safety Participant can continue study intervention. • Participant must return weekly for repeat liver chemistry tests (ALP, ALT, AST, total bilirubin) until the abnormalities resolve, stabilise, or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Table 8 • If ALT or AST decreases from ALT or AST≥5×ULN and <8×ULN to ≥3×ULN but <5×ULN, continue to monitor liver chemistries weekly • If, after 4 weeks of monitoring, ALT or AST<3×ULN and total bilirubin <2×ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilise, or return to baseline

Abbreviations: Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalised ratio; ULN=upper limit of normal

10.6 Appendix 6: Work Productivity and Activity/General Health Quality of Life Questionnaires

Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*
   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
   _____HOURS

4. During the past seven days, how many hours did you actually work?
   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10.7 Appendix 7: Impact of Treatment Administration Setting on Costs

This section of the survey will ask you questions about the costs, including travel time and personal time, associated with your lanreotide Autogel® treatment at home and in hospital.

Thinking about hospital visits you attended to receive your lanreotide Autogel® injection in hospital, prior to switching to the independent injection:
(at visit W48)

1. If you normally travelled to the hospital, how many kilometers did you travel one-way from your house to the hospital? Please write the estimated number of kilometers as below. If you do not know the exact number kilometers, please provide your best estimate.

___ (Estimated kilometers)

2. When you visited the hospital to receive your lanreotide Autogel® injection, how did you normally travel? Please select the option that best describes how you normally travelled from your home to the hospital If you normally used more than one form of transport, please select the form of transport used for the main (longest in terms of distance) part of your journey.

a. Car (by myself)
b. Car (accompanied by someone else)
c. Train
d. Bus
e. Taxi
f. Walking
g. Bicycle
h. Other

3. If you used public transport, and were accompanied by a friend or family member, how much did they spend on the cost of their journey? Please write the estimated cost as below. Put zero if you did not normally pay a fare.

Total cost of return fare (CNY) ___ (Yuan)

4. If you normally travelled to the hospital or clinic by public transport (i.e. bus or train), what was the approximate cost of the journey (there and back)? Please write the estimated cost as below. Put zero if you did not normally pay a fare.

Total cost of return fare (CNY) ___ (Yuan)

5. If you normally travelled to the hospital or clinic by taxi what was the approximate cost of the journey (there and back)? Please write the estimated cost in the box below. Put zero if you did not normally pay a fare.

Total cost of return fare (CNY) ___ (Yuan)

6. If you normally travelled to the hospital by car and had to pay parking and/or toll fees, how much did these fees amount to? Please write the estimated cost in the box below. Put zero if you did not normally pay a fee.

Parking/toll fees (CNY) ___ (Yuan)

7. When you visited the hospital to receive your lanreotide Autogel® injection, how long did it normally take one-way to travel there from your home? Please write the approximate number of hours and/or minutes as below.

__-__ (Hrs-Mins)

8. When you visited the hospital to receive your lanreotide Autogel® injection, how long did you normally spend there? Please write the approximate number of hours and/or minutes as below.

__-__ (Hrs-Mins)

9. What would you have normally been doing as your usual daily activities if you had not gone to the hospital to receive your lanreotide Autogel® injection? Please select the option that best describes what you would normally be doing as your main activity.

a. Housework
b. Childcare
c. Leisure activities
d. Attending school/university
e. Paid work
f. Volunteering
g. On sick leave
h. Seeking work
i. Other

Thinking about Impact of switch in administration setting on main daily activities:
(at visit W72)

10. How much has your ability to do your usual daily activities changed since switching from hospital to the independent administration of lanreotide Autogel®?

a. Overall ability to do my main activity has improved
b. Overall ability to do my main activity has not changed
c. Overall ability to do my main activity has worsened

10.8 Appendix 8: The Impact of Switch in Administration Setting on Overall Ability to Work

Question: (at visit W72)

Thinking about your overall experience of switch in lanreotide Autogel® injection administration setting:

(2) Do you think switching from hospital to independent administration of lanreotide Autogel® injection has had a positive or negative effect on your overall ability to work?

(d) Positive effect

(e) No effect

(f) Negative effect

10.9 Appendix 9: Eastern Cooperative Oncology Group (ECOG) Performance Status

Table 10 Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published by [Oken 1982]. Eastern Cooperative Oncology Group.

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