21 May 2026
EMADOC-1829012207-46105
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ablymico

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/006620/0000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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List of abbreviations

ADA	Anti-drug antibody
AF4-MALS	Asymmetric flow field-flow fractionation
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredient
ASMF	Active substance master file
AUC	Analytical ultracentrifugation
AUC	Area under the curve
AUC_{0-t}	Area Under the Curve from time zero to time (t)
BE	Bioequivalence
BLK	Blank sample
BMI	Body mass index
cAMP assay	Cyclic adenosine monophosphate assay
cAMP	Cyclic adenosine monophosphate
CD	Circular dichroism spectroscopy
CDC	Centres for Disease Control and Prevention
CHMP	Committee for medicinal products for human use
CI	Confidence interval
cIEF	Isoelectric point
CMAs	Critical Material Attributes
C_{max}	Maximum measured plasma concentration
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
CPMP	Committee for Proprietary Medicinal Products (now CHMP)
CQA	Critical Quality Attributes
CQAs	Identification of Critical Quality Attributes
CRF	Case report form
CRO	Contract Research Organization
CS	Calibration standard
CV	Coefficient of variation
CVMP	Committee for Medicinal Products for Veterinary Use
DLS	Dynamic light scattering
DMF	Dimethylformamide
DSC	Differential scanning calorimetry
EA	Elemental analysis
EC	European Commission

ECHA	European Chemicals Agency
EEA	European economy area
EMA	European medicines agency
EMEA	European medicines agency
ERA	Environmental Risk Assessment
ES	Spain
EU	European union
EWP	Efficacy Working Party
FDA	The U.S. Food and drug Administration
FFC	Fluorescence Fold Change
GC-MS, RP-HPLC	enantiomeric purity analysis
GCP	Good clinical practise
GLP	Good laboratory practise
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GMP	Good manufacturing practice
GSPR	General Safety and Performance Requirements
HDL	High-density lipoprotein
HPLC	High-Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
ICF	Informed consent form
ICH	International Conference on Harmonisation
inf	infinity
IOTF	International Obesity TaskForce
IRB	Institutional review board
IRB	Institutional Review Board
IS	Internal standard
ISR	Incurred sample reanalysis
JFDA	Jordan food and drug administration
K_2EDTA	Dipotassium ethylene diamine tetra acetate
$K_{elimination}$	Apparent first-order elimination or terminal rate constant
L	Litre
LDL	Low-density lipoprotein
LDPE	Low density polyethylene
LLOQ	Lower limit of quantification
LSM	Least-square means

MALDI	MS-based sequence analysis
MO	Major objection
NBO	Notified body opinion
NCA	National Competent Authority
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
OTC	Over the counter
PBT	Persistent, Bioaccumulative, and Toxic
PD	Pharmacodynamics
PDE	Permitted Daily Exposure
PET-Al-PA-PE	polyester-aluminium foil-polyamide-polyethylene
PK	Pharmacokinetics
PRAC	Pharmacovigilance Committee
PXRD	Powder X-ray diffraction analysis
QC	Quality control
QTPP	Quality Target Product Profile
QWP	Quality Working Party
RH	Relative Humidity
RP-LC	Reverse-phase liquid chromatography
SD	Standard deviation
SE	Sweden
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SPPS	Solid phase peptide synthesis
T	Time
T2DM	Type 2 diabetes mellitus
TFA	Trifluoroacetic acid
TGA	thermogravimetric analysis
T_{half}	Half life
T_{hT}	Thioflavin T
T_{max}	Time to Maximum Concentration
UPLC	Ultra-Performance Liquid Chromatography
UPLC-MS/MS	Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry
USA	United states of America
vPvB	Very Persistent and very Bioaccumulative
Vz_F	Volume of distribution based on the terminal phase

ZS	Zero sample

1. Background information on the procedure

1.1. Submission of the dossier

The applicant STADA Arzneimittel AG submitted on 3 March 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Ablymico, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2024.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Adults

Ablymico is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:

- ≥ 30 kg/m^2 (obesity), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Ablymico should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5 % of their initial body weight.

Adolescents (≥ 12 years)

Ablymico can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:

- obesity (BMI corresponding to ≥ 30 kg/m2 for adults by international cut-off points)* and
- body weight above 60 kg.

Treatment with Ablymico should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*IOTF BMI cut-off points for obesity by sex between 12-18 years (see table 1), in accordance with study design of the Trial 4180, see section 5.1.

Table 1 IOTF BMI cut-off points for obesity by sex between 12-18 years

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	Males	Females
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30.00	30.00

Subsequently, the applicant amended the indication by adding a paediatric target population from 6 to less than 12 years or age, to align with the reference product. The reference product Saxenda obtained an extension of indication for a broader patient population during assessment of this application.

Children (6 to < 12 years)

Ablymico is indicated as an adjunct to healthy nutrition and increased physical activity for weight management in children from the age of 6 to < 12 years with

- obesity (BMI ≥ 95th percentile)* and
- body weight ≥ 45 kg

Treatment with Ablymico should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*CDC BMI cut-off points for obesity y (≥ 95th percentile) by sex between 6 to < 12 years (see table 2), in accordance with study design of the Trial 4392, see section 5.1.

Table 2 Cut-off points for BMI (Weight in kg/Height in m^2) for obesity (≥ 95th percentile) by sex for children from 6 and < 12 years of age

Age (years)	Obesity BMI ≥ 95th percentile	
	Males	Females
6	18.41	18.84
6.5	18.76	19.23
7	19.15	19.68
7.5	19.59	20.17
8	20.07	20.70
8.5	20.57	21.25
9	21.09	21.82
9.5	21.62	22.40
10	22.15	22.98
10.5	22.69	23.57
11	23.21	24.14
11.5	23.73	24.71

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: **Saxenda 6 mg/ml solution for injection in pre-filled pen**
- Marketing authorisation holder: **Novo Nordisk A/S**
- Date of authorisation: **March 2015**
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: **EU/1/15/992/001-003**

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: **Saxenda 6 mg/ml solution for injection in pre-filled pen**
- Marketing authorisation holder: **Novo Nordisk A/S**
- Date of authorisation: **March 2015**
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: **EU/1/15/992/001-003**

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: **Saxenda 6 mg/ml solution for injection in pre-filled pen**
- Marketing authorisation holder: **Novo Nordisk A/S**
- Date of authorisation: **March 2015**
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: **EU/1/15/992/001-003**
- Bioavailability study number(s): **LIR.0.6/450**

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Nadrah

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	3 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 June 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 November 2025
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one manufacturing site in India between 19 and 23 January 2026. The outcome of the inspection carried out was issued on.	27 March 2026

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	6 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 January 2026
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	29 January 2026
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 April 2026
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 May 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ablymico on	21 May 2026

2. Scientific discussion

2.1. Introduction

This application concerns a version of liraglutide 6 mg/mL solution for injection in pre-filled pen under trade name Ablymico. The application is submitted in accordance with the article 10(3) hybrid application of Directive 2001/83/EC due to changes in the active substance compared to a reference medicinal product. The pro-peptide of the reference product Saxenda is of biological origin, whereas the pro-peptide of proposed product is of chemical origin. Subcutaneous liraglutide (brand name Victoza) was first approved for the treatment of Type 2 diabetes mellites in Europe in 2009 and in the USA in 2010. In December 2014, liraglutide 3.0 mg was approved by the FDA and in March 2015 by the EMA for the treatment of chronic weight management under the brand name Saxenda, marketed by Novo Nordisk.

The proposed medicinal product Ablymico 6 mg/ml solution for injection in pre-filled pen with active substance liraglutide was developed as a therapeutic equivalent to the reference product Saxenda 6 mg/ml solution for injection in pre-filled pen.

Liraglutide (pharmacotherapeutic group: drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues; ATC code: A10BJ02) is an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97 % amino acid sequence homology to endogenous human GLP-1. Liraglutide binds to and activates the GLP-1 receptor (GLP-1R).

GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear. In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions involved in regulation of appetite, where liraglutide, via specific activation of the GLP- 1R, increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

Liraglutide lowers body weight in humans mainly through loss of fat mass with relative reductions in visceral fat being greater than for subcutaneous fat loss. It regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption, thereby leading to reduced food intake. Liraglutide does not increase energy expenditure compared to placebo.

Liraglutide stimulates insulin secretion and lowers glucagon secretion in a glucose-dependent manner which results in a lowering of fasting and post-prandial glucose. The glucose-lowering effect is more pronounced in patients with prediabetes and diabetes compared to patients with normoglycaemia. Clinical trials suggest that liraglutide improves and sustains beta-cell function, according to HOMA-B and the proinsulin-to-insulin ratio.

Proposed indication:

Adults
Liraglutide is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:
• ≥ 30 kg/m^2 (obesity), or

• ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.
Treatment with liraglutide should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5 % of their initial body weight.

Adolescents (≥ 12 years)
Liraglutide can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:
• obesity (BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points) * and
• body weight above 60 kg.
Treatment with liraglutide should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

* IOTF BMI cut-off points for obesity by sex between 12–18 years (see table 1) in accordance with study design of the Trial 4180.

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Treatment with Ablymico should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.
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Table 2 Cut-off points for BMI (Weight in kg/Height in m2) for obesity (≥ 95th percentile) by sex for children from 6 and < 12 years of age

	Obesity

Age (years)	BMI ≥ 95th percentile	
	Males	Females
6	18.41	18.84
6.5	18.76	19.23
7	19.15	19.68
7.5	19.59	20.17
8	20.07	20.70
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9.5	21.62	22.40
10	22.15	22.98
10.5	22.69	23.57
11	23.21	24.14
11.5	23.73	24.71

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation. However, the applicant received scientific advice from two EU member states (Spain, dated 21st November 2023 and Sweden, 23rd September 2023 respectively). This advice concerned the following topics: quality aspects, immunogenicity studies requirement and clinical study requirement.

The applicant generally followed the scientific advice provided. From a quality perspective, comparability with the reference product was addressed, including evaluation of fibrillation and aggregation potential, in line with recommendations and the relevant EMA guideline on synthetic peptides. Stability studies were conducted appropriately, including assessment of batches of drug product stored at different orientations and in the final assembled device, confirming no impact on product performance or physicochemical properties. Regarding immunogenicity, the concern on aggregation and fibril formation was addressed through in vitro comparability studies. From a clinical perspective, the requirement to demonstrate comparable pharmacokinetics was fulfilled, and a bioequivalence study was conducted as advised.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing 6 mg/ml of liraglutide as active substance.

Other ingredients are: propylene glycol, disodium hydrogen phosphate dihydrate, phenol, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injections.

The product is available in a cartridge (type I glass) with a plunger (bromobutyl) and a laminate rubber sheet contained in a pre-filled multidose disposable pen made of acrylonate butadiene styrene, polyacetal and polycyclohexylenedimethyl terephthalate.

Each pen contains 3 mL solution and is able to deliver doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg.

2.2.2. Active Substance

An Active Substance Master File (ASMF) procedure is used for the active substance liraglutide. The assessment of the ASMF is provided in a separate ASMF Assessment Report with a confidential annex on the Restricted Part. A valid Letter of Access in relation to the finished product under assessment was provided.

In addition to the ASMF, CTD sections 3.2.S.4 and 3.2.S.5 were provided by the finished product manufacturer; OneSource Specialty Pharma Limited.

2.2.2.1. General Information

Liraglutide is a synthetic peptide.

The chemical name is L-histidyl-L-alanyl-L-alpha-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-alpha-glutamyl-glycyl-L-glutaminyl-L-alanyl-L-alanyl-*N*6-(*N*-(1-oxohexadecyl)-L-gamma-glutamyl)-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-L-arginyl-glycine.

It has the molecular formula $C_{172}H_{265}N_{43}O_{51}$, a relative molecular mass of 3751, and the following structure:

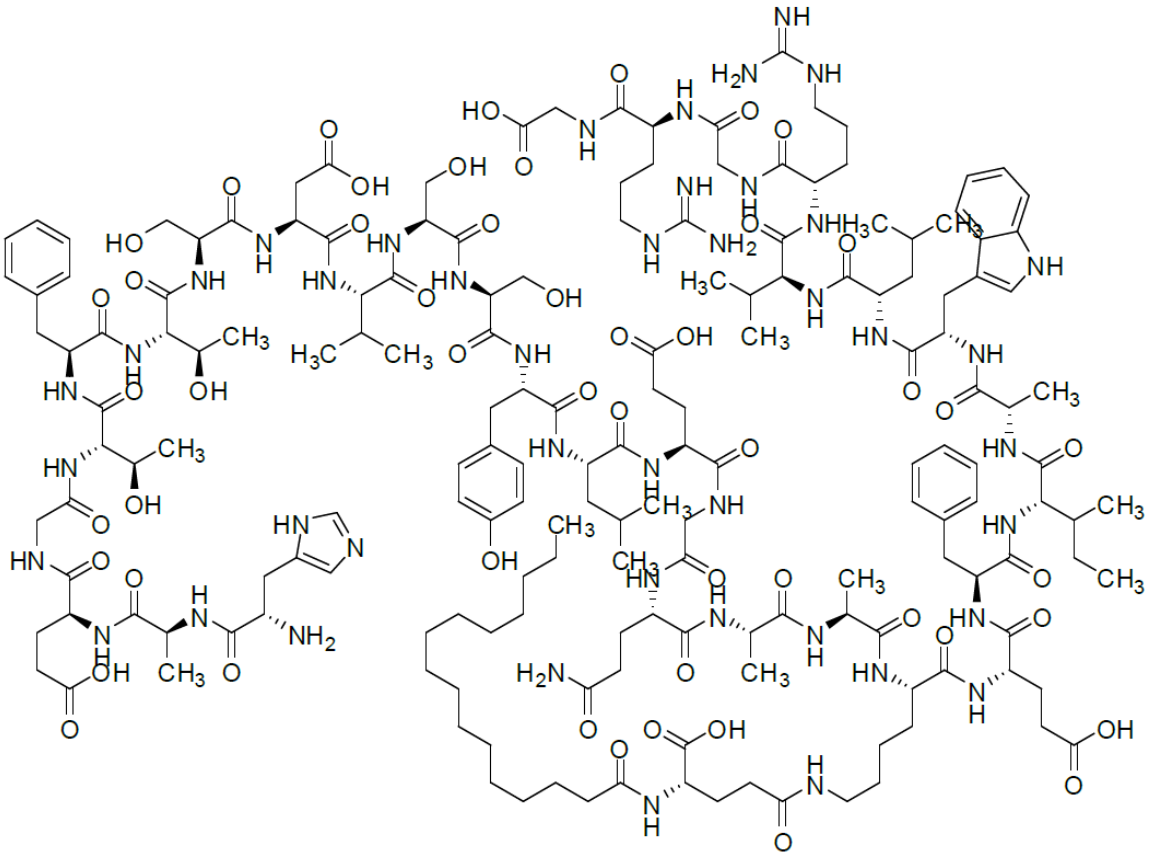

Figure 1: Active substance structure

Liraglutide is white or off-white loose powder, hygroscopic, soluble in water, very slightly soluble in methanol. The active substance is an amorphous powder, and it has no definitive melting point.

Liraglutide is not the subject of a monograph in the Ph. Eur.

The active substance was characterised with the following techniques: high resolution mass spectrometry (HRMS), MALDI (MS-based sequence analysis), Edman sequencing analysis, HPLC peptide mapping analysis, UPLC peptide mass mapping analysis, amino acids ratio, IR, UV, 1D, 2D, ^{1}H- and ^{13}C- NMR, far-UV CD spectroscopy, circular dichroism spectroscopy (CD), flow field-flow fractionation and multi-angle light scattering (AF4-MALS), analytical ultracentrifugation (AUC), differential scanning calorimetry (DSC), enantiomeric purity analysis (GC-MS, RP-HPLC), intrinsic fluorescence spectroscopy, thioflavin T (ThT) dye assay, elemental analysis (EA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction analysis (PXRD), GLP-1 receptor agonistic activity test biological activity test, isoelectric point (cIEF) and peptide fluorescence spectroscopy analysis.

Based on this characterisation exercise, the structure of liraglutide has been unambiguously confirmed, and the results were consistent with reference active substance batches.

2.2.2.2. Manufacture, process controls and characterisation

The active substance is manufactured by one manufacturing site. Evidence of GMP compliance was provided in the QP declaration.

Liraglutide is synthesised by solid phase peptide synthesis (SPPS) from well-defined starting materials (protected amino acids and dipeptides) with acceptable specifications. The choice of starting materials is justified and in line with EMA and ICH guidelines.

Following the repeated addition of protected amino acid and dipeptide starting materials via SPPS, the crude peptide is subjected to purification, salt exchange, freeze-drying and packaging steps. Detailed information on manufacturing process of the active substance has been provided in the restricted part of the ASMF and was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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

A detailed discussion has been provided regarding possible impurities/degradation products and carryover of potential impurities and solvents originating from the active substance synthesis. In general, relevant impurities are included in the specification with limits that are in line with the Ph. Eur. general monograph 'Substances for Pharmaceutical Use' which covers peptide-related impurities as well as ICH-guidelines Q3A and Q3C.

The content of each elemental impurity is far less than 30% of its PDE, and in the manufacturing of liraglutide, no metal catalyst and metal reagents are used. Therefore, Element impurities are not listed in the specification.

Even though peptides and peptide related impurities are not in scope of the ICH M7 guideline on mutagenic impurities, organic process related impurities from the synthesis were addressed. It was shown that potential genotoxic impurities are adequately controlled.

During the initial assessment of the ASMF, a number of major objections (MOs) were raised relating to the absence of a nitrosamines risk assessment, the risk of aggregation of peptides and the comparability studies of the synthetic active substance versus the biological recombinant active substance. A risk assessment of

the presence of nitrosamines in the active substance was provided in line with relevant EMA guidance and was considered acceptable. The conclusion is that the risk for the presence of nitrosamines in liraglutide is negligible.

Testing by complementary analytical test methods (asymmetric flow field-flow fractionation (AF4-MALS), analytical ultracentrifugation (AUC), dynamic light scattering (DLS)) showed that the state of aggregation is consistent with that of the reference product containing the recombinant peptide.

The substance has been satisfactorily characterised with regard to primary, secondary and tertiary structure, and relevant tests have been performed to evaluate higher order structures and to control the formation of unwanted oligomers.

The MOs were considered resolved.

The specifications for the control of the packaging materials are considered adequate, and the primary packaging material complies with the requirements of EU regulation 2011/10.

2.2.2.3. Specification

The active substance specification include tests for appearance, solubility, identification by monoisotopic mass and HPLC, pH, clarity and colour of solution, water content, specific rotation, acetic acid, TFA and DMF content (HPLC), related substances (HPLC), oligomer (HPLC, ratio of amino acids, assay (HPLC), residual solvents (GC, phosphate and chloride anions, ammonium and sodium cations, microbiological examination, bacterial endotoxins and bioassay.

According to the Ph. Eur. general monograph 'Substances for Pharmaceutical Use', peptide-related impurities should be reported above 0.1 %, identified above 0.5 % and qualified above 1.0%. The proposed limits are consistent with these thresholds. Limits for residual solvents are in-line with ICH Q3C. The limit for oligomer content was tightened in response to questions raised during assessment and was set based on test results and stability results for three consecutive commercial batches of Liraglutide.

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

The bioassay method was validated for specificity, range and linearity, accuracy, precision (repeatability and intermediate precision), and robustness (cell density) in line with ICH Q2 (R2) requirements for potency assay validation. The results obtained for all parameters are aligned with the defined acceptance criteria. Hence this method is considered suitable to estimate the relative potency of liraglutide samples in routine sample analysis.

Batch analysis data for three batches of the active substance are provided. The results comply with the specifications and are consistent from batch to batch.

2.2.2.4. Stability

Stability data from three batches of active substance from the proposed manufacturer stored in in a container closure system representative of that intended for the market for up to 60 months under long term conditions (5°C±3°C) and for up to 6 months under accelerated conditions (25±2°C & 60±5%RH) according

to the ICH guidelines were provided. Results under stressed conditions (temperature, humidity, photo stress study) were also provided on one batch.

The following parameters were tested (including stability indicated parameters)*:* appearance, solubility, identification, specific rotation, amino acid ratio, clarity and colour of solution, pH, acetic acid, TFA and *N*,*N*-dimethylformamide, water, oligomer, related substances, anions and cations assay, residual solvents, bacterial endotoxins, and microbiological examination.

The analytical methods used were the same as for release and are stability indicating. All tested parameters were within the specifications; no significant changes were observed. In the stress studies, slight degradation at 40 °C and further degradation at 60 °C was observed. Liraglutide is unstable at 75 % RH and at 90 % RH (hygroscopic). It is photosensitive and should be protected from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable under the proposed storage conditions. The stability results justify the proposed retest period of 60 months when stored at 5°C±3°C in the proposed container.

2.2.2.5. ***Active substance specification (applied by finished product manufacturer)***

The active substance specifications applied by the finished product manufacturer are aligned with those applied by the active substance manufacturer.

The analytical methods are the same as those from the active substance manufacturer (except for bioassay). Analytical method verification was performed and was considered acceptable.

Determination of the relative potency of liraglutide active substance was performed by *in vitro* cAMP assay. The method was validated in line with ICH Q2 (R2) requirements for potency assay validation. The results obtained for all parameters are aligned with the defined acceptance criteria. Hence this method is considered suitable to test the relative potency of liraglutide samples in routine sample analysis.

As a biological assay is not required for the release and stability testing of synthetic peptides, in line with EMA Guideline on the Development and Manufacture of Synthetic Peptides, the omission of bioassay as a routine test from the specification applied by the finished product manufacturer was considered acceptable.

2.2.3. Finished Medicinal Product

2 . 2 . 3 . 1 . Description of the product and Pharmaceutical Development

Liraglutide 6 mg/ml solution for injection in pre-filled pens is a clear and colourless or almost colourless, isotonic solution (pH=8.15) in a pen containing 6 mg/ mL of Liraglutide (18 mg liraglutide in 3 ml) which is practically free from visible particles.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. No overages are used to produce the finished product, but the product is overfilled to ensure it is possible to administer the labelled doses from the pen.

Liraglutide Stada and Ablymico. were developed in parallel by the same developer.

The finished product Liraglutide Stada has been developed to be equivalent to the reference medicinal product Victoza 6 mg/ml solution for injection in pre-filled pens (indication: Type II diabetes). The finished product Ablymico has been developed to be equivalent to the reference medicinal product Saxenda 6 mg/ml solution for injection in pre-filled pens (indication: obesity). Consequently, the objective was to prepare a solution for injection being equivalent to these reference medicinal products.

The finished product development was based on the Quality by Design approach as per ICH Q8(R2) guidance. Initially, the Quality Target Product Profile (QTPP) was defined based on the information available from literature searches and characterisation testing of the reference medicinal product. Identification of Critical Quality Attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the finished product. Investigation during pharmaceutical development focused on control of Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), which could potentially impact finished product quality.

The formulation chosen is qualitatively and quantitatively similar to that of the reference medicinal product.

Victoza and Saxenda belong to the same global marketing authorisation and have identical composition, strength and pharmaceutical form. While each marketing authorisation application is supported by a specific clinical bioequivalence study versus the reference product i.e. Liraglutide Stada Vs Victoza / Ablymico Vs Saxenda (see section 2.6 for further info), both Victoza and Saxenda were considered valid for the purpose of the *in vitro* analytical comparability exercise, to ensure the scientific rigour of the comparability exercise,

and the validity of the reference product quality attribute ranges, which were the basis for concluding the comparability of test and reference product.

Analytical comparability

It was considered that clinical PD studies, clinical efficacy studies and clinical immunogenicity studies could be waived if it will be demonstrated that all properties of liraglutide that are known to influence its PK, PD or immunogenicity are comparable between proposed and reference product by appropriate *in vitro* analyses.

An *in vitro* analytical comparability study was conducted to show the essential similarity between synthetic Liraglutide 6 mg/ml solution for injection and recombinant reference products Victoza and Saxenda. The study was conducted on three batches of Liraglutide Stada 6 mg/ml solution for injection and three batches of Ablymico 6 mg/ml solution for injection, versus one batch of Victoza and two batches of Saxenda respectively. The quantity of active substance is the same as in the reference product.

During the procedure, a multidisciplinary MO was raised on the *in vitro* analytical comparability study asking for further justification of the initial sample sizes of reference products (one lot of EU reference product Victoza and two lots of EU reference products Saxenda), and to provide suitable graphical representation describing min-max data for each quantitative attribute. In response, the applicant expanded the study by adding additional lots of each reference product, so that the Liraglutide test product batches were compared with four lots of EU reference product Victoza and three lots of EU reference product Saxenda, and the applicant presented the complete comparability study with graphical representations as requested.

All test batches used for analytical comparability were within the shelf life at the time of testing, batches were of comparable age. The test DP batch and reference DP batch used in the comparative analytical analysis were also included in clinical BE study (LIR.0.6/451). The batch size of the clinical test DP batch is the same as the planned production scale batch.

The following quality attributes were compared between the test and reference samples: primary structure secondary structure, higher order structure, oligomer/aggregation states and fibril content, bioactivity, peptide-related impurities, isoelectric point, optical rotation. The chosen panel of analytical methods is considered suitable for the intended purpose to detect potential differences between the test and the reference products. Acceptable method descriptions have been provided, and adequate method qualification data have been presented. In summary, structural comparability (primary, secondary, high-order structure) of test and reference products was considered to be demonstrated, however further discussion of oligomer, aggregation and fibril formation was needed (see below).

Physicochemical attributes were not compared directly however, the test and reference products are comparable in view of appearance, osmolality, pH, and phenol content. The specification for particulate matter is in line with Ph. Eur. 2.9.19 and 2.9.20 for the test product. The specification limit for pH for the test product is a very narrow range and therefore, minor changes in pH are not expected to influence fibrillation propensity.

Comparison of the pharmacological activity of liraglutide test and reference products was investigated by GLP-1 receptor binding , kinetic study and a cell-based assay. Based on the results, it was concluded that the test and reference products are comparable in this respect. Liraglutide test product batches were compared with one lot of EU reference product Victoza and three lots of EU reference products Saxenda only. As biological assays serve as additional tools for the characterisation of synthetic peptides and because the primary, secondary and higher order structure is sufficiently characterised by physicochemical tests and presence of aggregates excluded, this was considered acceptable.

The impurity profile was found to be comparable to reference medicinal product that was analysed using UPLC-UV and HRMS. There are no additional impurities, other than those already specified, detected above 0.10% in all test products compared to reference products. Some impurities were found at lower levels in the in-house batches compared to the reference medicinal products. Impurities found in test product only were below 0.10%.

With regard to the immunogenic potential of the test product, it was considered that clinical immunogenicity studies could be waived if it will be demonstrated that properties of liraglutide that are known to influence its immunogenicity are comparable between proposed and reference product by appropriate *in vitro* analyses. Peptide oligomers/aggregates and fibril formation were analysed.

Oligomer/aggregation states were analysed by SEC-UV including stress studies (photostability and thermal stability conditions). Total oligomer content under long term storage conditions (2-8 °C) was lower in test samples compared to reference. In a photolytic degradation study, the level of oligomers in test samples significantly increased, and were above levels found in reference product samples. However, these differences are not considered clinically relevant since the test and reference pens were disassembled and only their cartridges were used for the photostability study.

With regards to fibril formation, during the procedure multidisciplinary MOs were raised at D120 and D180 on the need to characterise fibril formation in the test product and compare it to the reference products.

Aggregate and fibril formation were confirmed . The applicant concluded that the test and reference products are comparable in this respect. The FFC values of all test formulation samples fell within the reference formulation FFC mean ± 3 standard deviations.

The applicant was also asked to exclude fibril formation under mechanic stress therefore the applicant developed a continuous method. A negative control was included, and a positive control was developed. Under applied stress conditions, neither the liraglutide test formulations nor the reference formulations exhibited any signs of fibrillation. In contrast, the positive control sample did show fibrillation under the same stress conditions, thereby confirming both the capability of the method and the effectiveness of the mechanical stress in inducing fibrillation in liraglutide. Detailed methodology and method qualification of the fibril kinetics method was provided.

Comprehensive evaluation of fibrillation kinetics was conducted under various stress conditions also. Specifically, storage stress was assessed by analysing test samples stored under long term storage conditions 2–8°C for around 15-16 months and compared with reference product samples of different ages including reference product stored for less time than test product.

Furthermore, the applicant analysed samples which were subjected to stressed conditions which mimic possible stressed conditions that the product could be exposed to during storage, handling and transport. The results from these stressed samples were comparable to those of the reference formulation, with no significant differences observed in their kinetic profiles. Overall, all these findings confirm that the test formulation exhibits fibrillation behaviour equivalent to that of the reference formulation, indicating no meaningful differences between them under the tested conditions. The MO was considered resolved and clinical immunogenicity studies were not considered necessary.

Manufacturing process development

The development of the finished product manufacturing process is well described. A risk assessment was performed, considering all CQAs in every unit operation step. The finished product manufacturing process is a

common process for solutions for injection using standard equipment and was developed to achieve optimal product quality and process consistency.

Sterilisation by filtration with aseptic processing was selected as the method of sterilisation for the finished product. Since the medicinal product contains an active substance susceptible to heat where it is well known that terminal sterilisation is not possible, the justification for sterilisation by filtration with aseptic processing is considered appropriate.

The composition of the test product was chosen based on the reference product. The concentration of phenol as a preservative in the test product is the same as in the reference product (5.5 mg/mL).

A thermal cycling study was carried out to investigate the impact of temperature excursions during transport and handling of the product. No changes were observed.

An extractables and leachables study was carried out and the finished product was shown to be compatible with the 3 mL cartridge and with the bromobutyl plunger. Other components do not contact the pen-injector during storage.

Critical functional components are described for the medical device selected and compared with the reference products. During the procedure, a MO was raised as the applicant had initially not provided a notified body opinion on the medical device confirming full compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745. In response, a notified body opinion (NBO) was provided, and the MO was considered resolved.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured at one site. This site is responsible for manufacturing of finished product, quality control testing, primary and secondary packaging. During the procedure, a MO was raised on the need for proof of GMP compliance. An updated GMP certificate was provided and the MO was considered resolved.

Sufficient evidence of GMP compliance has been provided for the sites responsible for batch release: Universal Farma, S.L, C. El Tejido, 2 19200 Azuqueca de Henares, Guadalajara, Spain; STADA Arzneimittel AG, Stadastraße 2 -18, 61118 Bad Vilbel, Hesse, Germany; and STADA Arzneimittel GmbH, Muthgasse 36/2, 1190 Vienna, Austria.

The batch formula was provided, and a commercial batch size of was defined.

The manufacturing process consists of the following main steps : dispensing of raw materials, bulk solution preparation, bioburden reduction filtration, sterilising filtration, filling, capping and stoppering of primary packaging. 2

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The proposed holding times have been validated.

The manufacturing process is considered to be non-standard due to the aseptic processing with sterile filtration. Appropriate bioburden controls have been set. Process validation was performed on four consecutive production scale batches. All CPPs identified during formulation development were tested and met the predefined acceptance criteria. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specifications

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form; appearance/description, identification of liraglutide (UPLC, UV), identification of phenol (UPLC), pH (Ph. Eur.), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), container closure integrity (leak test), assay of liraglutide (UPLC), phenol content (UPLC), related substances (UPLC), oligomer content (HPLC), visible particles (Ph. Eur.), subvisible particles (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), dose accuracy, dose dispensing force and bioassay (cell-based assay).

The specifications and limits are in line with relevant Ph. Eur. chapters and general monographs, and with relevant EMA and ICH guidelines.

During the procedure, the shelf-life specification for assay of liraglutide was tightened in line with results from stability studies. The shelf-life limits for one specified impurity and total impurities were tightened according to batch analysis and stability results.

For the medical device, two functional tests (dose accuracy and dose dispensing force) are specified. The minimum fill quantity for each individual container is indirectly controlled with the specified parameter extractable volume.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

For determination of assay of Liraglutide and phenol content, oligomer content, and related substances, transfer reports from the development site to the proposed commercial manufacturing and testing site were provided. All the results obtained during method transfer are within the acceptance criteria.

Data from forced degradation studies were submitted for assay of Liraglutide and phenol content related substances and oligomer content. The methods were shown to be stability indicating.

Determination of Relative Potency of Liraglutide Injection was performed by *in vitro* cAMP assay. The method was validated in line with ICH Q2 (R2) requirements for potency assay validation. During the procedure the applicant presented comparative analysis from 10 commercial batches of active substance and process validation batches of finished product showing a strong correlation between bioassay potency values and RP-LC assay results, indicating that the physicochemical assay reliably predicts biological activity. The applicant proposed to rely on the validated RP-LC assay methods for potency and purity in lot release testing, while maintaining bioassay in stability studies and investigational scenarios. As biological assay is not required for the release and stability testing in line with Guideline on the Development and Manufacture of Synthetic Peptides, omission of bioassay test from routine release testing was considered acceptable.

Batch analysis results were provided for three validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Elemental impurities and nitrosamine risk assessments were provided. Elemental impurities have been discussed in accordance with ICH Q3D requirements. As the results were well below limits and met the control threshold of 30% of permitted daily exposure (PDE), no routine analysis is deemed necessary. The nitrosamines risk assessment identified no risk of contamination of the finished product with nitrosamines.

2.2.3.4. Stability of the product

Stability studies in accordance with ICH Guideline Q1A for the three validation batches have been conducted. Samples were stored under the long-term (5±3°C/ambient RH) and accelerated (25±2°C/60±5% RH) conditions. The stability study protocols were provided. The analytical methods used were the same as for release and are stability indicating.

Long-term stability data are available for up to 18 months. Stability results under accelerated conditions were presented for up to 6 months. Under long-term storage conditions, no significant changes were observed in any of the quality attributes. Under accelerated conditions after 6 months, OOS results with respect to degradation products occurred demonstrating that the finished product is temperature sensitive.

In-use stability testing with two batches was performed – one recently manufactured and the other stored for 18 months under long term conditions. Additional in-use studies are planned after 24 and 36 months of long-term storage if required. In-use stability is tested at the start of the study (i.e. when the pen is used and the barrier pierced) and after 30 days either at 2-8°C or 15-30°C. Assay decreases slightly and there is an increase in impurities over time at 30°C. However, the results are well within specification limits. At 2-8°C the finished product is stable with no obvious trends. Therefore, an in-use shelf life after first use of 1 month when stored below 30°C or in a refrigerator (2 °C-8 °C) is acceptable.

The performed photostability study demonstrated that the finished product is susceptible to light and needs to be protected from direct light exposure.

According to applicable stability guidance, significant change during accelerated conditions calls for the proposed shelf life to be based only on real time data available from the long-term storage condition. Hence, the proposed shelf life of 18 months with storage conditions "Store in a refrigerator (2°C–8°C). Do not freeze. Store in the original package in order to protect from light" is supported considering the available stability data.

2.2.3.5. Post approval change management protocols

Not Applicable

2.2.3.6. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on the chemical, pharmaceutical and biological aspects

The finished product Ablymico is a solution for injection containing 6 mg/mL of the active substance liraglutide in a pre-filled pen. It contains the same active substance and excipients as the EU reference product Saxenda. But the active substance in Ablymico is chemically synthesised, whereas the active substance in the reference products is of biological origin.

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner.

During the initial assessment of the ASMF, a number of MOs were raised relating to the absence of a nitrosamines risk assessment, the risk of aggregation of peptides and the comparability studies of the

synthetic active substance versus the biological recombinant active substance. These were adequately answered by the ASMF holder and considered resolved.

During the procedure, multidisciplinary MOs were raised on the sample sizes and design of the *in vitro* comparability study between test and reference products, the risk of immunogenicity caused by aggregates and fibril formation. Quality MOs were raised due to missing proof of GMP compliance of the finished product manufacturing site and a missing Notified Body Opinion relating to the medical device component. In response, the applicant adequately demonstrated comparability between the proposed test and reference products with extensive analytical comparability data and a comprehensive evaluation of fibrillation kinetics. The relevant GMP and Notified Body documentation was provided, and the MOs were considered to be resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of liraglutide are well known. As liraglutide is a widely used, well-known active substance, an overview based on literature review provided by the applicant was considered appropriate. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology was provided, which was based on up-to-date and adequate scientific literature. The non-clinical aspects of the SmPC were in line with the SmPC of the reference product. The impurity profile was discussed and considered acceptable from the non-clinical point of view. The excipients used in the medicinal product are widely used in pharmaceutical formulations and comply with standard references. Therefore, the CHMP agreed that no further non-clinical studies are required.

However, two additional 14-days repeat dose studies in rat and rabbit were performed by the applicant and are described in the Toxicology chapter below.

2.3.2. Toxicology

2.3.2.1. Repeat dose toxicity

The toxicity of repeated subcutaneous doses of liraglutide 6 mg/ml solution for injection was assessed by the Applicant in two 14-day studies in rats and rabbits, consistent with the ICH requirements (BIO-CTX 778, 2024; BIO-CTX 779, 2024). Batch number L067A74D (EP0766) was used in both studies, which was comparable to the validation batch and was deemed adequately representative of the final product.

Based on the rat study results the No Observed Adverse Effect Level (NOAEL) of test item liraglutide 6 mg/mL solution for injection was 1.24 mg/kg/day when administered for 14 consecutive days under the experimental conditions and the doses employed. Food consumption and body weight were reduced throughout the dosing period (dose-related), which can be attributed to the pharmacologic effects of liraglutide.

Based on the rabbit study results and experimental conditions used in the study, it was concluded that liraglutide 6 mg/mL solution for injection administered in New Zealand White Rabbits for 14 consecutive days did not result in gross pathological changes in any of the dose groups. Food consumption and body weight were strongly reduced throughout the dosing period (dose-related) and markedly during the first days of the study (day 1-5). Microscopically, test item related, adverse change in the form of vacuolation of hepatocytes was observed in liver of both sexes from the dose level of 0.155mg/kg/day, therefore the NOAEL was below the low dose level and could not be determined.

2.3.3. Ecotoxicity/environmental risk assessment

As per ERA guideline, Phase I and PBT/vPvB screening assessment should have been performed for all active substances. Peptides and proteins that were structurally modified using non-natural amino acids to increase biostability are considered non-natural. When the non-natural peptide/protein is demonstrated to be excreted in amounts < 10% of the dose (or shown to be readily biodegradable in an OECD 301 test), the Phase I and PBT screening can stop in step Q3b of the corresponding decision trees. For liraglutide, for 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (<9% and <5% of total plasma radioactivity exposure). Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination. Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). Additionally, the studies previously conducted with liraglutide precursor (ECHA, 2024) showed that it is readily biodegradable, which could be extrapolated to the peptide. Hence, liraglutide is excreted in less than 10% of the dose and Phase I and PBT screening could be concluded at this step.

No risk to the environment is expected from putting this product to the market.

The applicant included a general warning in the SmPC chapter 6.6., which was accepted.

2.3.3.1. Summary of main study results

Table 5: Summary of main study results

Substance (INN/Invented Name): liraglutide			
CAS-number (if available): 204656-20-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Estimated, not measured	LogPow = approximately 0.4 (estimated at pH 7 .9 for aqueous solution; read-across data)	Potential PBT No.
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	LogPow = approximately 0.4 (estimated at pH 7 .9 for aqueous solution; read-across data)	not B
	BCF	NA	
Persistence	DT50 or ready biodegradability	Readily biodegradable (see below)	not P
Toxicity	NOEC or CMR		not T
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	NA	μg/L	NA
Other concerns (e.g. chemical class)	NA		N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	*NA*	
Ready Biodegradability Test	OECD 301F	10 day BOD was 75+/-8% 28 days BOD 83+/-3%	Ready biodegradable precursor

2.3.4. Discussion on non-clinical aspects

Liraglutide is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

Pharmacodynamic, pharmacokinetic and toxicological properties of liraglutide are well known. Overview based on the literature review submitted by the applicant was considered appropriate. Additionally, the applicant provided comparative in vitro physicochemical and biological data as part of the Quality dossier and executed two repeat dose toxicity studies as part of the Non-Clinical dossier. A bioequivalence study was conducted as part of the Clinical dossier.

Additional in vitro studies were carried out to show that there were no significant differences at the substance level (see Quality assessment).

The proposed product Ablymico is of the same type of solution (aqueous), contains the same concentration of the active substance liraglutide and the same excipients (propylene glycol, disodium hydrogen phosphate dihydrate, phenol) in similar amounts as the reference medicinal product (Saxenda 6 mg/mL solution for injection in pre-filled pen).

Analytical studies were conducted to compare physicochemical properties of proposed and reference product and comparative in vitro biological studies were conducted to demonstrate the pharmaco-toxicological similarity of proposed and reference product, as follows:

- Bioassays to compare receptor binding of liraglutide and its downstream cellular response.

- In vitro tests to establish comparability of oligomerisation properties, as differences in oligomerisation may influence the PK properties of the product. This was further confirmed in the BE study, which showed that there was no difference in the PK between the two products.

- In vitro tests to establish comparability of fibrillation properties, as fibrils may affect the immunogenic properties of the product.

- Albumin binding may influence the PK of the product. This was not investigated in vitro, but the PK characteristics of the product were addressed within the BE clinical study. Also, binding of liraglutide to albumin is a substance characteristic. The structure of the substance is the same for synthetic and biologic liraglutide. In analytical comparability studies it was shown that the drug substance is essentially similar to the reference product, therefore, binding to albumin is expected to be the same, and no other studies with regard to albumin binding were required (see Quality assessment).

The two repeat dose toxicity studies in rat and rabbit did not provide any information on similarity between the reference and the applied for product. However, the in vitro comparability testing and the BE study were designed to provide proof for essential similarity between this and the reference product, without the need for toxicity testing in animals.

In the two 14-days repeat dose toxicity studies in rat and rabbit, only the product under review was tested, and the studies were not aimed to compare any potential toxicity difference between the reference and the applied for product. However, it must be noted that comparative animal studies are not sensitive enough to discern minor differences in safety profiles between two similar products, toxicity studies are rarely recommended for abridge applications. Therefore, the lack of comparative animal data was considered acceptable.

In the rabbit study, test item related adverse change in the form of vacuolation of hepatocytes was observed in liver of both the sexes from the dose level of 0.155mg/kg/day, therefore the NOAEL was below the low dose level. As no recovery period was included in the study design, it was unclear whether this effect was reversible, but blood chemistry results (decrease in blood urea nitrogen, aspartate aminotransferase, increase in cholesterol, HDL and LDL) and liver weight decrease indicated that there were some hepatic effects. In clinical trials for weight management, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with liraglutide than in patients on placebo. The fact that substantial weight loss can increase the risk of cholelithiasis and thereby cholecystitis only partially explained the higher rate with liraglutide. Since it was already indicated that liraglutide treatment can cause hepatic effects in clinical setting, and cholelithiasis and cholecystitis are listed as possible side effects, this issue was not further pursued.

The two studies did not include any toxicokinetic data, so the exposures achieved with doses up to 4x human MDD are not unknown. Also, no analysis of ADA was included in the two studies, further obscuring the information on exposure. But, from the observed body weight and food consumption effects it can be concluded that pharmacologically active exposures had been achieved.

In vitro product characterisation and comparability plan was deemed sufficient to waive any additional non-clinical studies.

The non-clinical sections of the SmPC were in line with the SmPC of the reference product and were acceptable. No additional information was added to the 5.3 section of the SmPC, which was supported.

Liraglutide is not expected to pose a risk to the environment.

2.3.5. Conclusion on the non-clinical aspects

The CHMP considers Liraglutide STADA approvable from the non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

This is an initial marketing authorisation application for a version of a solution for injection in pre-filled pen containing active substance liraglutide, under trade name Ablymico. The application was submitted in accordance with the article 10(3) hybrid application of Directive 2001/83/EC due to differences in the manufacturing of the active substance in the proposed product compared with a reference medicinal product. The pro-peptide of the reference product Saxenda is of biological origin, whereas the pro-peptide in the proposed medicinal product is of chemical origin. The medicinal product subject to this assessment was developed as a solution for injection in a pre-filled pen using a disposable pen injector that is therapeutically equivalent to the reference product Saxenda 6 mg/ml solution for injection.

Active substance of the proposed medicinal product has the same concentration, strength, pharmaceutical form (solution for injection in pre-filled pen) and quantitative composition as the reference medicinal product Saxenda.

Liraglutide is a well-known active substance with an established efficacy and safety profile. Clinical PD studies, clinical efficacy studies and clinical immunogenicity studies could be waived as it was demonstrated by appropriate in vitro analyses that all properties of liraglutide that are known to influence its PK, PD or immunogenicity are comparable between the proposed and reference product. As this is an abridged application, it is considered acceptable that the applicant did not conduct efficacy or safety clinical studies with their formulation in support of this application.

The application is based on a literature overview with regard to the established efficacy and safety profile of liraglutide and was supported by one bioequivalence study where Ablymico was compared to the reference product Saxenda. Given the complexity of the active substance molecule, bioequivalence study may not have been sufficient to establish bioequivalence. Therefore, an additional analytical comparability study was carried out concluding no significant differences at the API level.

The clinical overview on the clinical pharmacology, efficacy and safety was based on up-to-date and adequate scientific literature. Sufficient information on pharmacodynamics of liraglutide and pharmacokinetics of subcutaneous liraglutide injection were provided. The Clinical overview addressed the proposed therapeutic indication, provided references supporting efficacy of liraglutide for the proposed indication and demonstrated acceptable safety profile.

Clinical sections of the proposed SmPC were aligned with the SmPC of reference product Saxenda.

GCP aspects

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

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

- **Tabular overview of clinical studies**

To support the application, the applicant has submitted one bioequivalence study (study No. LIR.0.6/450).

Table 6: summary of study No. LIR.0.6/450

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	Sponsor Protocol No.: 2024-LIRA-0433-PK-06 CRO Protocol No.: LIR.0.6/450	Clinical Study & PK Report and Adverse Event Listing (5.3) CRFs (5.3.1.2) and Subjects Individual CRF (5.3.7) Literature References (5.4)	Primary objective of the study: to assess the bioequivalence between Liraglutide 6 mg/ml Solution for Subcutaneous Injection in Pre-filled Pen (Test Product/ manufactured by OneSource Speciality Pharma Ltd (formerly Stelis Biopharma Ltd), India) and Saxenda® 6 mg/ml Solution for Subcutaneous Injection in Pre-filled Pen (Reference Product/ manufactured by Novo Nordisk A/S, Denmark) in healthy, adult, human, subjects under fed conditions. Secondary objective: to monitor the safety of the participating subjects as determined by means of laboratory assessments, vital signs, ECG, physical examination, and AE/SAE monitoring.	A Randomized, Two-Treatment, Two-Period, Two-Sequence, Crossover, Open label, Laboratory Blind, Single Dose Bioequivalence Study between Liraglutide 6 mg/ml Solution for Subcutaneous Injection in Pre-filled Pen (Test Product) and Saxenda® 6 mg/ml Solution for Subcutaneous Injection in Pre-filled Pen (Reference Product), following a Single 0.6 mg Subcutaneous Dose, in Healthy, Adult, Human, Subjects Under Fed Conditions.	**Test Product-T (A):** Liraglutide 6 mg/ml Solution for Subcutaneous Injection in Pre-filled Pen (Manufactured by: OneSource Speciality Pharma Ltd (formerly Stelis Biopharma Ltd), India). **Dosage Regimen:** 0.6mg/dose **Route of administration:** Subcutaneous **Reference Product-R (B):** Saxenda® 6 mg/ml Solution for Subcutaneous Injection in Pre-filled Pen (Manufactured by: Novo Nordisk A/S, Denmark). **Dosage Regimen:** 0.6mg/dose **Route of administration:** Subcutaneous	No. of Subjects Dosed (Male & Female, respectively): Period I: 34 & 13 Period II: 33 & 13 No. of Subjects Completed: 46 Subjects considered for bioequivalence evaluation: 44	Healthy Adult Human Subjects	1 x 0.6 mg of Liraglutide per dose, into two sequences (AB, BA).	Complete Study Report

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

One randomized, two-period, two-sequence, single dose crossover bioequivalence study to support this application was considered sufficient for the proposed product. It is a recommended standard design according to the Guideline on the investigation of bioequivalence.

Study No LIR.0.6/450 (2024-LIRA-0433-PK-06): A randomized, two-treatment, two-period, two-sequence, crossover, open label, laboratory blind, single dose bioequivalence study between Liraglutide 6 mg/ml solution for subcutaneous injection in pre-filled pen (test product) and Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen (reference product), following a single 0.6 mg subcutaneous dose, in healthy, adult, human, subjects under fed conditions

Protocol code: LIR.0.6/450 , document number: TRI-20357 Rev 01 (dated 3rd October 2024)

Table 7: Summary of study information

Clinical Facility, Medical Writing and Data Analysis/Reporting:	Triumpharma 07 Bulg., Al-Yaroot Street, Al-Jubaiha, P.O. Box: 2233, Amman, 11941, Jordan
Clinical laboratories (Site of clinical lab investigations):	University Gate laboratories, Queen Rania St./ in front of the main gate of Jordan University
Bioanalytical laboratory:	Anapharm Europe, S.L.U., Spain. C/Encuny 22, 2nd floor, 08038 Barcelona, Spain
Sponsor:	LABORATORIOS LICONSA S.A. Av. de Miralcampo, 7, 19200 Azuqueca de Henares, Guadalajara, Spain
Study Period:	Study initiation date: 26th September 2024 (first screening date) Study completion date: 23rd October 2024 (final examination date)
Period dates (check in date - last PK blood sample date):	Period I: Group I: 5th October 2024 – 9th October 2024 Group II: 9th October 2024 – 13th October 2024 Period II: Group I: 14th October 2024 – 18th October 2024 Group II: 19th October 2024 – 23rd October 2024
Bioanalytical Phase Dates:	Experimental start date: 16th October 2024 Experimental completion date: 25th November 2024
Date of the Clinical Study Report:	22nd December 2024 (report document TRI-30254 Rev00)

Methods

- **Study design**

This study was open label, laboratory-blind, randomized, single dose, two treatments, two periods, two sequence, crossover bioequivalence study in normal, healthy, adult human subjects. The study was carried out in fed conditions. According to the reference SmPC, the medicinal product can be taken independent of meals and therefore study should be conducted under fasting conditions, which are more sensitive. The study was conducted under fed conditions to minimize the gastrointestinal adverse events (nausea and vomiting) of the administered drug. Since food consumption does not affect pharmacokinetics after subcutaneous

application and since medicinal products were taken with food due tolerability reasons, fed conditions are considered acceptable.

A single 0.6 mg dose was given subcutaneously in each period. The rationale for using the lowest dose (0.6 mg) instead of the highest dose (3 mg) is the better tolerability profile expected from the lower dose due to decreased incidences of gastrointestinal and hypoglycaemic adverse events. Lowest dose (0.6 mg) is used as a starting dose with the reference product Saxenda to improve gastro-intestinal tolerability. According to the Guideline on the investigation of bioequivalence, the bioequivalence study should be performed with the highest dose strength. However, in this case selection of the lowest dose strength of 0.6 mg is justified for safety and tolerability reasons. In addition, as liraglutide shows linear dose-proportional pharmacokinetics, the PK results obtained in the bioequivalence study with the lower dose strength can be extrapolated to proportionally higher dosages.

Following an overnight fasting of at least 8 hours, the subjects started their low calories/low fat breakfast meal (two slices of white toast, two tablespoons of strawberry jam, and one serving of feta cheese) one hour before dosing, then they were given the assigned dose (0.6 mg subcutaneous dose of test product or reference product) in each study period according to the randomization schedule. The drug was given as a subcutaneous injection in the upper arm (the dose was given in one arm in period I and in the other arm in period II), by the clinical sub-investigator.

Dosing dates were 6th October 2024 and 10th October 2024 (group I and group II in Period I) and 15th October 2024 and 20th October 2024 (group I and group II in Period II).

A washout period of 9 and 10 days was maintained between the between doses for each group, respectively. The washout period of 9 or 10 days is long enough in regard to the half-life of the studied active substance liraglutide. It is longer than 5 times half-life of active substance (5 x 13 hours).

Study subjects showed up at the clinical site of Triumpharma in the morning of day -1 (approximately 21 hours pre-dosing) and were confined for 48 hours after dosing in each period. Subjects returned to the clinical site at 72 hours post-dosing to give the scheduled pharmacokinetic blood samples (in each period) and to undergo the final examinations in period II.

Parent compound (liraglutide) was analysed in plasma samples.

A total of 23 blood samples were collected for this study, in each period, according to the following schedule: one pre dose sample, 0.50, 1.00, 2.00, 4.00, 6.00, 7.00, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00, 11.50, 12.00, 13.00, 14.00, 16.00, 24.00, 36.00, 48.00, and 72.00 hrs post dosing. All samples up to 16.00 hrs were withdrawn via the cannula. The 24.00, 36.00, 48.00 and 72.00 hours blood samples were withdrawn by direct venipuncture. The sampling scheme to estimate pharmacokinetic parameters for conclusion regarding bioequivalence is adequate (frequent sampling around predicted T_{max} (according to reference SmPC T_{max} of liraglutide is approximately 11 hours), at least 3 samples during the terminal log-linear phase for individual subject). Sampling period 72 hours is long enough for concerned drug product (elimination half-life of liraglutide is approximately 13 hours, in none of the subjects AUC_{0-t} was less than 80% of AUC_{0-inf}).

Information on fluid and food intake and information on posture and physical activities after investigational products administration in both periods has been provided. It is considered that fluid and food intake, posture and physical activities were standardised. The study subjects had to comply with a restriction on taking prescribed medication, OTC medicinal products, vitamins and herbal medications prior to and during the course of this study.

Test and reference products

Detailed information on the proposed and reference product used in bioequivalence study LIR.0.6/450 are provided in the following table:

Table 8: Bioequivalence study LIR.0.6/450

Product Characteristics	Test product	Reference Product
Drug Name:	Liraglutide	Saxenda®
Strength:	6 mg/ml	6 mg/ml
Dosage Form:	Solution for Subcutaneous Injection in Pre-filled Pen	Solution for Subcutaneous Injection in Pre-filled Pen
[redacted]		
Lot number	7000284B	NT6CC78
[redacted]		
Measured content(s) (% of label claim)	100.9 %	100.4 %
Commercial Batch Size	N/A	N/A
Expiry Date	Mar/2026	Nov/2025
Manufacturing date	Apr/2024	N/A
Location of Certificate of Analysis	Page no. 18/ Appendix 16.1.7	Page no. 23/ Appendix 16.1.7
Member State where the reference product is purchased from:	N/A	N/A
This product was used in the following trials	LIR.0.6/450	LIR.0.6/450

Certificates of analysis for the test and reference product bio-batch were provided. According to the Certificates of analysis the assayed content of the batch used as test product does not differ more than 5% from that of the batch used as reference product.

Batch analysis for 3 validation batches has been performed. Results (including protein content and delivered volume) were comparable and within specification limits for all 3 batches. It is considered that the selected test biobatch is representative batch of the proposed product.

No such data for more batches of reference product have been provided. However, 3 batches of reference product Saxenda were included in quality comparability testing (structural characterization) and were considered comparable. The protein content in reference and test products was 99.8% and 100.9%, respectively.

The reference product is registered in EU and obtained from the EU Member State Denmark, which is acceptable.

It was confirmed that the test product used in the bioequivalence study had the same qualitative and quantitative composition and was manufactured by the same manufacturing process as the medicinal product submitted for authorisation.

- **Population(s) studied**

The population chosen is according to the Guideline on the investigation of bioequivalence. Healthy male and female subjects participated in the study; they met all the inclusion criteria and none of the exclusion criteria

described in the study protocol. Healthy volunteers are the preferred population to identify formulation related differences in PK studies and based on the known acceptable safety profile of the reference product, the proposal to conduct the study in healthy volunteers is therefore endorsed.

A total of 47 healthy male and female human subjects eligible for participation, as per the selection criteria of the protocol, were enrolled in period I in two groups (34 and 13 subjects respectively).

One subject was withdrawn before admission of period II (14th October 2024).

A total of 46 subjects completed the study. The concentration data for the 46 subjects who completed the study were included in liraglutide PK analysis, statistical analysis, and BE evaluation.

The PK blood samples for the 47 subjects were analysed in the bioanalytical laboratory.

The demographic data were presented and were considered appropriate.

Sample size calculation was presented and was considered appropriate. Sample size was adequate.

Protocol deviations

Some deviations were reported, in relation to: total number of subjects, adherence to protocol (two subjects smoked, without any expected effect on the study outcome), sample collection times and one missing sample. It is considered that the deviations didn't affect the study outcome as actual sampling times were considered for PK and statistical analyses. List of sampling time deviations and list of study subject sampling times have been presented.

Analytical methods

Pre-study method validation

The bioanalytical UPLC-MS/MS method for the quantification of liraglutide in human plasma (containing K_2EDTA as an anticoagulant) was validated as presented in the following table:

Table 9: Study number 23ANE-3964V

Study Number (Version)	Historical File
23ANE-3964V (Version 3.0)	Full validation
23ANE-3964V01 (Version 1.0)	Partial Validation 1 was performed: ▪ To assess the assays of ADA sensitivity ▪ To extend long-term stabilities of analytes and internal standards in stock solution at -20 °C ([redacted] days) ▪ To extend long-term stabilities of analytes in working solutions and internal standards in secondary solution at -20 °C ([redacted] days) ▪ To extend long-term stabilities of analytes in matrix at -20 °C and -80 °C ([redacted] days at QC1 and QC3 levels and [redacted] days at HDQC level)
23ANE-3964V02 (Version 1.0)	Partial Validation 2 was performed to change the calibration range from [redacted] ng/mL to [redacted] ng/mL.
23ANE-3964V03 (Version 1.0)	Partial Validation 3 was performed: ▪ To extend long-term stabilities of analyte in matrix at -20 °C and -80 °C ([redacted] days) (calibration range from [redacted] ng/mL).

Main bioanalytical method validation was performed between 5th April and 24th July 2023, and validation report dated 5th July 2024 has been enclosed. Later, partial validation 1 was performed (11th December 2023 – 17th January 2024, report dated 9th February 2024).

Validation report for main bioanalytical method validation and partial validation 1 were enclosed. Validation plan (for main validation and partial validation) and some of the bioanalytical method validation SOPs have been enclosed.
GLP/GCP compliance statement and Quality assurance unit statement were included in main validation report and partial validation report. Certificates of analysis of reference standards and internal standards used in main validation and partial validation were enclosed.

There was no observed deviation in main method validation. During partial method validation two deviation from validation plan has been observed (Minor text modifications were corrected. Acceptance criteria for specificity assay have been modified to within 100 ± 25% instead of 100 ± 20%, according to the literature). Modified acceptance criteria for specificity assay (100 ± 25%) are considered acceptable according to ICH guideline M10 on bioanalytical method validation and study sample analysis, specificity validation in ligand binding assays.

The following parameters requested according to ICH guideline M10 on bioanalytical method validation and study sample analysis have been successfully validated during main study validation: selectivity (in normal, haemolysed and hyperlipidaemic matrices), specificity in the presence of concomitant drugs (acetaminophen (paracetamol), caffeine, ibuprofen, nicotine, acetylsalicylic acid, salicylic acid, ethinyl estradiol, drospirenone, levonorgestrel, etonogestrel (3-ketodesogestrel), gestodene, norelgestromin and dienogest), matrix effect (in normal, haemolysed and hyperlipidaemic matrices), calibration range and linearity, within-run and between-run precision and accuracy (including maximum run size), autosampler carryover, dilution integrity, recovery of analyte and internal standard, reinjection reproducibility, stability (post-preparative stability, sample collection and handling stability, freeze and thaw stability, short-term and long-term stability of analyte in matrix, short-term stability of analyte in stock solution and in working solution, short-term stability of internal standard in stock solution and in secondary solution, long-term stability of analyte in stock solution and in working solution, long-term stability of internal standard in stock solution and in secondary solution).

The following additional parameters have been successfully validated during partial validation: selectivity assay fortified with anti-liraglutide at low and at high concentration, specificity assay fortified with anti-liraglutide at low and at high concentration, extended stability (long-term stability of analyte in matrix, long-term stability of analyte in stock solution and in working solution, long-term stability of internal standard in stock solution and in secondary solution).

Summary of analytical runs (including rejected runs) with analysis dates, table of calibration standard concentration and response functions results (calibration curve parameters) of all accepted runs with accuracy and precision, instrument ID, 100% of run results tables of accepted and failed runs, and 100% of method validation chromatograms of accepted and failed runs have been provided for main validation and partial validation.

Bioanalytical method validation is considered to ensure the acceptability of assay performance and the reliability of analytical results.

Analysis of study samples and within-study validation

Analytical report 'Determination of liraglutide in human K_2EDTA plasma samples from study: A randomized, two-treatment, two-period, two-sequence, crossover, open label, laboratory blind, single dose bioequivalence study between Liraglutide 6 mg/ml solution for subcutaneous injection in pre-filled pen (test product) and Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen (reference product), following a single 0.6 mg subcutaneous dose, in healthy, adult, human, subjects under fed conditions (Study No. 24ANE-4203, version 1.0) dated 12th December 2024' was enclosed.

The bioanalytical phase of the study was conducted as per analytical study plan 'Determination of liraglutide in human K_2EDTA plasma samples from study: A randomized, two-treatment, two-period, two-sequence, crossover, open label, laboratory blind, single dose bioequivalence study between Liraglutide 6 mg/ml solution for subcutaneous injection in pre-filled pen (test product) and Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen (reference product), following a single 0.6 mg subcutaneous dose, in healthy, adult, human, subjects under fed conditions, version 1.0, dated 14th October 2024', which was enclosed.

It is considered that there are no changes in the analytical methods that would require additional validation.

The sample analysis was performed at the bioanalytical facility Anapharm Europe, S.L.U., C/ Encuny 22, 2nd floor, 08038 Barcelona, Spain. Bioanalytical phase has been performed from 16th October to 25th November 2024.

First study sample was collected on 6th October 2024 and last study sample was analysed on 22nd November 2024. Maximal storage period of study samples was 47 days at -20°C. Long-term stability of liraglutide in K_2EDTA human plasma was established for 263 days at -20°C in polypropylene LoBind tubes. In addition, the stability in human K_2EDTA plasma at -80 ºC in polypropylene LoBind tubes has been proved for 263 days with the aim to guarantee the stability of the samples during the transport.

Table 10: Study samples details

Number of subjects as per protocol	48
Number of study periods as per protocol	2

Number of sampling points per period as per protocol	23
Number of study samples as per protocol	2208 (48 x 2 x 23)
Number of samples received	2140 (including stand-by subject S1 pre-dose sample and aliquot 2, period I, 9.00h sample of subject 38)
Missing samples	70 46 samples (period I and II of subject 48) 23 samples (period II of subject 7) 1 sample (period I, 1.00h sample of subject 41)
Total number of samples with valid results	2139 (aliquot 2, period I, 9.00h sample of subject 38 was not analysed)

Bioanalytical method has been within-study validated. Samples were analysed in the following order: the stabilisation sample, first replicate of BLK, ZS and each calibration standard in ascendant order of concentrations, followed by study samples bracketed by QCs. The remaining QCs were interspersed amongst the study samples. The number of QCs should be at least 5% of the number of study samples included in each analytical run. Finally, the second replicate of BLK, ZS and each calibration standard in ascendant order of concentrations were added at the end of the analytical run.

Due to carryover issues, during study sample analysis, additional blank samples were extracted and injected after the injection of the most concentrated calibration standards and quality control samples (CS8, QC2 and QC3 samples), as well as before the injection of QC1 and QC4 samples. Moreover, a blank sample was injected before each pre-dose sample to ensure that, if the elimination phase of the previous subject is not complete, it will not affect the pre-dose sample of the next subject. No additional blank samples were required between study samples, as these are injected in chronological order of concentration. Accordingly, additional blank samples between calibration standards samples are not required since those samples are run on ascendant concentration order, therefore there was no impact on accuracy levels. These additional blank samples were not considered for the analytical run acceptance criteria.

To minimise the effect of variability among analytical runs, all samples from each subject were analysed in the same run (except reanalysis).
Accepted analytical runs are considered to have met analytical run acceptance criteria. The range of accuracy and precision of the back-calculated concentrations of the calibration curve standard points during the study were 98.33% to 101.52% and 3.56% to 9.96% respectively. Correlation coefficient was more than 0.99. The overall mean accuracy and precision of quality control samples during the study were 99.34% to 101.48% and 3.53% to 9.44% respectively. At least the 67% of the analysed quality controls were acceptable. At least the 50% of the quality controls of each level were acceptable. However, there was one SOP deviation (an extra CO-BLK sample was extracted and injected after the QC1-2 samples, so that, according to the run sequence order, was injected just before one of the blank samples of the calibration curve (BLK-2)). Additional analysis (analyte and internal standard carryover calculation for the extra CO-BLK sample) was performed and the results confirmed that all CO-BLK samples met the acceptance criteria.

Two individual samples were reintegrated. SOP-LAB-20 Integration criteria and acceptance of chromatograms was followed. Reintegrations performed were reported in the study's final report. A table presenting all the reintegrated samples and the reason for the reintegration was included. Original and reintegrated chromatograms and initial and repeat integration results were provided.

One whole analytical run and 4 individual samples were reinjected. Data on it were provided and were considered acceptable. SOP-LAB-32 General procedure for analysis with chromatographic techniques was requested to confirm acceptability of reasons for reinjection.

Forty-nice (49) individual samples were reanalysed. Two (2) samples were reanalysed due to Sample manipulation and extraction error – IS response < 5%. This reason is predefined in SOP-LAB-16 Sample reassays and final reported concentrations. Original, repeat and reported values are presented. Repeat values were reported, which is in line with SOP. 74 samples were reanalysed as part of technical investigation. The results obtained after the reanalysis confirmed the first concentration values (< 0.50 ng/mL).

One hundren fifty-seven (157) of 2139 study samples were considered for ISR evaluation. It represents more than 10% of the first 1000 study samples + 5% of the number of samples that exceed 1000 samples. Results of incurred sample reanalysis confirmed the reproducibility of the bioanalytical method.

Summary of analytical runs with analysis dates, table of calibration standard concentration and response function results (calibration curve parameters) of all accepted runs with accuracy and precision, instrument ID for each run, IS response plots for each analytical run and 100% of run summary table of analytical runs have been provided. 100% chromatograms are presented.

LLOQ for liraglutide (0.50 ng/mL) is less than 5% of min C_{max} (11.71 ng/mL for test product (excluding 2 subjects with all non-quantifiable concentrations) and 14.31 ng/mL for reference product) and therefore acceptable.

One subject received concomitant medications (metoclopramide and esomeprazole) during the study. The potential interference of the concomitant medications metoclopramide and esomeprazole was evaluated during partial validation, the results demonstrated that these medications did not interfere with the determination of liraglutide.

GLP/GCP compliance statement and Quality assurance unit statement were included in the analytical report. Certificates of analysis of reference standard and internal standard used in study sample analysis have been enclosed.

There was one SOP deviations observed during this study (an extra CO-BLK sample was extracted and injected after the QC1-2 samples as mentioned above). There were neither amendments nor deviations to the study plan.

- **Pharmacokinetic Variables**

Pharmacokinetic parameters for liraglutide plasma concentrations were calculated:
- Primary endpoints: C_{max}, AUC_{0-t}, and AUC_{0-inf}.
- Secondary end points: T_{max}, $AUC\_{\%Extrap\_obs}$, T_{half}, Vz_F, and $K_{elimination}$.

It is according to the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, for a single dose PK study with medicinal product for subcutaneous administration.

Pharmacokinetic analysis of Liraglutide bioanalysis data was carried out using non-compartmental analysis model of Phoenix WinNonlin software version 8.3.4 (Pharsight Corporation, USA).

The actual times of blood samples collection are recorded, and the actual times are computed for pharmacokinetics and statistical analysis.

All concentration values below limit of quantification are replaced by zero for the pharmacokinetic and statistical analysis.

In line with Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, in any PK study, anti-drug antibodies should be measured in parallel to PK assessment using appropriate sampling time points. In concerned study anti-drug antibodies have not been measured. This is acceptable considering BE study short duration and the cross-over design. Moreover, in individual subject no systematic significant decrease of AUC in Period II in comparison to Period I was observed. According to literature data the frequency and levels of anti-liraglutide antibodies were low and did not impact glycaemic efficacy or safety. It appeared that anti-drug antibodies were not present, therefore it is considered acceptable not no measure them.

- **Statistical methods**

Statistical analysis of Liraglutide is carried out using Phoenix WinNonlin version 8.3.4.

Analysis of variance is performed on ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} data.

The analysis of variance model includes sequence, subjects nested within sequence, period, and drug formulation as fixed factors.

A 5% level of significance was used for within-subject comparisons (i.e. period and formulation) and between-subject comparisons (i.e. sequence and subjects nested within sequence). Each analysis of variance includes calculation of least-squares means, adjusted differences between formulation means and the standard error associated with these differences.

The 90% confidence intervals for the difference between drug formulation LSM were calculated for the primary PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) using ln-transformed data. The confidence intervals are expressed as a percentage relative to the LSM of the reference formulation.

Ratios of means are calculated using the LSM of ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}).

The power of a test to detect 20% difference between test and reference were displayed in ANOVA output for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}.

Discontinued subjects were not included in pharmacokinetic and statistical analysis. Handling of missing values of these subjects was appropriate (were disregarded in pharmacokinetic and statistical analysis). There was one individual missing sample from subject included in PK and statistical analysis. In pharmacokinetic calculations the default method for NCA "Linear_Trapezoidal_Linear_Interpolation" was used, applying the linear trapezoidal rule to each pair of consecutive point in the data set that have non-missing values and sums up these areas.

<u>Bioequivalence Criteria:</u>

Bioequivalence is demonstrated under fed conditions if: The 90% CI for the Test/Reference ratios of geometric means for C_{max}, AUC_{0-t}, and AUC_{0-inf} are within acceptance range of 80.00%-125.00% for liraglutide.

Results

Table 11: Pharmacokinetic parameters for liraglutide (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (h*ng/mL)	984.95**	325.941	1010.85	267.671
$AUC_{(0-\infty)}$ (h*ng/mL)	1012.30**	321.812	1037.14	263.707
C_{max} (ng/mL)	38.34	15.859	39.41	10.217
T_{max}* (h)	11.50 (7.00*** - 16.00)		11.50 (6.00-16.00)	
$AUC\_{\%Extrap\_obs}$	3.15**	2.550	2.83	2.024
T_{half} (h)	9.73**	1.862	9.97	1.535
Vz_F	9270.10**	4074.714	8880.61	3022.386
$K_{elimination}$ (h^{-1})	0.0738**	0.01397	0.0711	0.01059

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)
$AUC\_{\%Extrap\_obs}$	the extrapolated AUC estimated as ((AUC_{0-inf} - AUC_{0-t})/ AUC_{0-inf})*100.
T_{half}	the elimination or terminal half-life will be calculated as 0.693/$K_{elimination}$
Vz_F	volume of distribution based on the terminal phase
$K_{elimination}$	Apparent first-order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations. $K_{elimination}$ is calculated while maintaining the following factors: - Rsq adjusted ≥ 0.8 - A negative slope - BLOQ values should not be considered in the regression line - Only include data points after T_{max}

** N=44 for subjects who have quantifiable concentrations (two subjects reported < LLOQ values, thus WinNonlin displayed 0.00 for their C_{max} and T_{max} and missing values for the other PK parameters in period I)

*** Min value for the subjects who have quantifiable concentrations

Table : Statistical analysis for liraglutide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$ (h*ng/mL)	94.77	85.30 – 105.30	29.98
AUC_{0-inf} (h*ng/mL)	95.14	86.00 – 105.25	28.72
C_{max} (ng/mL)**	98.71	88.73 – 109.80	30.34

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
* estimated from the Residual Mean Squares			

Bioequivalence has been demonstrated under fed conditions for Ablymico (test product) and Saxenda (reference product) as the 90% CI for the Test/Reference ratios of geometric means are within the acceptance range of 80.00 %-125.00 % for Liraglutide ln transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} data. However, the following issue was observed and has been clarified:

Two subjects reported values below LLOQ in period I (after administration of test product. All investigations concluded that there was neither an error in dosing nor in bioanalysis.

Furthermore, the devices used in the clinical study were examined at the Applicant's assay laboratory.. The most probable cause for the lack of plasma levels for one of the subjects was an error in dosing at the clinic.

Additional evidence supporting the bioequivalence of the Test product comes from another bioequivalence study (2023-LIRA0433-PK-05) using the same Test product batch (7000284B) as used in the EU study and Canadian reference product Saxenda. Results from this study in 48 subjects demonstrated bioequivalence for all PK parameters.

Finally, the Applicant carried out a clinical robustness study , at the same CRO conducted the study as in the EU study, replicating the conditions of the BE study to clinically assess the device's performance and safety, considering variability in patient characteristics and usage conditions as primary objective. The study design included new measures to reduce the risk of device misuse by healthcare professionals administering doses in the bioequivalence study. The results of the study showed plasma concentrations successfully measured at the two planned post-dose timepoints (4.00 hr and 11.50 hr). None of the 100 subjects had plasma concentrations at any timepoint below 5% of the respective mean value.

Based on the provided additional data (the device investigation report, the additional BE study against the Canadian reference product and the results of the clinical robustness study) it is agreed that the absence of plasma levels in the two subjects were caused by errors in the administration procedure by clinical staff, resulting in an incorrect handling of the device rather than a device malfunction.

T_{max} values have been determined, which were comparable between test and reference products.

Comparable C_{max} and T_{max} between test and reference product suggest that there is no difference in albumin binding affinity between test and reference product.

C_{max} of liraglutide was not the first point of a concentration time curve in any subject.

Pre-dose plasma concentration of liraglutide was below the limit of quantitation (0.50 ng/mL) for all subjects in both periods.

All subjects had liraglutide plasma concentration curves where extrapolated area was <20%.

Following ANOVA evaluation of pharmacokinetic parameters statistically significant period effect was observed for AUC_{0-t}, and AUC_{0-inf}. The applicant has provided adequate clarification that this significant period effect is not clinically relevant.

In the bioequivalence study, two groups were dosed several days apart in both period 1 and period 2. It was clarified why group effect was nullified and can be ignored. Additionally, an analysis of the group effect based

on the article from Schütz et.al, 2024 has been performed. By additional analysis the test/reference ratio and the confidence intervals for C_{max} and AUC_{0-t} were still within the bioequivalence limits of 80% - 125%.

- ***Safety data***

There were no deaths or serious adverse events during the conduct of the study. Twelve (12) adverse events were reported during the study, all subjects completely recovered. The test and reference products were found safe following administration of a single 0.6 mg Liraglutide subcutaneous dose to healthy adult male and female subjects, in each study period, under fed conditions.

One (1) subject received concomitant medications due to adverse events. According to the Study report upon testing by the bioanalytical lab, none of the medicines (metoclopramide and esomeprazole) were identified as having the potential to interact with liraglutide. The potential interference of the concomitant medications metoclopramide and esomeprazole has been evaluated during partial validation, the results demonstrated that these medications do not interfere with the determination of liraglutide.

2.4.2.2. Pharmacokinetic Conclusion

Based on the presented bioequivalence study LIR.0.6/450 proposed product Ablymico 6 mg/ml solution for subcutaneous injection in pre-filled pen is considered bioequivalent with reference product Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen.

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented. Clinical PD studies could be waived, since comparability of the pharmacological activity of liraglutide products can be sufficiently investigated *in vitro* by a variety of bioassays that analyse on the one hand receptor binding of liraglutide and on the other hand the subsequent cellular response (namely cAMP formation etc).

2.4.3. Discussion on clinical pharmacology

Pro-peptide in the reference product Saxenda (liraglutide) is of biological origin, whereas the pro-peptide in the proposed medicinal product Ablymico (liraglutide) is of chemical origin. To support the application, a bioequivalence study comparing the applicant's product Ablymico 6 mg/mL solution for injection in pre-filled pen with the reference product Saxenda 6 mg/mL solution for injection in pre-filled pen was conducted. Additionally, analytical studies to compare physico-chemical properties of the proposed and reference products were conducted, as well as comparative *in vitro* biological studies to demonstrate the pharmaco-toxicological similarity and potential impact on efficacy and safety.

The proposed medicinal product contains a synthetically manufactured active substance referring to a biotechnological/biological reference product. The basic principles to demonstrate biosimilarity should be considered for synthetic peptide development programmes in line with the draft Guideline on the development and manufacture of synthetic peptides (EMA/CHMP/CVMP/QWP/367182/2025). According to the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), the clinical biosimilar comparability exercise is normally a stepwise procedure that should begin with PK and, if feasible, PD studies

followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical biosimilar comparability.

The design of reported PK study is a randomised, two-period, two-sequence single dose crossover bioequivalence study, which is a recommended standard design according to Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The washout period of 9 or 10 days is long enough in regard to the half-life of the studied active substance liraglutide. Sampling period was sufficient and the sampling time schedule was considered adequate. The testing dose of 0.6 mg was considered acceptable since it is the starting daily dose recommended in the reference product to improve gastro-intestinal tolerability. Since liraglutide shows linear dose-proportional pharmacokinetics, the PK results obtained in the bioequivalence study with the lower dose strength can be extrapolated to proportionally higher dosages. According to the reference SmPC medicinal product can be taken independent of meals and therefore study should be conducted under fasting conditions, which are more sensitive. The study was conducted under fed conditions to minimize the gastrointestinal adverse events (nausea and vomiting) of the administered drug. Since food consumption does not affect pharmacokinetics after subcutaneous application and since medicinal products were taken with food due tolerability reasons, fed conditions were considered acceptable. Fluid and food intake, posture and physical activities were standardized.

Data regarding the test and reference product were provided. The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product. Selected test biobatch is representative batch of the proposed product, selected reference biobatch is acceptable. The reference product is authorised in an EU and obtained from the EU Member State Denmark. It is confirmed in the submitted application that the test product used in the bioequivalence study has the same qualitative and quantitative composition and is manufactured by the same manufacturing process as the medicinal product submitted for authorisation.

A total of 47 healthy male and female human subjects eligible for participation, as per the selection criteria of the protocol, were enrolled in period I in two groups (34 and 13 subjects respectively). Healthy volunteers are the preferred population to identify formulation related differences in PK studies and based on the known acceptable safety profile of the reference product, the proposal to conduct the study in healthy volunteers is therefore endorsed. One subject was withdrawn due to positive result for drugs of abuse test, before admission of period II on 14th October 2024. A total of 46 subjects completed the study. The concentration data for the 46 subjects who completed the study were included in Liraglutide PK analysis, statistical analysis, and BE evaluation. The PK blood samples for the 47 subjects were analysed in the bioanalytical laboratory and are reported in the tables of Analytical report. Case Report Forms for discontinued subject were provided and confirmed information on discontinuation. Two subjects did not adhere to instructions and smoked one cigarette approximately one-hour before dose (protocol deviation). The study investigators did not report any related safety issues for those cases as there were no effect on the subject's safety, nor expected effect on study outcome as there is no reference that explicitly indicated smoking's effect on the pharmacokinetics of liraglutide. Statistical analysis without the two subjects confirmed bioequivalence.

The bioanalytical method (UPLC-MS/MS) for quantification of liraglutide (parent drug) in human K2EDTA plasma samples was validated pre-study and within study according to ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019). Bioanalytical report and validation reports have been enclosed. Handling of samples was adequate. Issues with SOP deviation (an extra CO-BLK sample) and rejected analytical runs within analysis of study samples have been clarified. Bioanalytical method has been validated in the presence of metoclopramide and esomeprazole. Bioanalytical method is considered acceptable for study samples analysis.

The following pharmacokinetic parameters for liraglutide plasma concentrations were calculated: C_{max}, AUC_{0-t}, and AUC_{0-inf} (primary end points) and T_{max}, $AUC_{\_\%Extrap\_obs}$, T_{half}, Vz_F, and $K_{elimination}$ (secondary end points). They are in line with the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (for a single dose PK study, after subcutaneous administration). Pharmacokinetic parameters for liraglutide were calculated using non-compartmental methods. The software used for determination of pharmacokinetic parameters was Phoenix WinNonlin Version 8.3.4. Actual time points of the sample collection were used for the calculation of pharmacokinetic parameters.

In line with Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, in any PK study, anti-drug antibodies should be measured in parallel to PK assessment using appropriate sampling time points. In the concerned study anti-drug antibodies have not been measured. This is acceptable considering BE study short duration and the cross-over design. Moreover, in individual subject no systematic significant decrease of AUC in Period II in comparison to Period I was observed. According to literature data the frequency and levels of anti-liraglutide antibodies were low and did not impact glycaemic efficacy or safety. It appears that anti-drug antibodies are not present, therefore it is considered acceptable not no measure them.

The statistical method used for the pharmacokinetic analyses: Data transformations are acceptable. Analysis of variance was performed on ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} data. The analysis of variance model included sequence, subjects nested within sequence, period, and drug formulation as fixed factors. Statistical analysis of liraglutide was carried out using Phoenix WinNonlin version 8.3.4.

The criteria for bioequivalence were predefined and are acceptable. The test formulation Ablymico 6 mg/ml solution for subcutaneous injection in pre-filled pen (Test Product) met the protocol-defined criteria for bioequivalence when compared with the reference product Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen (Reference Product) as the 90% CI for the Test/Reference ratios of geometric means were within the acceptance range of 80.00 %-125.00 % for Liraglutide ln transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} data. In the bioequivalence study, two groups were dosed several days apart in both period 1 and period 2. It was clarified why group effect was nullified. Additionally, an analysis of the group effect based on the article from Schütz et.al, 2024 has been performed. By additional analysis the test/reference ratio and the confidence intervals for C_{max} and AUC_{0-t} were still within the bioequivalence limits of 80% - 125%.

Two subjects reported values below LLOQ in period I (after administration of test product). All investigations concluded that there was neither an error in dosing nor in bioanalysis.

There were no deaths or serious adverse events during the conduct of the study. The test and reference products were found safe following administration of a single 0.6 mg liraglutide subcutaneous dose to healthy adult male and female subjects, in each study period, under fed conditions.

Appropriate statements on GCP have been provided. The applicant provided a list of inspections of clinical site and bioanalytical site where the bioequivalence study was conducted. All deviations were positively addressed, the GLP certificates have been provided. Furthermore, it is considered that the study had been conducted using validated method and in accordance with applicable regulatory guideline and requirements. There are no other observations, which could have raised concerns about the quality or validity of the sampling process or study sample analyses, the bioanalytical method validation or the statistical analysis. There is no concern with regard to the GCP compliance of the study.

No new pharmacodynamic studies were presented. Clinical PD studies could be waived, since comparability of the pharmacological activity of liraglutide products can be sufficiently investigated in vitro by a variety of bioassays that analyse on the one hand receptor binding of liraglutide and on the other hand the subsequent cellular response (namely cAMP formation etc).

2.4.4. Clinical efficacy

No new efficacy studies were submitted. Efficacy of the present formulation is based on the efficacy of the previously approved reference product.

The bridging of efficacy data to the approved reference product is based on *in vitro* comparability studies and bioequivalence study.

2.4.5. Clinical safety

No new safety studies were submitted. Safety of the present formulation is based on the safety of the previously approved reference product.

The bridging of safety data to the approved reference product is based on *in vitro* comparability studies and bioequivalence study. All properties of liraglutide that are known to influence its immunogenicity have been sufficiently well characterized by *in vitro* analyses within a comparability study.

Use trial was not conducted. and the product was administrated in the presented study by healthcare professionals. Justification for not performing a usability study for the pre-filled pen has been provided and considered acceptable. A series of thorough investigations and evaluations to identify and analyse the potential causes of the below lower limit of quantification (<LLOQ) plasma concentrations observed in two subjects following administration of the test product has been conducted. Based on the provided additional data (the device investigation report, the additional BE study against the Canadian reference product and the results of the clinical robustness study) it is agreed that the absence of plasma levels were caused by errors in the administration procedure by clinical staff, resulting in an incorrect handling of the device rather than a device malfunction.

The instructions for use, user interface, handling steps, and performance characteristics are essentially equivalent to those of the reference product Victoza. The minor differences identified did not impact the user experience or the safe and effective use of the device. Therefore, it was concluded that existing data and comparative analysis are sufficient to demonstrate that users familiar with Victoza can safely and effectively user the proposed generic pen injector.

2.4.5.1. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study LIR.0.6/450, the proposed medicinal product Ablymico 6 mg/ml solution for subcutaneous injection in pre-filled pen is considered bioequivalent to the reference product Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen.

Efficacy and safety of the present formulation is based on the efficacy and safety of the previously approved reference product. The bridging of efficacy and safety data to the approved reference product is based on *in vitro* comparability studies and bioequivalence study. Waiver of a usability study for the pre-filled is considered adequately justified.

The clinical overview on the clinical pharmacology, efficacy and safety of liraglutide is adequate. Clinical sections of proposed SmPC are aligned with the SmPC of reference product Saxenda.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 13: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

It was noted that the reference product Saxenda has an ongoing Medullary thyroid carcinoma surveillance study (MTC-22341) – case series registry (NN221-3965), a category 3 PASS conducted in the United States as an FDA post-marketing requirement for long-acting GLP-1 receptor agonists. The study monitors the annual incidence of MTC in the US through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 ARAs into the US market; and registers cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with long-acting GLP-1 RAs.

This activity is conducted outside the EU and is not part of the EU pharmacovigilance plan. Therefore, inclusion in the RMP for the present application is not necessary.

2.5.3. Risk minimisation measures

None

2.5.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report. The applicant has performed a bridging study to the User consultation for previously accepted user-tested leaflet material [Design/layout] and European Reference Product [safety information]. The bridging report submitted by the applicant has been found acceptable..

3. Benefit-Risk Balance

3.1. Benefit-risk assessment and discussion

This application concerns a hybrid version of liraglutide solution for subcutaneous injection in a pre-filled pen. A hybrid application was submitted due to differences in the manufacturing of the active substance in the proposed product compared with the reference medicinal product. The pro-peptide of the reference product Saxenda is of biological origin, whereas the pro-peptide in the proposed medicinal product Ablymico is obtained by chemical synthesis.
The reference product Saxenda is indicated for weight management in adults, adolescence and children aged 6 and older. The full indication is:

Adults

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:

- ≥ 30 kg/m^2 (obesity), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5 % of their initial body weight.

Adolescents (≥ 12 years)

Saxenda can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:

- obesity (BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points)* and
- body weight above 60 kg.

Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*IOTF BMI cut-off points for obesity by sex between 12-18 years (see table 1), in accordance with study design of the Trial 4180, see section 5.1.

Table 1 IOTF BMI cut-off points for obesity by sex between 12-18 years

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	Males	Females
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30.00	30.00

Children (6 to < 12 years)

Saxenda is indicated as an adjunct to healthy nutrition and increased physical activity for weight management in children from the age of 6 to < 12 years with

- obesity (BMI ≥ 95th percentile)* and
- body weight ≥ 45 kg

Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*CDC BMI cut-off points for obesity (≥ 95th percentile) by sex between 6 to < 12 years (see table 2), in accordance with study design of the Trial 4392, see section 5.1.

Table 2 Cut-off points for BMI (Weight in kg/Height in m^2) for obesity (≥ 95th percentile) by sex for children from 6 and < 12 years of age

Age (years)	Obesity BMI ≥ 95th percentile	
	Males	Females
6	18.41	18.84
6.5	18.76	19.23
7	19.15	19.68
7.5	19.59	20.17
8	20.07	20.70
8.5	20.57	21.25
9	21.09	21.82
9.5	21.62	22.40
10	22.15	22.98
10.5	22.69	23.57
11	23.21	24.14
11.5	23.73	24.71

Non-clinical studies provided for this application and were considered sufficient. From a clinical perspective, this application did not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance.

The bioequivalence study formed the pivotal basis with an open label, laboratory-blind, randomized, single dose, two treatments, two periods, two sequence, crossover design under fed conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The study was carried out in fed conditions. According to the reference SmPC, the medicinal product can be taken independent of meals and therefore study should be conducted under fasting conditions, which are more sensitive. The study was conducted under fed conditions to minimize the gastrointestinal adverse events (nausea and vomiting) of the administered drug. Since food consumption did not affect pharmacokinetics after subcutaneous application and since medicinal products were taken with food due to tolerability reasons, fed conditions are considered acceptable. Concentration of the reference medicinal

product liraglutide was measured in the plasma samples. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The bioanalytical method was validated and the pharmacokinetic methods applied were considered adequate.

The test formulation of liraglutide 6 mg/ml solution for subcutaneous injection in pre-filled pen met the protocol-defined criteria for bioequivalence when compared with the reference product Saxenda 6 mg/ml solution for subcutaneous injection in pre-filled pen. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%.

CHMP concluded that the clinical PD studies, clinical efficacy studies and clinical immunogenicity studies could be waived since it was demonstrated that all properties of liraglutide that are known to influence its PK, PD or immunogenicity were comparable between the proposed and reference product by appropriate *in vitro* analyses. The Applicant has provided an acceptable justification for not performing a usability study for the pre-filled pen. It was considered that existing data and comparative analysis were sufficient to demonstrate that users familiar with Saxenda can safely and effectively use the generic pen injector supplied with Ablymico.

It was concluded that the benefit/risk ratio of Ablymico is comparable to the reference product Saxenda.

3.2. Conclusions

The overall benefit/risk balance of Ablymico is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ablymico is not similar to Imcivree within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

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

Adults

Ablymico is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:

- ≥ 30 kg/m^2 (obesity), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Ablymico should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5 % of their initial body weight.

Adolescents (≥ 12 years)

Ablymico can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:

- obesity (BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points)* and
- body weight above 60 kg.

Treatment with Ablymico should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*IOTF BMI cut-off points for obesity by sex between 12-18 years (see table 1), in accordance with study design of the Trial 4180, see section 5.1.

Table 1 IOTF BMI cut-off points for obesity by sex between 12-18 years

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	Males	Females
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14	27.63	28.57
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15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30.00	30.00

Children (6 to < 12 years)

Ablymico is indicated as an adjunct to healthy nutrition and increased physical activity for weight management in children from the age of 6 to < 12 years with

- obesity (BMI ≥ 95th percentile)* and
- body weight ≥ 45 kg

Treatment with Ablymico should be discontinued and re-evaluated if patients have not lost at least 4 % of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*CDC BMI cut-off points for obesity (≥ 95th percentile) by sex between 6 to < 12 years (see table 2), in accordance with study design of the Trial 4392, see section 5.1.

Table 2 Cut-off points for BMI (Weight in kg/Height in m^2) for obesity (≥ 95th percentile) by sex for children from 6 and < 12 years of age

Age (years)	Obesity BMI ≥ 95th percentile	
	Males	Females
6	18.41	18.84
6.5	18.76	19.23
7	19.15	19.68
7.5	19.59	20.17
8	20.07	20.70
8.5	20.57	21.25
9	21.09	21.82
9.5	21.62	22.40

10	22.15	22.98
10.5	22.69	23.57
11	23.21	24.14
11.5	23.73	24.71

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

5. Appendix

5.1. CHMP AR on similarity dated 21 May 2026