11 February 2015
EMA/143005/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Saxenda

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/003780/0000

Note

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

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
AHI	apnoea-hypopnoea index
Ala	alanine
All trials	trials 1807, 1839, 1922, 3970, 1923
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
Arg	arginine
AU	absorption units
AUC	area under the curve
BDP	bulk drug product
BES	Binge Eating Scale
BMI	body mass index
BOCF	baseline observations carried forward
BP	blood pressure
cAMP	cyclic adenosine monophosphate
CAS	chemical abstract service
CE	Conformité Européenne
CI	confidence interval
CPAP	continuous positive airway pressure
CT	computerised axial tomography
CTD	common technical document
CTR	clinical trial report
CV	cardiovascular
Da	Dalton
DEXA	dual energy x-ray absorptiometry
DNA	desoxyribo nucleic acid
DTSQs	Diabetes Treatment Satisfaction Questionnaire (status version)
EC_{50}	median effective concentration
EEA	European Economic Area

EEC	European Economic Community
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOSS	Edmonton Obesity Staging System
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	full analysis set
FFA	free fatty acids
FOSQ	Functional Outcomes of Sleep Questionnaire
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
Glu	glutamate
GMP	good manufacturing practice
HbA_{1c}	glycosylated haemoglobin A_{1c}
HCP	host cell protein
HCP	health care professional
HDL	high-density lipoprotein
HDPE	high-density polyethylene
His	histidine
HOMA	homeostasis model assessment
hsCRP	high sensitivity C-reactive protein
ICH	International conference on harmonisation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IPC	in-process control
ISO	International Organization for Standardization
IU	international unit
IWQoL-Lite	Impact of Weight on Quality of Life-Lite version
LCD	low-calorie diet
LDL	low-density lipoprotein
Lira 3.0 mg	liraglutide 3.0 mg
LOCF	last observation carried forward

LoQ	list of questions
LRQA	Lloyd's Register Quality Assurance
LS	least square
Lys	lysine
MAA	marketing authorization application
N/A	not applicable
NA	not applicable
NGSP	National Glycohaemoglobin Standardization Program
OAD	oral antidiabetic drug
OD	optical density
OGTT	oral glucose tolerance test
OR	odds ratio
OSA	obstructive sleep apnoea
PAI-1	plasminogen activator inhibitor-1
PBO	placebo
PCR	polymerase chain reaction
PDE	permissible daily exposure
PESU	polyethersulfone
PG	plasma glucose
Ph.3 56-week trials	trials 1839, 1922 and 1923
Ph.Eur.	European Pharmacopoeia
pM	picomolar
PP	per protocol
ppm	part per million
PSG	polysomnography
PYE	patient years of exposure
QA	quality assurance
r-DNA	recombinant DNA
s.c.	subcutaneous(ly)
SAE	serious adverse event
SCALE	Satiety and Clinical Adiposity – Liraglutide Evidence in non-diabetic and diabetic subjects
SCE	Summary of Clinical Efficacy (CTD module 2.7.3)

SCS	Summary of Clinical Safety(CTD module 2.7.4)
SD	standard deviation
Ser	serine
SF-36	36-item Short-Form health status survey
SmPC	summary of product characteristics
SU	sulphonylurea
T2DM	type 2 diabetes mellitus
T2DM	type 2 diabetes mellitus
Thr	threonine
TRIm-Weight	Treatment Related Impact measure-Weight
TSE	transmissible spongiform encephalopathy
TTC	threshold of toxicological concern
U	Unit
US	United States
UV	ultraviolet
Val	valine
VLDL	very low-density lipoprotein
WASO	wake time after sleep onset
WG	weight gain
WL	weight loss

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 20 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Saxenda, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

- 30 kg/m² or greater (obese), or
- 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as dysglycemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidemia, or obstructive sleep apnoea.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that liraglutide was considered to be a known active substance.

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0084/2012) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0084/2012) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

Additional Data/Market exclusivity

The applicant requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004. The applicant withdrew this request by a letter dated 20 May 2014.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 April 2008 and on 18 March 2010. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product has been given a Marketing Authorisation in the United States (US) on 23 December 2014

1.2. Manufacturers

Name and address of the manufacturers of the biological active substance

Novo Nordisk A/S
Hallas Alle,
4400 Kalundborg
Denmark

Novo Nordisk A/S
Novo Alle,
2880 Bagsvaerd
Denmark

Manufacturers responsible for batch release

Novo Nordisk A/S
Novo Alle
2880 Bagsvaerd
DENMARK

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff

Co-Rapporteur: Jens Heisterberg

CHMP Peer reviewer:Ondřej Slanař

- The application was received by the EMA on 20 December 2013.
- The procedure started on 22 January 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 April 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 April 2014.
- PRAC RMP Advice and assessment overview, adopted on 8 May 2014.
- During the meeting on 22 May 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 May 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 September 2014.
- PRAC RMP Advice and assessment overview, adopted on 9 October 2014.

- During the CHMP meeting on 23 October 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 November 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 November 2014.

- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 4 December 2014.

- During the CHMP meeting on 16 December 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- The Rapporteurs circulated an updated Joint Assessment to all CHMP members on 2 January 2015.

- During the meeting on 22 January 2015, 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 Saxenda.

- The European Commission (EC) requested some clarifications on 5 February 2015 regarding the discussion on the benefit-risk assessment.

- On 11 February 2015, the CHMP adopted a revised opinion and assessment report via written procedure to address the EC request.

2. Scientific discussion

2.1. Introduction

Problem statement

Obesity is one of the most significant public health challenges globally. Its impact is considerable in the Western world and it is now also an emerging epidemic in developing countries. Overweight and obesity are commonly classified using the body mass index (BMI), calculated as weight in kilograms divided by the square of height in metres. More than one-third of adults in the US and in countries across Europe are classified as obese, defined as a BMI of 30 kg/m2or greater, and 30-70% are overweight, with a BMI of 25-29.9 kg/m2.

Obesity has many serious health consequences, and a decreased life expectancy of 5–10 years, which make reducing its high prevalence a public health priority. It is a chronic condition associated with major comorbidities that include hypertension, hyperglycaemia, dyslipidaemia, certain types of cancer, obstructive sleep apnoea (OSA) and atherosclerosis. Obesity and overweight are also independent risk factors for myocardial infarction and ischaemic heart disease, the leading cause of death worldwide. The relationship between obesity and type 2 diabetes mellitus (T2DM) is well established, and the global obesity epidemic largely explains the 3-fold increase in the rates of T2DM in recent years. Obesity-related pre-diabetes increases the risk of developing T2DM 5-to 6-fold. It is also estimated that up to 5% of adults in Western countries may have undiagnosed OSA, and up to 20% may have at least mild OSA. Obesity adversely affects physical and mental health and reduces quality of life. Obese individuals often suffer from physical symptoms, such as joint pain, and psychosocial problems.

Increased caloric intake and a sedentary lifestyle have contributed to the increased prevalence of obesity in recent decades. Although not all people with obesity develop health problems, the risk of obesity-related complications and comorbidities increases with increasing BMI, and even a moderate weight loss of 5–10% has been shown to have significant health benefits in terms of improving glycaemic control, reducing progression to T2DM and improving other weight-related comorbidities, as mentioned above, as well as physical symptoms and quality of life. Current American Diabetes Association (ADA) treatment guidelines also recommend that individuals with T2DM achieve modest weight loss (5–7%) to improve glycaemic control and reduce cardiovascular risk.

Lifestyle intervention in the form of dietary, behavioural and exercise counselling is traditionally the primary treatment for obesity. However, the causes of obesity are multifactorial and associated with numerous complex environmental, physiological and genetic factors, making treatment challenging. Scientific evidence suggests that weight gain and obesity lead to hormonal, metabolic and neurochemical adaptations that may affect the regulation of energy balance, promoting maintenance of the increased weight and making weight loss difficult. Moreover, during weight loss the body appears to compensate by reducing metabolism and increasing the production of hormones that stimulate appetite. These combined effects tend to favour weight regain, and explain why sustained weight loss is difficult to achieve and why many people struggle to maintain their weight loss by lifestyle intervention alone.

Surgical treatments offer an effective alternative for some people with severe obesity; however, these are unavailable or unsuitable for many obese individuals and are often associated with risks and complications related to the problems inherent in operating on obese individuals. Major and minor complications occurred in 3.3% and 27% of patients, respectively, in one study. Few effective treatment options are therefore available for obese individuals, especially those who suffer from

obesity-related health problems. Pharmacotherapy may serve as a valuable adjunct to lifestyle intervention in achieving and sustaining clinically relevant weight loss; it may also have the potential to moderate the metabolic responses that favour weight regain. However, there is a limited range of weight management medications currently available.

Orlistat is a gastrointestinal lipase inhibitor that has been on the market since 1998. Whilst it has shown moderate beneficial effects on weight loss and blood pressure, orlistat is associated with an array of side effects that limit its tolerability, including steatorrhoea, faecal incontinence and rectal discharge. Since then, new products for the treatment of obesity have been authorised in the EU and US, but also several approved obesity medications have been withdrawn or their marketing authorisation has been suspended due to safety issues. Liraglutide is in a different pharmacological class to the other weight management products currently or previously approved, with a different mechanism of action.

About the product

Saxenda is proposed as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients (≥ 18 years) with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m² (obese), or
- ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analogue classified as a 'GLP-1 receptor agonist', with 97% homology to human GLP-1. Liraglutide has unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycaemic control and other weight-related comorbidities, as described below. The well-characterized effects of liraglutide in the body are mediated via specific activation of the GLP-1 receptor. During eating, multiple hormonal and neuronal signals are released in the body and these signals are processed by the brain and translated into feelings of hunger or satiety, in order to control food intake. Gut hormones, including GLP-1, are modulated by acute food ingestion. In animal studies, peripheral administration of liraglutide leads to decreased food intake and weight loss. Animal studies have demonstrated that liraglutide can access brain regions that are critical to the regulation of energy intake, thus indicating the potential of liraglutide to activate the GLP-1 receptor in the brain.

In humans, weight loss with liraglutide is primarily mediated by its effects on appetite. Body weight is regulated by complex homeostatic mechanisms, and obesity is a result of caloric/energy intake chronically exceeding expenditure. Liraglutide treatment affects the four main components of appetite regulation (fullness, satiety, hunger and prospective food consumption [how much a person thinks he/she can eat]), leading to reduced caloric intake, which is not due to reduced meal palatability. Liraglutide-induced weight loss is primarily due to reduction in fat mass rather than lean body mass. Liraglutide is associated with a small decrease in energy expenditure. Furthermore, liraglutide stimulates insulin secretion, lowers inappropriately high glucagon secretion, and improves beta-cell function in a glucose-dependent manner, which results in a lowering of fasting and post-prandial glucose. The mechanism of blood glucose lowering also involves a delay in gastric emptying, which may contribute to the observed reductions in postprandial glucose.

Liraglutide demonstrates benefits for glycaemic control at doses up to 1.8 mg/day and has been authorised in the EU, as Victoza on 30 June 2009 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001026/WC500050016.pdf), as well as in other countries including the US, Japan (up to 0.9 mg), Australia and China for the treatment of adults with T2DM. The cumulative post-marketing

exposure is estimated to be 1,500,000 to 2,200,000 patient years, assuming an average daily dose of 1.8 mg or 1.2 mg, respectively, based on the released volume of Victoza in units between 30 June 2009 and 02 July 2013 (the cut-off date for this application).

The moderate dose-dependent weight loss observed in clinical trials with liraglutide in T2DM, together with the reductions in glycosylated haemoglobin A_{1c} (HbA_{1c}) and improvements in beta-cell function and cardiometabolic risk factors such as systolic blood pressure, led to investigations into its potential therapeutic use in weight management. The intended liraglutide dose for use in weight management is 3 mg, administered as a once-daily subcutaneous injection.

2.2. Quality aspects

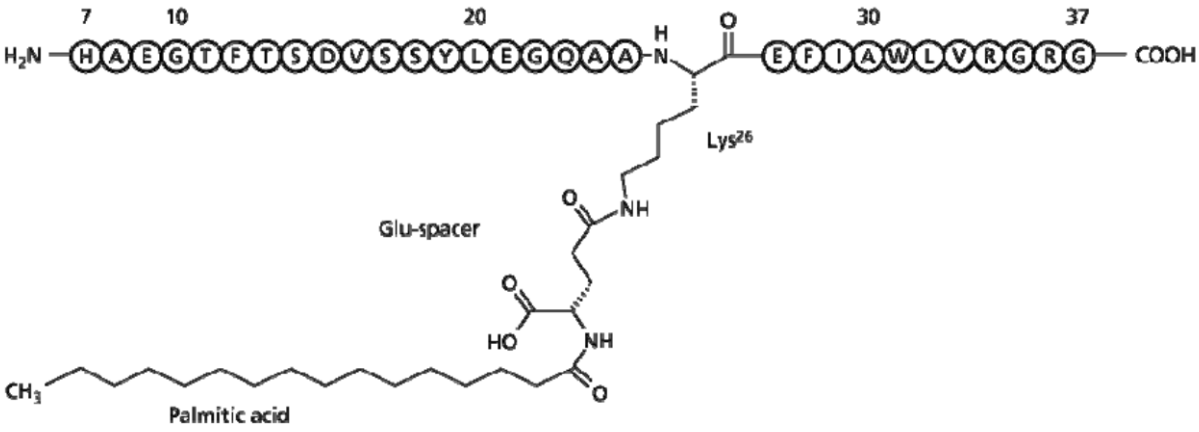
2.2.1. Introduction

Liraglutide under the invented name Victoza (EMEA/H/C/001026) is currently approved in the EU for the treatment of diabetes mellitus at doses up to 1.8 mg/day. The active substance and the composition of the bulk finished product (filled cartridges) of Saxenda and Victoza are identical. As the final finished product differs from Victoza with respect to a different pen injector device, specific information related to the new device has been provided, including device safety, assembly/ controls, dose accuracy specifications, validation and usability, notified body certificate and stability. Furthermore, the maximum daily dose for Saxenda is 3.0 mg/ day therefore data from clinical batches used in weight management studies have been provided.

2.2.2. Active Substance

General information

Liraglutide is a long acting analogue of the naturally occurring human glucagon-like peptide-1 (GLP-1(7-37)). Liraglutide has a substitution of the naturally occurring amino acid residue in position 34 (Lys) by Arg and addition of a Glu-spaced hexadecanoic acid (palmitic acid) to the ε-amino group of Lys in position 26. See Figure below. The analogue is produced using the recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and is further chemically modified by addition of the Glu-spaced hexadecanoic (palmitic) acid in order to prolong its biological activity.



Manufacture, characterisation and process controls

The liraglutide active substance manufacturing process includes fermentation of yeast cells, recovery and purification of liraglutide precursor, acylation of the precursor and further purification of liraglutide to active substance. The production process includes pooling of fermentation batches, recovery batches and pooling at several purification steps. A suitable control system is in place. The scale and the yield of the different fermentation, recovery and purification stages are described. Manufacturing process development, filling, storage and transportation (shipping) procedures are adequately described. Furthermore, the manufacturing process development satisfactorily details the development of the liraglutide manufacturing process.

Control of materials

The generation of the *Saccharomyces cerevisiae* strain producing liraglutide precursor, the cell banking system and stability of the cell banks has been adequately described in the 'control of materials' section.

Control of critical steps and intermediates

To control the manufacturing process, critical process parameters and critical in-process controls for fermentation, recovery and purification steps are laid down in the dossier. Operational limits and acceptance criteria for critical process parameters and in-process controls are specified. The strategy to handle changes to non-critical process parameters and non-critical IPCs is based on the change control system in place. This strategy is deemed adequate to assure that the process is run in a validated state.

Process validation

Three consecutive active substance batches were used to validate the fermentation, recovery and purification process. Data was collected for critical in-process controls, specification tests on liraglutide active substance and additional analyses. Results demonstrated that the liraglutide manufacturing process is robust, yielding a product of acceptable and reproducible quality. Removal of process related impurities including host cell proteins and DNA and other impurities is adequately described.

Characterisation studies

Extensive structural characterisation studies have been performed on the active substance and the physico-chemical properties have been demonstrated. The product related impurities are studied in sufficient depth. The bioactivity of the main fractions have been characterised by a cell-based bioactivity assay. This measures adenylate cyclase activation, by liraglutide, of the cloned human GLP-1 receptor, resulting in cAMP accumulation in a dose dependent manner. The bioassay reflects the expected physiological mechanism in the clinical situation. Product related impurities are impurities structurally related to liraglutide. They are generated during fermentation or downstream processing or storage. Related impurities associated with liraglutide and potential degradation products have been identified by collection and structural characterisation and/or by spiking with purified and structurally characterised impurities. The product related impurities are routinely controlled by in-process controls as well as the active substance specification.

Specification

The liraglutide active substance is routinely controlled by a range of chemical-physical and biological tests to assure consistent production of the active substance. The active substance specification contains parameters defining identity, content, potency and purity. The specification and control of the drug substance is acceptable.

The analytical assays and their validation are acceptable.

An overview of the analytical results for relevant liraglutide drug substance batches is presented. The batches have been used for non-clinical studies, clinical studies, stability studies, reference material, process validation and setting of specifications.

Stability

Results of long-term , accelerated and stress stability studies have been provided. The stability data provided supports the proposed shelf lives of intermediates and drug substance.

Comparability exercise for Active Substance

During development of liraglutide active substance, changes in the active substance manufacturing process have been introduced, which are related to different production campaigns. Comparability (batch release, stability and characterisation) has been demonstrated for all campaigns.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The product is a solution for subcutaneous injection containing 6.0 mg/ml of the active substance.
The product is packaged in a type I clear glass 3 ml cartridge with Ph.Eur. compliant closures.
The cartridge is assembled in a pen-injector. The dose scale of the pen-injector reflect the recommended dosages in the SmPC: doses of 0.6, 1.2, 1.8 and 2.4 mg (dose escalation) and 3 mg (maintenance dose) can be delivered. The dose accuracy of the pen-injector system has been demonstrated.

The list of excipients includes disodium phosphate dihydrate, phenol, propylene glycol, sodium hydroxide, hydrochloric acid, and water for injections. These are all known excipients complying with at least Ph. Eur.

The development of the product has been described, the choice of excipients is justified and their functions explained. Extensive development studies have been submitted. The formulation, which is already marketed as Victoza indicated for treatment of Type 2 diabetes mellitus, is identical to the clinical batches provided in support of the Saxenda application.

The optimal phenol concentration was chosen following investigations of the required amounts needed to comply with Ph. Eur. Antimicrobial effectiveness has been adequately demonstrated.

As concerns the primary packaging i.e. a 3 ml cartridge, the compatibility with the drug, the assessment of extractables and of leachables have been considered acceptably demonstrated. The description of the pen-injector design and the conformance to the relevant standards are also considered acceptable.

Manufacture of the product and process controls

Overall, the manufacturing process for Saxenda has been sufficiently described and validated. Critical steps in the production have been adequately identified and are monitored by in-process controls.

Satisfactory process validation has been conducted verifying that the manufacturing process is capable of consistently and reproducibly producing liraglutide 6.0 mg/ml, 3 ml cartridge in the pen-injector of the predetermined quality.

Product specification

The finished product release specifications include appropriate tests for this product including: identity, content and purity of the product. The analytical methods have been described and validated according to ICH guidelines, where applicable.

The pen-injector was developed in accordance with relevant ISO standards. The presented certificates of the Notified Body Lloyds Register Quality Assurance (LRQA) are adequate.

Batch analytical data from the production sites have been provided. These cover batches used in pre-clinical, clinical and stability studies. The results demonstrate compliance with the specification.

Stability of the product

Stability of the finished product (manufacturing scale batches) in the 3 ml cartridge has been studied under long term (2-8°C) and accelerated conditions . In-use stability has been acceptably studied as well. Two additional studies, including one photostability study, were performed. The influence of light was investigated in the primary (3 ml cartridge) and secondary (pen-injector) packaging intended for the market. As expected, the primary container does not provide adequate protection from exposure to light but the pen-injector with the cap on provides adequate protection of the finished product in the primary container.

The results provided support the proposed shelf life of 30 months at 2-8°C and a subsequent in-use period of one month at room temperature (not above 30°C) or in a refrigerator (2-8°C).

Adventitious agents

No animal derived raw materials or excipients are used in the production of liraglutide. The TSE and viral safety evaluation covers the complete manufacturing process. Liraglutide is produced in yeast cells, which are not a natural host for human viruses. The manufacturing and formulation of liraglutide finished product does not include any additional animal derived raw materials or excipients.

Thus, the overall conclusion of this adventitious agents safety evaluation is that the finished product is safe with regard to both viral and TSE agents.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Quality documentation on Saxenda (liraglutide) supports assurance of acceptable product quality.

Liraglutide is already marketed under the brand name Victoza indicated for treatment of type 2 diabetes mellitus. The manufacturing process and composition of the active substance and finished products is identical. The pen-injector is new compared to Victoza.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical studies of liraglutide from the development program for the use of liraglutide in patients with T2DM (Victoza, EMEA/H/C/001026) have been submitted within this application. For the current procedure, additional non-clinical primary pharmacodynamic studies have been performed specifically for the liraglutide obesity program to assess how liraglutide affects the energy intake related mechanisms, and from where within the brain and nervous system such effects may be mediated.

2.3.2. Pharmacology

Primary pharmacodynamics

Liraglutide is a long-acting GLP-1 analogue, designed to bind to albumin as the main molecular mechanism of protraction. In vitro, this was shown in the receptor cAMP as well as binding assay where addition of albumin right-shifted the dose-response and/or binding curve. The apparent reduced potency of liraglutide underlines that only the free fraction of liraglutide is responsible for its pharmacological effect in vitro as well as in vivo. Furthermore, liraglutide in a pharmaceutical solution forms a micell-like heptamer which may contribute to the slow absorption from the subcutis.

Liraglutide is a potent, selective and efficacious agonist on the human as well as mouse, rat, rabbit, pig and Cynomolgus monkey GLP-1 receptor. Liraglutide has been shown to exert a number of actions in vitro that are known to be specific GLP-1 effects. Liraglutide has also been shown to glucosedependently stimulate insulin secretion from isolated β-cell islets in vitro. Liraglutide attenuated β-cell apoptosis in vitro under adverse conditions with high concentrations of free fatty acids and proinflammatory cytokines. Moreover, a proliferative effect on primary rat β-cells could be demonstrated for liraglutide in vitro whereas no consistent effect was observed under hyperglycaemic conditions in vivo.

In vivo, liraglutide lowers blood glucose and body weight in a number of diabetic and obese models using rodents, pigs and monkeys. The mechanism of action in vivo involved glucose-dependent increase in insulin secretion, lowered glucagon secretion, decreased gastric emptying, loss of body fat, lowered food intake, altered food preference, and maintained energy expenditure. The mechanism of action is consistent with a specific GLP-1 effect.

For the current procedure for the indication of obesity, a number of new studies were performed to elucidate the mechanism by which liraglutide acts to reduce energy intake.

Administration of liraglutide resulted in activation of some regions of the brain as measured by increased expression of immediate early gene cFOS. This activity was seen in the area postrema (AP) and the nucleus of the solitary tract (NTS) in the brain stem, the lateral parabrachial nucleus (lPBN) and the central amygdala (CeA) in the midbrain and the paraventricular nucleus (PVN) in the hypothalamus; areas known to be involved in energy intake. Dosing in rats further revealed a decrease in the hunger signals neuropeptide Y (NPY) and agouti-related peptide (AGRP) in arcuate nucleus (ARC), to normal levels, whereas these signals are increased in obese rats. The satiety signal, cocaine- and amphetamine-regulated transcript (CART) was increased after liraglutide treatment to even higher levels than normal. These data indicate that liraglutide has an effect on the brain, and in

mice it was shown that liraglutide is present in some parts of the brain devoid of blood brain barrier; the circumventricular organs (median eminence (ME) in the hypothalamus, the area postrema (AP) and the subfornical organ (SFO) in the brainstem, and the vascular organ of the terminal field (VOLT)), where is binds to GLP-1 receptors. To a lesser extent liraglutide was also measured in the ARC and especially after chronic administration in the paraventricular nucleus (PVN) and the dorsomedial region (DMH). A similar pattern was seen in the monkey brain.

Further studies in rats revealed that the effect of liraglutide is not mediated solely by the AP or the PVN, since rats lacking these areas were still responsive to treatment. Likewise rats with a dysfunctional vagal nerve also responded to liraglutide treatment, indicating that the vagal nerve is not the main mediator of the effect.

Secondary pharmacodynamics

Liraglutide had no cross-reactivity to a panel of 75 different receptors and ion channels. Moreover, it displayed no affinity to other closely related receptors in the glucagon-receptor super family including receptors for glucagon, GLP-2, secretin, GHRH, VIP and PACAP.

Safety pharmacology programme

The safety pharmacology programme, focusing on central nervous, respiratory, and cardiovascular systems and renal function, raised no serious issues. Liraglutide was well tolerated, especially in mice and monkeys. The only effects observed were confined to the rat. These adverse effects consisted of decreased specific urinary gravity and osmolality, accompanied by a dose-dependent increase in urine volume and electrolyte excretion. With respect to the cardiovascular system, liraglutide (at 0.2 and 2.0 mg/kg) induced dose-related increases in blood pressures and heart rate in rats, which were generally maintained for up to 24 hours after dosing. Moreover, body temperature was slightly reduced at 0.2 mg/kg and significantly reduced for 13.5 hours at 2.0 mg/kg. According to previous studies performed in rodents, the rat is especially sensitive to GLP-1 agonists, since no adverse effects on the cardiovascular and renal system have been observed in other animals or humans.

Pharmacodynamic drug interactions

Liraglutide has been shown to lower blood glucose synergistically in combination with the PPARγ agonist pioglitazone, and to increase insulin secretion synergistically in combination with the sulphonylurea glipizide. Although no considerable effect on blood glucose was obtained with the liraglutide-atorvastatin combination treatment in severely diabetic and insulin-resistant ZDF rats, a number of critical diabetic parameters were improved. Concomitant liraglutide and metformin treatment did not give rise to any additive effect on blood glucose during a 15-day study in ob/ob rats.

2.3.3. Pharmacokinetics

The pharmacokinetics of liraglutide has been studied adequately. RIA and ELISA methods were used in the analyses performed.

Liraglutide was well absorbed from the injection site after a single subcutaneous (SC) administration. Overall bioavailability following SC administration was estimated to be 53% in monkey, 76% in pig and 55% in human. The distribution volume is low and close to plasma volume, which indicates that a high fraction of liraglutide is circulating in plasma. All species except Sprague Dawley rats demonstrated a plasma protein binding of approximately 99% or higher. The plasma proteins responsible for the high degree of observed plasma protein binding were HSA (99.4%) and AAGP (99.3%).

The observations are consistent among species and demonstrate linear pharmacokinetics of liraglutide with dose-proportional exposures as measured by Cmax and AUC values or an exposure

slightly higher than dose-proportional. No apparent gender-related differences were observed in the animal species. Following repeated administration of liraglutide to mice, rats and monkeys, only a minor tendency towards accumulation was observed. The accumulation ratio was comparable to that observed in humans (<2).

The terminal half-life of liraglutide seems to be similar in pigs (~14 h) and humans (~15 h) while shorter in mice, rats, rabbits and monkeys (4-8 h). Several studies in monkeys, pigs and humans indicated that extravascular administration (SC and pulmonary) of liraglutide prolongs the terminal half-life as compared to intravenous (IV) administration. Furthermore, the terminal half-life seemed also to be prolonged by repeated dosing in rats, monkeys, pigs and humans. This tendency was not apparent for mice and rabbits. The observed time to the maximum concentration seemed also to be affected by repeated dosing in some studies. The differences in the pharmacokinetic parameters can be explained by the study design or absorption rate limited kinetics (in the latter case following SC administration in pigs and humans).

A low distribution of radioactivity was detected when comparing the results from administration of ^{125}I-liraglutide, ^{14}C-liraglutide and ^{3}H-[Pal]-liraglutide with radioactivity predominantly detected in plasma. This is in accordance with what would be expected for this type of molecule and correlates well with the low volume of distribution found for liraglutide in monkey, pig and human.

The metabolic and excretion patterns were highly similar across species with liraglutide being fully metabolised in the body by sequential cleavage of small peptide fragments and amino acids. The in vitro metabolism studies indicate that the initial metabolism involves cleavage of the peptide backbone with no degradation of the glutamate-palmitic acid side-chain. Mice, rats and monkeys displayed similar plasma profiles and showed no significant gender differences. A higher number of metabolites were observed in plasma from the animal species (especially the rat and monkey) as compared to human plasma. This disparity can partly be explained by differences in the sample preparation as human plasma samples were freeze dried prior to analysis causing a removal of volatile metabolites (including tritiated water). All detected metabolites were minor and obtained in low amount (<15%) and therefore no structural identification of these was performed. This is acceptable since the metabolites are only formed in low amounts and since the metabolites are expected to resemble endogenous substances with well-known metabolic pathways.

Clearance of liraglutide is suggested to take place by multiple organs/tissues and a low potential for pharmacokinetic drug interactions related to CYP and protein binding has been demonstrated. Liraglutide crosses the placental barrier in rats and rabbits. However, the uptake of liraglutide into the amniotic fluid and foetuses is low (<9%). Liraglutide is secreted into milk, but the amount of liraglutide that a pup would receive per day via breast milk is low (at most 3% of the maternal dose). This information is reflected in section 4.6 of the SPC.

2.3.4. Toxicology

Single dose toxicity

Single dose studies were performed in mice and rats in standard design studies and in monkeys in a maximum tolerated dose (MTD) study. A single dose of 10 mg/kg was generally well tolerated by mice and rats without mortality. In monkeys, a single SC administration of 5 mg/kg was well tolerated without mortality. The observed reductions in body weight and food consumption can be regarded as pharmacologically mediated.

Repeated dose toxicity

Pivotal repeat dose studies were performed in mice, rats and Cynomolgus monkeys.

Liraglutide was well-tolerated in rats and monkeys with NOAEL values corresponding to plasma exposure levels approximately 8- and 70-fold higher than observed in the clinic, respectively. In all species, decreased body weight gain and food consumption were seen in the first weeks of dosing. These effects are result of the pharmacological action of liraglutide. Following this initial period, in general, the animals resumed a more “normal” growth pattern (i.e. comparable to that of the control group) and food consumption. In rats, males seemed more affected than females. A slight trend towards increased effects in males was also noted in the monkey. Some effects on haematology, clinical chemistry and sometimes also urine were seen. However, the effects were generally small, and for most parameters there was no consistent pattern across the studies. Histological examination did not reveal any clear treatment-related effects apart from C-cell hyperplasia in the thyroid of treated mice seen after 9-13 weeks of dosing. Effects on C-cells (focal accumulations of C-cells) were already seen in the 4-week mice study but these findings were not considered to be treatment-related. No effects on C-cells were seen in the rat and monkey studies up to 26 and 52 weeks.

An increased pancreatic weight was observed in cynomolgus monkeys following 52 weeks treatment at plasma exposure levels below and 8-9-fold higher than is observed in the clinic, respectively. Further investigations of the pancreatic tissues collected in the 52-week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group. Considering that concerns have been raised regarding the potential induction of acute pancreatitis following treatment with GLP-1 receptor agonists, there was a request to evaluate the clinical relevance of this finding. The applicant substantiated that the statistical significant differences in pancreatic weight observed in mid and high dose animals were driven by the pancreas weight of the controls, which was low compared to that of the CRO historical control data. Moreover, normal histological morphology of the pancreas was seen in all studies and no clinical or biochemical changes were seen in any of the four non-human primate studies and also there was no histopathology indicative of inflammation. In addition, no effect on pancreatic weight was observed in the 87-week study. Based on the above, it was concluded that the findings made in the 52-week cynomolgus monkeys study do not suggest a safety concern for humans with respect to treatment related pancreatitis.

At the end of the 52-week monkey study, antibodies were found in a few monkeys which crossreacted with GLP-1. This implies that an immunological reaction against the body’s own GLP-1 could be possible. Data on antibody formation will be reported in the PSURs.

Toxicokinetics

Toxicokinetic analysis was performed as part of every study with blood samples collected and analysed for the presence of liraglutide. Liraglutide was not detected in blood samples of control animals. In the 26-week rat study, only two animals per sex were subjected to blood sampling and the samples were collected pre-dosing. This is not in line with CPMP/SWP/1094/04 “Guideline on the evaluation of control samples in non-clinical safety studies” but the study was conducted before the release of the guideline.

Genotoxicity

Results of the Ames test, the in vitro chromosome aberrations assay and the in vivo micronucleus tests indicate no genotoxic potential.

Carcinogenicity

In carcinogenicity studies, C-cell tumours were observed in mice and rats. A NOAEL value for these findings was established in mice at 0.2 mg liraglutide/kg/day, which results in plasma exposure levels similar to what is obtained in the clinic. A NOAEL value was not established in rats. A number of

exploratory studies have been conducted in order to evaluate the mechanism behind liraglutide's nongenotoxic carcinogenic effect on rodent C-cells (see below).

Uterus leioma and leiosarcoma were observed in mice but not in rats. Although there seemed to be an increased number of tumours in treated mice, there was no dose-response relationship and furthermore, mice are very sensitive to this tumour. Skin sarcomas were increased in mice at high dose. In many of these animals, sarcomas were situated around the microchip which may have influenced their appearance. At the NOEL of 1.0 mg/kg/day, the safety margin was 13. In rats, pituitary gland carcinomas in the anterior lobe as well as uterus stromal polyps were increased in high dose females. However, when benign and malignant tumours of pituitary gland and uterus were combined, there was no relevant dose related effect. Furthermore, on an individual animal basis there was no relation between stromal polyps and pituitary carcinoma or adenoma. It is not considered likely that the pituitary carcinoma and stromal polyps are a risk for humans.

An extensive package of mechanistic studies was performed to investigate the human relevance of the C-cell tumours which was considered of crucial importance and identified as a major objection during the procedure. In these studies, GLP-1 receptors were shown to be present in C-cells of all investigated species. GLP-1 receptors were present in higher amounts per cell in rat cell lines than in a human cell line. In addition, literature indicates C-cells are less abundant compared to other endocrine cells in human thyroid than in rodent thyroid. In rat C-cell lines, liraglutide induced cAMP and calcitonin secretion (though at much higher EC50 than exenatide). In a human cell line, the response was marginal.

Using human thyroid tissue, co-localization of the GLP-1 receptor and calcitonin within C-cells was confirmed by double-staining, while GLP-1 receptor mRNA was non-detectable via in situ hybridisation in human C-cells. In all other mechanistic studies, the human TT cell line was used; however concerns were raised whether this cell line was representative for normal (non-transformed) human tissue. To address this concern a new study was performed in order to compare GLP-1 receptor mRNA content in thyroid extracts from human donors with levels in the TT C-cell line. It was however not possible to correct the calculated mRNA content for the ratio of C-cells to total thyroid. The species difference in GLP-1 expression was however confirmed by in situ ligand binding. Overall, data show that GLP-1 expression in human C-cells is likely to be low, but not completely absent. In mice, liraglutide produced a sustained increase in plasma calcitonin. An increase in calcitonin mRNA, indicating increased calcitonin synthesis, was visible after 2 weeks. Focal accumulation of C-cells which was not considered to be treatment- related started to be visible after 4 weeks. Treatmentrelated C-cell hyperplasia was observed after 9 weeks. C-cell hyperplasia was also observed after exenatide continuous infusion up to 16 weeks, but not after bolus injections during the same period of time.

In rats, increased plasma calcitonin levels were observed after 4 weeks administration. No information was provided regarding weeks 1-3 in this study. After a single dose, a decrease was observed in plasma calcitonin after an initial increase. This lowering in calcitonin can be explained by a massive loss of calcium in the urine due to a marked diuretic effect of a single dose of liraglutide in rats. In a long-term study (up to 16 months), plasma calcitonin showed no overall consistent change. This may be because the half-life of calcitonin is very short in rats, approximately 4 minutes; this may have played a role in this respect that it may be difficult to observe increases in plasma calcitonin in rats; however, half-lives in other species are not mentioned. In rats, following long-term dosing, the increase in calcitonin did not persist. This may be due to a high spontaneous frequency of C-cell hyperplasia in combination with a decrease in diffuse C-cell hyperplasia in aging rats. This is supported by the higher incidence in control rats compared to control mice. In literature, spontaneous C-cell tumours have been reported to occur with high frequency in rats. Martin-Lacave (2002) reports a frequency between 16% and 40% in most strains and Kaspareit-Rittinghausen (1990) reported

51.5 – 60% in Han:SPRD rats. Statistical analyses of individual animal data in rats revealed a correlation between early plasma calcitonin change (day 0 to day 28) and terminal focal C-cell hyperplasia score. In addition, the early calcitonin change was clearly larger in rats that later developed adenomas than in rats that did not. This finding supports the hypothesis that the C-cell hyperplasia and adenomas observed in the rodent carcinogenicity studies are caused by the continuous release of calcitonin due to persistent activation of C-cell GLP-1 receptors and the accompanying increased demand for calcitonin synthesis. The possibility that an additional mechanism for C-cell stimulation on calcitonin, not related to GLP-1R, may exist was addressed during the procedure. Data regarding a large number of receptors and ion channels indicate that liraglutide only shows affinity to the GLP-1 receptor.

C-cell hyperplasia started to occur from 28 days dosing in aged rats and from 210 days dosing in young rats. Adenoma started to occur in both aged and young rats from 210 days of dosing. No changes in C-cell mass were observed after 26 weeks in young rats. In cynomolgus monkeys, no effect of liraglutide on plasma calcitonin was observed up to 87 weeks. No C-cell hyperplasia was observed after 87 weeks (animals were 15-19 months old at start). No changes in C-cell mass were observed after 52 weeks (animals were 12-17 months old at start). Literature data indicate that if there would have been evidence for a carcinogenic mechanism in monkeys based on C-cell proliferation in response to receptor stimulation, it would have been visible within these periods of time.

It is concluded that the findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. Section 5.3 of the SPC reflects this information.

Reproduction Toxicity

Studies were performed in rats in which male and female fertility and embryonic development were combined. Decreased body weight gain, decreased food consumption, and reduced faecal output are considered due to the pharmacological action of liraglutide. As decreased body weight gain and decreased food consumption can be considered desired effects of liraglutide, they were not considered adverse effects in the determination of the NOAEL. Fertility parameters were not affected except for a slight decrease in the number of live implants/ slight increase in early embryonic deaths at 1.0 mg/kg. In the foetuses, a slight increase in skeletal variations was observed. The safety margin for the effects on live implants and foetal effects was 3. In a pre and postnatal study in rats, in F0 animals, pharmacologically mediated effects were observed on body weight gain and food consumption. In F1 animals, a decreased weight gain was observed in all treated groups in the pre-weaning period. Post-weaning, at high dose, a slightly decreased body weight gain was also observed in F1 males up to week 16 and in F1 females during gestation and lactation but not in the pre-mating phase. In the F2 generation, a slight decrease in mean pup weight which was consistent among males and females was observed at high dose. This finding was not statistically significant, but considered remarkable because it suggests that there could be an effect on body weight up to the second generation.

In embryofoetal toxicity studies in rabbits, a large decrease in food consumption was observed in rabbits. Again, decreased body weight gain, decreased food consumption, and reduced faecal output in the F0 generation are considered due to the pharmacological action of liraglutide. Foetal effects were a reduced foetal weight, an increase in the number of skeletal variations and a slight increase in the number of gall bladder abnormalities. There was no safety margin for these effects, but they may well have been due to the markedly decreased food consumption.

No studies were performed in juvenile animals.

Local tolerance

Single SC injection of liraglutide or vehicle in pigs caused a mild subacute inflammation in the injection site tissue. These studies evaluated the local tissue reaction after one SC injection and not after repeated dosing or after IV, intramuscular or intra arterial injection. Repeated dose administration was sufficiently investigated in the repeated dose studies. Generally mild effects at the injection site have been noted in rats and monkeys in the repeated dose toxicity studies.

Local tolerance following intramuscular, IV or intraarterial injection was studied in rabbits, with no relevant differences between liraglutide-treated sites and vehicle-treated sites observed after intramuscular or IV administration. Injection site reactions consisting mainly of perivascular haemorrhage and periarterial fibrosis/oedema were slightly more pronounced following intraarterial administration. A slight, treatment-related reaction can not be excluded should accidental intraarterial injection occur in humans.

Other toxicity studies

Immunotoxicity

Immunotoxicity studies were not performed. This is acceptable as no relevant findings on the immune system organs were observed in the repeat dose studies, and immunotoxicity is not expected based on the mechanism of action.

Metabolites

The major metabolite of liraglutide is at least 235-fold less potent than liraglutide. All human metabolites were also observed in the animal species studied in the toxicology studies and therefore, it is considered that these metabolites have been sufficiently investigated.

2.3.5. Ecotoxicity / environmental risk assessment

Liraglutide is a peptide, consisting of natural amino acids and a natural fatty acid. Therefore, liraglutide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Non-clinical studies of liraglutide from the development program for the use of liraglutide in patients with T2DM (Victoza, EMEA/H/C/001026) have been submitted with this application. The pharmacological properties of liraglutide in terms of regulation of blood glucose have been already assessed previously in the initial Marketing Authorisation Application of Victoza (EMEA/H/C/001026). For the current procedure, additional non-clinical primary pharmacodynamic studies have been performed specifically for the liraglutide obesity program to assess how liraglutide affects the energy intake related mechanisms, and from where within the brain and nervous system such effects may be mediated.

Data from these studies indicate that liraglutide has an effect on the brain. Overall, the mechanism by which liraglutide treatment results in reduced energy intake is not completely understood. It is likely that liraglutide has a direct effect via the GLP-1 receptor on different areas of the brain, which are important in regulating signals for hunger and satiety.

No additional safety pharmacology studies were submitted for the current application beyond those which had been undertaken for the development program for the use of liraglutide in patients with T2DM (Victoza) . The safety margins for the *in vivo* safety pharmacology studies top dose (2.0 mg/kg) resulted in plasma levels estimated to be approximately 15, 27- and 37 fold the C_{max} in obese subjects

at steady state at the maximum recommended human dose (MRHD) at 3.0 mg (C_{max}: 39 nmol/L; NN8022-3630), in mice (C_{max}: 592,5 nmol/L; NN990267), rats (C_{max}: 1044.9 nmol/L; NN990268) and monkeys, respectively.

Liraglutide did not augment the proliferative effect of insulin detemir in an *in vitro* study in the breast cancer cell line MCF-7. No GLP-1 receptors were found on breast cancer cells (from breast carcinoma and several mammary cell lines). Artificial expression of the GLP-1 receptor in MCF-7 cells increased the proliferative capacity of this cell line. This is however considered not clinically relevant as GLP-1 receptors were not found on breast cancer cells.

No additional pharmacokinetic studies and toxicology studies were submitted for the current application beyond those which had been undertaken for the development program for the use of liraglutide in patients with T2DM (Victoza) as the pharmacokinetic and the toxicology profile of liraglutide has been investigated with those studies satisfactorily, to which the CHMP agreed.

According to the documentation in the quality part of the dossier, the product may contain residues from leachables from the packaging of the product, comprising of xylenes and bromo-phenols. The amount of xylenes that can maximally be taken in by users of Saxenda is far below the Permitted Daily Exposure of 21.7 mg/day. For bromo-phenols no limit or permissible dosage is available, but genotoxicity has been satisfactorily ruled out. Therefore, no relevant risk is expected for these leachables.

2.3.7. Conclusion on the non-clinical aspects

In addition to the non-clinical studies for the development program for the use of liraglutide in patients with T2DM a number of studies have been performed to investigate the mechanism by which liraglutide acts to reduce energy intake. Although the mechanism is not fully elucidated, it is likely that liraglutide has a direct effect via the GLP-1 receptor on different areas of the brain, which are important in regulating signals for hunger and satiety. No further pharmacodynamic studies were required by CHMP for this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

Approximately 70 studies with liraglutide have been executed. For brevity, only the trials from the weight management programme are show in Table 3.

Table 3. Overview of clinical studies from the weight management program.

Trial ID Country	Type of study	Trial design; Type of control	Test drugs and route of administration	Number of exposed subjects (males/females randomised)	Type of subjects	Treatment duration	Study status Type of report Location

NN8022-1807 DK, SE, FI, GB, NL, BE, ES, CZ	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind (orlistat open-label) trial Placebo and active (orlistat) control	Liraglutide: Once-daily s.c. doses of 1.2, 1.8, 2.4, or 3.0 mg, dose-escalated in weekly steps of 0.6 mg Orlistat: t.i.d. p.o. doses of 120 mg	564 (135/429) Liraglutide 1.2 mg: 95 Liraglutide 1.8 mg: 90 Liraglutide 2.4 mg: 93 Liraglutide 3.0 mg: 93 Orlistat: 95 Placebo: 98	Healthy, obese	20 weeks	Complete; Full; Module 5.3.5.1
NN8022-1807 extensions DK, SE, FI, GB, NL, BE, ES, CZ	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind (orlistat open-label) extension trial Placebo and active (orlistat) control	Liraglutide: Once-daily s.c. doses of 1.2, 1.8, 2.4, or 3.0 mg Orlistat: t.i.d. p.o. doses of 120 mg	394 (298/100) Liraglutide 1.2 mg: 67 Liraglutide 1.8 mg: 58 Liraglutide 2.4 mg: 65 Liraglutide 3.0 mg: 71 Orlistat: 67 Placebo: 66	Healthy, obese	32 weeks + 52 weeks	Complete; Full; Module 5.3.5.1
NN8022-1839 AT, AU, BE, BR, CA, CH, DE, DK, ES, FI, FR, GB, HK, HU, IE, IL, IN, IT, MX, NL, NO, PL, RS, RU, TR, US, ZA	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3.0 mg, dose-escalated in weekly increments of 0.6 mg	3723 (803/2928) **Main period (56 weeks)** Liraglutide 3.0 mg: 2481 Placebo:1242 **Re-randomised period (12 weeks)** Cont. liraglutide 3.0 mg: 351 Cont. placebo:304 Switched from liraglutide 3.0 mg to placebo: 350	Obese, overweight, with co-morbidities	56 weeks + 12-week re-randomised period	Complete; Full; Module 5.3.5.1
NN8022-1922 DE, ES, FR, GB, IL, SE, TR, US, ZA	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind, parallel-group trial Placebo control Background medication: metformin, sulphonylurea and glitazone	Liraglutide: once-daily s.c. doses of 1.8 or 3.0 mg, dose-escalated in weekly increments of 0.6 mg Metformin and glitazone: individual, stable pre-trial dose and frequency Sulphonylurea: individual, stable pre-trial frequency; dose reduced with 50%.	844 (425/421) Liraglutide 1.8 mg: 210 Liraglutide 3.0 mg: 422 Placebo: 212	Obese or overweight with type 2 DM	56 weeks	Complete; Full; Module 5.3.5.1
NN8022-3970 CA, US	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3.0 mg, dose-escalated in weekly increments of 0.6 mg	355 (258/101) Liraglutide 3.0 mg: 176 Placebo: 179	Obese subjects with moderate or severe sleep apnoea	32 weeks	Complete; Full; Module 5.3.5.1
NN8022-1923 CA, US	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3.0 mg, dose-escalated in weekly increments of 0.6 mg	422 (79/343) Liraglutide 3.0 mg: 212 Placebo: 210	Healthy, obese	56 weeks	Complete; Full; Module 5.3.5.1

2.4.2. Pharmacokinetics

Introduction

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue obtained by derivatising GLP-1 with a fatty acid side chain. In this application the use of liraglutide 3 mg for weight management was proposed. Liraglutide at doses up to 1.8 mg has been approved in several countries for treatment of type 2 diabetes (T2DM) as Victoza (EMEA/H/C/001026).

The clinical pharmacology programme for weight management is based on the Victoza programme, in which the characteristics of liraglutide at doses up to 1.8 mg were comprehensively evaluated in healthy subjects and in subjects with T2DM. The initial dossier included four trials that evaluated the PK and PD of liraglutide in weight management. For the clinical pharmacology assessment of liraglutide 3.0 mg for weight management, the following trials have contributed with data:

- Trial 3630 (clinical pharmacology trial)
- Trial 1807 (phase 2 trial) for exposure-response analyses (obese non diabetic subjects)
- Trial 1839 (phase 3 trial) for population pharmacokinetic analyses and exposure-response analyses

- Trial 1922 (phase 3 trial) for population pharmacokinetic analyses and exposure-response analyses.

As only few additional studies were performed for the current indication for liraglutide in weight management beyond those for the original Victoza application the assessment report is based on the studies provided for Victoza and extended with the additional submitted studies. The following subsections in the pharmacokinetics assessment were extended with the information from the weight management program: Methods, Distribution, Elimination, Dose proportionality and time dependency, Pharmacokinetics in target population, Special populations, and Interactions.

The drug product used in all the clinical trials in the weight management development program, is identical to the drug product marketed for the treatment of type 2 diabetes (Victoza). Consequently, no bioavailablity or bioequivalence trials have been performed in the weight management development program.

Absorption

The absorption of liraglutide following subcutaneous administration was slow, reaching maximum concentration approximately 11 hours post dosing. The injection sites (abdomen, thigh, upper arm) can be used interchangeably. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution

The mean apparent volume of distribution after subcutaneous administration is 22-25 L (for a person weighing approximately 100 kg). Liraglutide is extensively bound to plasma protein (>98%).

Metabolism / biotransformation

During 24 hour following administration of a single [^{3}H]-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.

Elimination

Following a [^{3}H]-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). The urine and faces radioactivity was mainly excreted during the first 6-8 days, and corresponded to three minor metabolites, respectively. The mean clearance following s.c. administration of liraglutide is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours.

Dose proportionality and time dependency

Liraglutide exposure increased proportionally with dose up to 3.0 mg. The accumulation ratio was 1.4 to 1.8 which is in agreement with the elimination pharmacokinetics and dosing frequency of liraglutide.

Intra- and inter-individual variability

The coefficient of variation for AUC_τ was 26% and the intra-subject coefficient of variation was 19%.

Pharmacokinetics in target population

The pharmacokinetics of liraglutide 3.0 mg in obese subjects were consistent with that previously observed in the Victoza programme for T2DM and healthy volunteers. The average liraglutide steady

state concentration (AUCτ/24) reached approximately 31 nmol/L in obese (BMI 30-40 kg/m2) subjects following administration of 3.0 mg liraglutide in obese patients.

Special populations

The exposure of liraglutide decreases with an increase in baseline body weight. According to the Applicant, the 3 mg daily dose of liraglutide provided adequate systemic exposures over the body weight range of 60-234 kg evaluated for exposure response in the clinical trial (see clinical part). Liraglutide exposure was not studied in subjects with body weight >234 kg.

Liraglutide exposure was decreased by 13-23% in patients with mild to moderate hepatic impairment compared to healthy subjects. Exposure was significantly lower (44%) in patients with severe hepatic impairment (Child Pugh score >9). Liraglutide exposure was reduced in patients with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and 26%, respectively, in patients with mild (creatinine clearance, CrCl 50-80 mL/min), moderate (CrCl 30-50 mL/min), and severe (CrCl <30 mL/min) renal impairment and in end-stage renal disease requiring dialysis.

Age and ethnic origin had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results from a population pharmacokinetic analysis of data from overweight and obese patients (18 to 82 years) of White, Black, Asian and Hispanic/non-Hispanic groups. Thus, no dosage adjustment is required based on age or ethnic origin. Based on the results of population pharmacokinetic analyses, females have 24% lower weight adjusted clearance of Saxenda compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender. Saxenda has not been studied in paediatric patients (age <18 years).

Interactions

Liraglutide has shown very low potential to be involved in pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Drug-drug interaction studies have been performed with 1.8 mg liraglutide. The effect on rate of gastric emptying was equivalent between liraglutide 1.8 mg and 3 mg, (**paracetamol** AUC0-300 min). Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 mg. Paracetamol Cmax was decreased by 31% and median tmax was delayed up to 15 min. No dose adjustment for concomitant use of paracetamol is required.

Liraglutide did not change the overall exposure of **atorvastatin** following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin Cmax was decreased by 38% and median tmax was delayed from 1 h to 3 h with liraglutide.

Liraglutide did not change the overall exposure of **griseofulvin** following administration of a single dose of griseofulvin 500 mg. Griseofulvin Cmax increased by 37% while median tmax did not change. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

A single dose administration of digoxin 1 mg with liraglutide resulted in a reduction of **digoxin** AUC by 16%; Cmax decreased by 31%. Digoxin median tmax was delayed from 1 h to 1.5 h. No dose adjustment of digoxin is required based on these results.

A single dose administration of lisinopril 20 mg with liraglutide resulted in a reduction of **lisinopril** AUC by 15%; Cmax decreased by 27%. Lisinopril median tmax was delayed from 6 h to 8 h with liraglutide. No dose adjustment of lisinopril is required based on these results.

Liraglutide lowered **ethinylestradiol** and **levonorgestrel** Cmax by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product. tmax was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

No interaction study has been performed with **warfarin** and other coumarin derivatives. Upon initiation of Saxenda treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR (International Normalised Ratio) is recommended which is in accordance with Victoza.

2.4.3. Pharmacodynamics

Primary pharmacodynamics

The primary PD of liraglutide 3.0 mg has been investigated in trial 3630, to investigate the effects of liraglutide 3.0 mg on gastric emptying compared to liraglutide 1.8 mg and placebo. Furthermore, effects on fasting and postprandial glucose, insulin, glucagon parameters were explored, as well as the effects on energy expenditure, substrate oxidation rates, appetite ratings and weight loss were investigated. Further evidence comes from trials from the Victoza development. In Table PD1 an overview of the pharmacodynamic studies is displayed.

Table PD1. Overview of PD studies, Victoza (2211) and Saxenda (8022) program

Study ID	Group/ Number/ Sex	Dose mg/day s.c.	Duration	Type of trial	Major findings
8022-3630	Overweight subjects N=49 41% female	Liraglutide 1.8 mg Liraglutide 3.0 mg Placebo	5 weeks	Single-center, RCT, double-blind, incomplete cross-over trial	AUC0-300 acetominophen equivalent in all 3 groups
2211-1219	Diabetic subjects N=11 45 % female	Liraglutide 10 µg/kg Placebo	2 single doses	Single-center, RCT, cross-over trial	No difference in pulsatile insulin secretion
2211-1224	Diabetic subjects N=19 26% female	Liraglutide 7.5 µg/kg Placebo	2 single doses	2-center,RCT, cross-over trial	Mean plasma glucagon increased 1.5 fold, no sign. difference
2211-1332	Diabetic subjects N=13 38% female	Liraglutide 6 µg/kg Placebo	9 days	Single-center, RCT, cross-over trial	AUC0-24 glucose was significant lower with liraglutide

2211-1589	Diabetic subjects N=46 41% female	Liraglutide 1.8 mg Glimepiride 1,2,4 mg Placebo	4 weeks	Double-dummy RCT	9% reduction of energy intake with liraglutide intake
2211-1689	Diabetic subjects N=18 22% female	Liraglutide 1.8 mg Placebo	3 weeks	Single-center, RCT, 2 period cross-over trial	Paracetamol 0-480, 0-∞ equivalent between groups
2211-2063	Diabetic subjects, N=10 Healthy controls, N=10 45% female	Liraglutide 7.5 µg/kg single dose Placebo No therapy	Single dose	Single-center, RCT, cross-over trial	Increased insulin secretion rate with liraglutide
2211-1644	Healthy subjects N=51 50% female	Liraglutide 1.8 mg Placebo Moxifloxacin 400 mg	3 weeks Single dose	Qtc trial, RCT, 2 period cross-over, open label moxifloxacin (positive control)	Negative Qtc study

Study 3630

Trial 3630 was a randomised, placebo-controlled, double-blind, incomplete crossover trial designed to evaluate the effects of liraglutide on gastric emptying, appetite, energy intake and energy expenditure, and to evaluate the pharmacokinetic properties of liraglutide in obese, but otherwise healthy subjects. The trial had a 2-period incomplete crossover design and the 2 treatment periods consisted each of 5 weeks at home plus a subsequent 2-day stay in the clinic. The pharmacokinetic and pharmacodynamic assessments were conducted at the 2-day stay in the clinic. An inherent potential limitation of the incomplete crossover design is that no subject received all three treatments (liraglutide 3.0 mg, 1.8 mg or placebo).

Participants were instructed not to change their diet, exercise program or daily routines during the trial to maintain their pre-trial body weight to minimise the effect of weight loss on the pharmacodynamic parameters. A wash-out period of 6-8 weeks was included between the two trial periods to avoid any metabolic carry-over effects of a body weight loss. However, some weight loss was observed with liraglutide treatment during the 5-week period. The mean weight loss was 2.5 kg with liraglutide 3.0 mg and 2.1 kg with liraglutide 1.8 mg compared to placebo. An impact of this weight loss on trial endpoints cannot be excluded.

29 male and 20 female obese subjects were included in the trial.

The ratio of paracetamol $AUC_{0\text{-}300min}$ between liraglutide 1.8 and 3.0 mg was 1.03 and since the 90% confidence interval (CI) for the estimated ratio ([0.92 ; 1.15]) was fully contained within the pre-specified interval (0.80, 1.25), equivalence with respect to gastric emptying was demonstrated between the 2 groups. Equivalence was also observed between the two liraglutide doses and placebo.

(Liraglutide 1.8 mg vs. placebo 0.90 [0.81 ; 1.01] and Liraglutide 3.0 mg vs. placebo 0.93 [0.83 ; 1.04])

- There were no treatment-related differences in gastric emptying, as assessed by $AUC_{0-300min}$, compared to placebo; however, a reduction (23%) of paracetamol absorption in the first hour ($AUC_{0-60min}$) of the standardised breakfast meal test was observed with liraglutide 3.0 mg compared to placebo and a similar trend, albeit of smaller magnitude, was observed with 1.8 mg (13%, p=0.14)

- Liraglutide treatment reduced fasting plasma glucose and improved overall postprandial glucose and glucagon concentrations, as well as postprandial insulin and C-peptide concentrations at early time points during the standardised breakfast meal.

- Liraglutide 1.8 mg and 3.0 mg similarly reduced appetite sensations during the standardised breakfast meal and mean energy intake during a subsequent *ad libitum* lunch meal, compared to placebo.

- Mean total energy expenditure (TEE) assessed during the 24-hour respiratory chamber stay was slightly, but significantly reduced with liraglutide 1.8 mg and 3.0 mg compared to placebo (by 3.0% and 4.9%, respectively) and substrate oxidation rate assessments indicated an overall relative shift towards more fat and less carbohydrate oxidation with liraglutide 1.8 mg and 3.0 mg compared to placebo.

Secondary/safety pharmacodynamics

In QTc trial NN2211-1644, the effect of liraglutide on cardiac repolarisation was assessed in healthy subjects with doses up to 1.8 mg. Liraglutide at steady state concentrations did not induce QTc prolongation and no exposure-response relationship between change in QTc and liraglutide concentration was observed.

Liraglutide exposures, in terms of Cmax, obtained in trials 1839 (mean BMI 38 kg/m2), 1807 (mean BMI 34 kg/m2) and 3630 (mean BMI 34 kg/m2) with liraglutide 3.0 mg in the population of obese and overweight subjects overlapped with those obtained in healthy subjects in trial NN2211-1644 at lower body weights (mean BMI 25 kg/m2). However, the highest values for Cmax seen in trials 1807 and 3630 were almost double the highest values seen in trial 1644. (Table PD2). Also in trial 1839, where PK values were obtained for 50 subjects, the Cmax range of trial 1644 was exceeded.

As liraglutide elimination is not organ specific, conditions such as renal or hepatic impairment are not associated with higher plasma exposure of liraglutide.

Table PD2. Summary of maximum liraglutide concentrations across four clinical trials.

					Maximum concentrations		
Trial ID	N	Dose (mg)	Mean Age (years)	Males (%)	Median (pM)	95% Range (pM)	Range (pM)
NN2211-1644	51	1.8	28.5	49	33174	(18925-56069)	(15421-58030)
NN8022-1839[a]	50	3.0	50.4	26	45835	(8698-73337)	(3449-82240)
NN8022-1807[b]	86	3.0	46.3	26	41503	(38-94091)	(2-114028)
		1.8					Max 110719
NN8022-3630	29	3.0	47.8	62	35940	(19174-74185)	(18950-74290)
		1.8					Max 118900

[a]Cmax substudy. [b]OGTT visit Source: Modelling report, table 4. See LoQ 29, 30a.

GLP-1 agonists are known for their effects on heart rate. Likewise, liraglutide 3.0 mg increased the heart rate with 4-5 beats/min during the day and 6-9 beats/min during sleep and this is further discussed in the safety section.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Weight management programme vs type 2 diabetes (Victoza) programme

The pharmacokinetics of liraglutide 3.0 mg in obese subjects were consistent with that previously observed in the studies to support the use of liraglutide in T2DM (Victoza development programme) and healthy volunteers. The average liraglutide steady state concentration ($AUC_T/24$) reached approximately 31 nmol/L in obese (BMI 30-40 kg/m2) subjects following administration of 3.0 mg liraglutide in obese patients. At 1.8 mg liraglutide in patients with T2DM, the average steady state concentration of liraglutide ($AUC_T/24$) reached approximately 34 nmol/l.

At liraglutide 1.8 mg the AUC_T and Cmax were between 650-1050 nmol*h/L and 36-55 nmol/L, respectively in healthy volunteers. At liraglutide 1.8 mg the AUC_T and Cmax were approximately 546 nmol*h/L and 265 nmol/L, respectively in obese volunteers (study 3630). In study 3630 after administration of 3.0 mg liraglutide to obese subjects, the AUCt and Cmax at steady state were 743 nmol*h/L and 36.8 nmol/L, respectively.

This is corresponding to the observation in the population pharmacokinetic analysis that showed a 44% lower exposure (corresponding to 78% higher CL/F) for a subject weighing 234 kg (the maximum observed weight) relative to a reference weight of 100 kg. Likewise, the exposure was 41% higher (corresponding to 29% lower CL/F) for a subject weighing 60 kg (the minimum observed weight) relative to the reference weight.

Therefore, the pharmacokinetic properties of liraglutide 3.0 mg in obese or overweight subjects were overall similar to that for liraglutide at doses up to 1.8 mg in healthy subjects and subjects withT2DM. Liraglutide 3.0 mg generally resulted in higher exposure than liraglutide 1.8 mg in obese and overweight subjects and the exposure increased in an approximately dose-proportional manner. As expected, and seen previously with liraglutide at doses up to 1.8 mg, gender and body weight were the main covariates for liraglutide exposure: exposure decreased with increasing body weight and was lower in male than in female subjects. Dose (as covariate for dose-normalised AUC), age, race, ethnicity and glycaemic status were found not to be relevant covariates for exposure.

The Applicant recognised several factors which influence the exposure to liraglutide for instance gender and weight, also in lesser extent T2DM and injection site, albeit they are considered non clinically relevant when evaluated separately. There might be a risk that in extreme scenarios the exposure is either too low or too high to be in the therapeutic window. This is of special importance as the efficacy in the clinical study for obese males seems to be decreased compared to the female population. The Applicant has addressed this question by presenting a multivariate analysis of exposure in extreme scenarios. Overall, the conclusion of this is that the clinical effect on body weight in females is generally better than in males for all weight categories. With increasing body weight, absolute weight reduction increases while relative weight reduction decreases. This is likely related to lower exposures in higher-weight subjects. Nevertheless, the results are not considered to pose any clinical relevant problems as the proposed stopping rule will ensure that patients without clinically relevant benefit of the treatment will be terminated within 16 months.

Similar effect on absorption of concomitantly administered oral drugs is anticipated for liraglutide 3.0 mg and 1.8 mg as equivalence in 5-hour gastric emptying has been demonstrated between the two liraglutide doses (study 3630). Consequently, as no dose adjustment was found to be required for

co-administration of oral drugs in the Victoza drug-drug interaction programme with liraglutide 1.8 mg, it is concluded that the same applies with liraglutide 3.0 mg. The comparable pharmacokinetic characteristics for liraglutide 3.0 mg in obese or overweight subjects with that previously found for liraglutide in doses up to 1.8 mg in healthy subjects and subjects with T2DM, support the reference to the clinical pharmacology characteristics of liraglutide as provided in the Victoza programme.

Pharmacodynamics

The pharmacodynamic **trial 3630** in the Saxenda intervention programme overall has an appropriate study design. Since the study was powered on the primary endpoint (gastric emptying), the secondary endpoints should be interpreted with caution, because no correction for multiple testing was performed.

Equivalence in gastric emptying between liraglutide 3.0 mg, liraglutide 1.8 mg and placebo was demonstrated with AUC of acetaminophen over 5 hours. AUC(0-300) of acetaminophen is considered an established marker for gastric emptying, albeit scintigraphy is known as the gold standard. Tmax and Cmax of the PK of acetaminophen are also considered established markers for the investigation of the effect of drugs on rate and extent of gastric emptying. In this study a lower Cmax acetaminophen was found for liraglutide 1.8 mg compared to placebo, no difference was found between liraglutide 3.0 mg and placebo. Furthermore, the first hour gastric emptying was delayed in liraglutide 3.0 mg and 1.8 mg versus placebo. From the Victoza investigation programme it was known that, although there were differences in Cmax and tmax, the overall exposure to medication (AUC) was comparable for the tested medications.

This study confirms the effect of liraglutide on satiety. This can partly be explained by delayed gastric emptying, but probably other mechanisms, in paricular effects of GLP-1 on the brain play a role. This leads to less caloric intake of circa 140 kcal/meal, which seems clinically important.

There was a small effect of liraglutide treatment on TEE. In the clinical studies it is difficult to disentangle direct effects of liraglutide on TEE and indirect effects of liraglutide on TEE, but it is likely that the decrease in TEE is, at least in part, explained by changes in body weight (and possible changes in physical activity). Furthermore, from these data, no real benefit is observed for liraglutide 3.0 mg compared to 1.8 mg.

Based on this pharmacodynamic study and the trials in the Victoza intervention program, there is a clear benefit for liraglutide 1.8 mg or 3.0 mg compared to placebo on fasting and postprandial glucose levels, as well as on postprandial insulin response. However, there is no clear benefit for liraglutide 3.0 mg over liraglutide 1.8 mg. There was a small difference in iAUC glucose in favour for liraglutide 3.0 mg compared to liraglutide 1.8 mg.

Overall, the study design of the **thorough QTc trial 1644** was acceptable using an open-label positive control (moxifloxacin). The mean Cmax levels of liraglutide were comparable for 1.8 mg liraglutide used in lean subjects in trial 1644 and for liraglutide 3.0 mg in obese subjects in trials 1807 and 3630. However, in accordance with ICH E14 it is customary to provide data of supra-therapeutic doses in the investigation programme of a new product to study QTc. In the Victoza development programme doses up to 1.8 mg were assessed, which is even lower than this therapeutic agent, Saxenda. In the phase 2/3 program, much higher values for Cmax were seen than in the QTc trial.

It is difficult to extrapolate findings from the T2DM programme (QTc trial with maximum dose 1.8 mg) to the 3.0 mg dose. Therefore, the Applicant systematically analysed the QTc intervals from the available ECGs in a subset of European subjects from trial 1839. The mean treatment difference and 90% CI between the baseline-adjusted QTc values were -0.31 ms [-3.80 ; 3.18] for QTc using Fredericia's correction for heart rate (QTcF) and 4.46 ms [0.59 ; 8.33] for QTc using Bazett's correction for heart rate (QTcB). These are below the threshold level of regulatory concern, which is

around 5 ms as evidenced by an upper bound of the one-sided 95% confidence interval around the mean effect on QTc of 10 ms.

The liraglutide 3.0 mg treatment effect on the QTcB interval observed may be due to the limitation of the Bazett correction method. Bazett's correction overcorrects at elevated heart rates and hence is not an ideal correction. Liraglutide treatment is associated with a slight increase in HR. We agree with the company that Fridericia's correction is more accurate in subjects with altered heart rates. Using the Fridericia's correction, liraglutide 3.0 mg did not importantly prolong the QTc interval compared to placebo in the subset of subjects from the clinical trial 1839.

In addition, the proportions of subjects with QTcF intervals ≥450, 480 and 500 ms as well as the proportions of subjects with changes from baseline of ≥30 and 60 ms were comparable between liraglutide 3.0 mg and placebo (for both QTcF and QTcB).

Thus it was concluded that liraglutide 3.0 mg did not importantly prolong the QTc interval compared to placebo in the clinical trial 1839.

There was a significant effect on heart rate in both studied dosages of liraglutide. This will be further evaluated in the safety part.

After a short time follow-up there was no significant difference in change in body weight between the two liraglutide groups. After 6-8 weeks of wash-out, the weight loss was neutralised to baseline values, indicating no continuous effect after cessation of the medication.

The exposure-response analyses showed that increasing exposure to liraglutide, leads to greater weight loss both in obese and overweight subjects without diabetes, as in diabetic subjects. Comparable exposure-response curves were seen for glucose control (HbA1c) in subjects with diabetes, with more pronounced effects for subjects with higher baseline HbA1c values.

The risk of medications such as insulin or insulin secretagogues to cause hypoglycemia may be increased when co-administered with liraglutide, even more explicit possibly, when liraglutide is used in a higher dose. This is further discussed in the safety section of this report.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

The comparable pharmacokinetic characteristics for liraglutide 3.0 mg in obese or overweight subjects with that previously found for liraglutide in doses up to 1.8 mg in healthy subjects and subjects with T2DM, support the reference to the clinical pharmacology characteristics of liraglutide as provided in the Victoza programme.

Pharmacodynamics

Taken together, PD activity of liraglutide 3.0 mg has sufficiently been demonstrated in the Saxenda and Victoza intervention program. Equivalence in gastric emptying was demonstrated between liraglutide 3.0 mg, liraglutide 1.8 mg and placebo, only a transitory delay in gastric emptying in the first hour was observed with liraglutide 3.0 mg and of smaller magnitude with liraglutide 1.8 mg compared to placebo. Remarkably, a significant reduction in total energy expenditure was observed in liraglutide treated subjects. Liraglutide induced weight loss mainly acts through reduced appetite sensations and therefore less energy intake. As with liraglutide 1.8 mg, liraglutide 3.0 mg has beneficial effects on fasting plasma glucose and postprandial glucose, insulin and glucagon levels. Cardiovascular related findings in safety pharmacology studies such as increased heart rate are a class effect of GLP-1 analogues and are further evaluated in the safety part.

In the Victoza (liraglutide 1.8 mg) QTc trial, no QTc interval prolongation was observed and QTc prolongation is not regarded as a concern in subjects with high BMI.

2.5. Clinical efficacy

2.5.1. Dose response study

Trial NN8022-1807

see below

2.5.2. Dose response and main studies

Trials NN8022-1807 extension, NN8022-1839, NN8022-1922, NN8022-1923 andNN8022-3970 (also known as SCALE trial program)

Methods:
The clinical development programme to evaluate the efficacy of liraglutide for weight management includes one phase 2 dose-finding trial (trial 1807) and four confirmatory phase 3 trials (trials 1839, 1922, 3970 and 1923), conducted worldwide and involving 5813 obese (BMI of ≥30 kg/m2) or overweight (BMI of ≥27 kg/m2) subjects with or without T2DM. All were randomised, double-blind, placebo-controlled trials.

The clinical trial programme was designed both to assess the weight loss potential of liraglutide in several different clinical situations and to assess its effects on some of the comorbidities associated with obesity. Each of the trials had a specific focus that in composite allows a full understanding of the efficacy and safety of liraglutide in the treatment of obesity.

The phase 2 trial (trial 1807) was designed to establish the most efficacious dose of liraglutide after an initial 20 weeks period of exposure followed by an interim analysis at 52 weeks, which was included to assess the persistence of response over 52 weeks. The full 104-week trial period provided an initial evaluation of long-term safety beyond one year.

Three of the phase 3 trials (trials 1839, 1922 and 1923) were of 56 weeks duration (52 weeks exposure on target dose):

- Trial 1839, the largest in the programme, was focused specifically on weight loss (56 weeks) and the effects of liraglutide on preventing progression of pre-diabetes to T2DM (an additional 104-week treatment period for subjects at high risk of developing diabetes [i.e., subjects with pre-diabetes at screening]). This extension is currently on-going and is not be included in this application (expected completion in February 2015).

- Trial 1922 specifically focused on the effect of two different doses of liraglutide on weight loss and glycaemic control in subjects with obesity and diagnosed T2DM.

- Trial 1923 was designed specifically to assess the ability of liraglutide to maintain weight loss induced by a low-calorie diet (LCD).

Trial 3970, conducted in subjects with obstructive sleep apnoea (OSA), was a 32-weeks trial as the maximal weight loss with liraglutide was expected around 32 weeks based on the findings of trials 1807 and 1923. OSA is a sleep-related breathing disorder, characterised by a decrease or total arrest in airflow in breathing during sleep, which is associated with comorbidities such as insulin resistance, hypertension, cognitive function and depression. Recent studies have shown that people with OSA

can benefit from weight loss and weight loss is considered a primary modality of therapy in a recent treatment guideline.

The elements of the proposed indication closely follow the trial programme as described.
The population for the trials is the target population for Saxenda, although this population is divided across several phase 3 studies.

The common features of the various phase 2 and 3 trials are addressed in this section together.

Objectives, outcomes and endpoints

The set of efficacy trials have a consistent design and definition of endpoints. There are in general no concerns regarding definition or measurement of these endpoints.

The efficacy endpoints of all 5 trials are presented in **Table E1**

Pre-specified efficacy endpoints of the phase 2 and 3 clinical trials

Trial	**1807**	**1807**	**1807**	**1839**	**1922**	**3970**	**1923**
Timepoint (week)	**20**	**52**	**104**	**56**	**56**	**32**	**56**
Body weight and other weight-related (change from baseline)							
Body weight (mean and categorical) (Table E2)	primary	primary	X	primary	primary	X	primary
BMI	-	-	-	X	X	X	X
Waist circumference	X	X	X	X	X	X	X
Visceral and s.c. fat	subgroup	-	-	-	-	-	-
Liver-to-spleen attenuation ratio	subgroup	-	-	-	-	-	-
Binge eating	-	-	-	X[a]	X[a]	-	X
Glycaemic control parameters (change from baseline)							
HbA_{1c} and fasting parameters[b]	X	-	X	X	X	X	X
HOMA-B and HOMA-IR	X	-	X	X	X	-	X
Parameters in OGTT	X	-	X	X	-	-	-
Glycaemic status[c]	X	X	X	X	-	-	-
Additional glycaemic control measures[d]	-	-	-	X	X	-	-
Cardiometabolic parameters (change from baseline)							
Vital signs	X	X	X	X	X	X	X

Trial	1807	1807	1807	1839	1922	3970	1923
Timepoint (week)	**20**	**52**	**104**	**56**	**56**	**32**	**56**
Fasting lipids	X	X	X	X	X	X	X
CV biomarkers[e]	X	-	X	X	X	X	X
Sleep-apnoea related endpoints (change from baseline)							
AHI	-	-	-	-	-	primary	-
Neck circumference	-	-	-	-	-	X	-
Other sleep-apnoea related		-	-	-	-	X	-
Patient reported outcomes (change from baseline)							
IWQoL-Lite	X	-	X	X	X	-	-
SF-36	-	-	-	X	-	X	-
TRIm-Weight	-	-	-	X	-	-	-
DTSQs	-	-	-	-	X	-	-
ESS	-	-	-	-	-	X	-
FOSQ	-	-	-	-	-	X	-
Concomitant medications (change from baseline)							
Lipid-lowering drugs	-	-	-	X	X	-	X
Anti-hypertensive drugs	-	-	-	X	X	-	X
Oral antidiabetic drugs	-	-	-	X	X	-	-

AHI: apnoea-hypopnoea index. BMI: body mass index. CV: cardiovascular. DTSQs: Diabetes Treatment Satisfaction Questionnaire (status version). ESS: Epworth Sleepiness Scale. FOSQ: Functional Outcomes of Sleep Questionnaire. HbA_{1c}: glycosylated haemoglobin A_{1c}. HOMA: Homeostasis Model Assessment. HOMA-B: a measure of beta-cell function. HOMA-IR: a measure of insulin resistance. IWQoL-Lite: Impact of Weight on Quality of Life-Lite version. OGTT: oral glucose tolerance test. s.c.: subcutaneous. SF-36: 36-item Short-Form health status survey. TRIm-Weight: Treatment Related Impact measure-Weight.

[a]Included as a safety endpoint. [b]Fasting glucose (all trials), insulin (1807, 1839, 1922, 1923), C-peptide (1839, 1922), glucagon (1922). [c]Normoglycaemia, pre-diabetes and T2DM. [d]Fasting proinsulin/insulin ratio, 7-point plasma glucose profile, proportion of subjects reaching target HbA_{1c} levels (1922). [e]High sensitivity C-reactive protein (all trials), fibrinogen and adiponectin (1807, 1839, 1922, 1923), plasminogen activator inhibitor-1 (1807, 1839, 1922), urinary albumin/creatinine ratio (1839, 1922, 3970).

Table E2 Key efficacy endpoints related to body weight by trial

Trial ID	1st endpoint	2nd endpoint	3rd endpoint
Key primary endpoints related to body weight			
1807 (at 20 and 52 weeks)	Change in body weight from baseline (kg)	Proportion of subjects achieving >5% reduction of baseline body weight	-
1839 1922 (at 56 weeks)	Change in body weight from baseline (% and kg)	Proportion of subjects achieving ≥ 5% reduction of baseline body weight	Proportion of subjects achieving >10% reduction of baseline body weight
1923 (at 56 weeks)	Change in body weight from baseline (after LCD run-in period) (% and kg)	Proportion of subjects that maintained the ≥ 5% reduction in initial body weight achieved during the LCD run-in period	Proportion of subjects achieving ≥ 5% reduction of baseline body weight
Key secondary endpoints related to body weight			
3970 (at 32 weeks)	Change in body weight from baseline (% and kg)	Proportion of subjects achieving ≥ 5% reduction of baseline body weight	Proportion of subjects achieving >10% reduction of baseline body weight

Primary endpoint

The primary endpoints of trials 1807, 1839, 1922 and 1923 were related to body weight, and included both mean and categorical changes in body weight (Table **E2**).

Epidemiological studies have identified weight as a risk factor for a number of diseases, and have also shown that an increase or decrease in weight is associated with a corresponding increase or decrease in other risk factors. Demonstration of weight loss is considered to be an appropriate surrogate measure of efficacy in the guideline (CPMP/EWP/281/96 Rev.1 - 2007) and hence a suitable primary endpoint. According to this guideline:

- Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10 per cent of initial weight. Demonstration of a significant degree of weight loss of at least 10 per cent of baseline weight which is also statistically greater than that associated with placebo is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. The company did not specify in the definition of the primary endpoint what weight change would be considered clinically relevant. This point was also raised in the 2008 CHMP scientific advice.

- Weight loss should be documented both as actual weight loss and by other appropriate measures (such as percentage body weight loss). Baseline weight may be used as a covariate in the analysis. A further illustration of the size of the treatment effect should be provided by looking at the proportion of responders in the various treatment arms - where response is more than 10% weight loss at the end of a 12-month period. Results should be discussed both in terms of their statistical and clinical significance. The company did not predefine the relation of weight loss to further benefits.

Because of the hierarchical testing that was defined for the co-primary, weight-related endpoints, full power was available for the endpoint “10% weight loss responders” while controlling the type I error rate.

Secondary endpoints

According to the guideline (CPMP/EWP/281/96 Rev.1 - 2007), choice of secondary efficacy variables should be justified by the Applicant and could include variables such as quality of life parameters, biochemical parameters of lipid and glucose metabolism as well as blood pressure, cardiac function and sleep apnoea episodes. An associated reduction in cardiovascular risk factor(s) is an important secondary end point (e.g. waist hip ratio). The selected secondary endpoints fit this profile.

The maintenance of weight loss or the prevention of weight regain, after the plateau in weight has been reached, was adequately addressed in trial 1923 (after weight loss in run-in period) and 1839 (re- randomisation after 1 year).

Body weight

According to the guideline (CPMP/EWP/281/96 Rev.1 – 2007), measurements using accepted methods selected and justified by the Applicant should demonstrate that weight loss is associated with appropriate loss of body fat (as distinct from muscle or body water). Measurement of changes in body composition and in fat distribution can be useful to better define weight loss. Methods such as waist circumference measurement, waist to hip ratio, magnetic resonance imaging and computer tomography may be used to assess abdominal fat content. Items to consider in assessing and discussing efficacy include the distinction between weight loss and maintenance of weight loss. Such measurements are systematically provided by the Applicant and are at least available for some of the trials.

Risk Factors

In line with the guideline (CPMP/EWP/281/96 Rev.1 - 2007), cardiovascular risk factors associated with obesity (blood pressure, lipid profile, glucose homeostasis, fibrinogen) were measured and monitored. According to the guideline, if claims are made in relation to risk factors, any improvement should be clinically relevant and be independent of the effect on obesity, and studies in support of these claims should be conducted in accordance with relevant guidelines. However, the Applicant did not document appropriate threshold values for clinical relevance and did not specify if any changes were above what could be expected on basis of weight loss alone.

Patient reported outcomes

The Applicant employed suitable questionnaires for Patient reported outcomes, although complete documentation was not always achieved for some questionnaires.

Participants

According to the guideline (CPMP/EWP/281/96 Rev.1 - 2007), patients entering these studies should have a degree of obesity, which has been shown to be associated with a significant health risk and especially a risk of increased mortality. The study population will therefore depend on the degree of obesity and the presence of coexisting risk factors. Efficacy should be demonstrated in patients of both sexes. Obesity in otherwise healthy adult patients should be diagnosed on the basis of a body mass index (BMI) of 30 or more in both males and females. Patients with associated or secondary effects of obesity (such as hypertension, hyperlipidaemia, diabetes mellitus, or cardiovascular disease), should be considered for such studies if BMI is greater than 27. Trials should be designed to take account of predictive risk factors of morbidity and mortality that include BMI, adipose tissue distribution (with an increased risk in the case of abdominal/android obesity), and association with other cardiovascular risk factors (such as smoking, diabetes or hypertension) and episodes of sleep apnoea. Prospective stratification for some of these factors may be appropriate.

This guideline is closely followed by the definition of the inclusion criteria as applied by the Applicant; these criteria for BMI (>30 or >27 + co-morbidity) are also retained in the proposed indication.

Subjects with obesity that is secondary to endocrinologic disorders (e.g. Cushing's Syndrome) or to treatment with drugs that may cause weight gain (e.g. insulin, psychotropic drugs) or eating disorders were not included in the trials. The lack of data about these patients has been included in Section 4.4 of the SmPC. The other exclusion criteria (including those related to suicidality) are considered appropriate to ensure proper execution of the trial; not taking these criteria to the SmPC is accepted.

Treatments

Dose

The 3.0 mg dose was selected prior to the phase 3 trials and implemented throughout. However, the long-term data in trial 1807 are based on treatment with 2.4 mg during part of the treatment period based on a preliminary choice.

Comparator

According to the guideline (CPMP/EWP/281/96 Rev.1 - 2007), studies adding active controls may be necessary, when standard therapies are available. However, there is no current and generally accepted standard pharmacological approach for weight management. In trial 1807, orlistat was included as an open label comparator. It is agreed with the Applicant, that placebo-controlled studies are currently appropriate.

Since weight control can be achieved by a reducing diet, exercise and behaviour modification alone, the use of a placebo group is necessary to show clearly that the drug and appropriate non pharmacological treatments are more effective than the same non pharmacological treatment alone. This was correctly implemented. The design of trial 1923 allowed separating the effects of non-pharmacological means and liraglutide.

The placebo solution contained the same excipients and preservatives as the active drug product and therefore could under-estimate adverse effects including injection site reactions that are related to these excipients.

Duration of treatment

According to the guideline (CPMP/EWP/281/96 Rev.1 - 2007), the optimum duration of treatment is unknown. To date all studies suggest an immediate cessation of treatment effect as soon as treatment is stopped. Trials documenting the effect of treatment for at least one year are required but an applicant intending to demonstrate the effect of weight loss on morbidity and mortality would require a longer prospective study.

Sample size

Trial 1807

The sample size calculation was reasonable for a Phase 2 trial. The trial lacks sensitivity to dose-responsiveness of rare adverse events.

Trial 1839

With respect to 10% weight loss responders, the sample size would be adequate to detect 14% on liraglutide v 10% placebo, a difference of only 4% which would not be considered clinically relevant. On a continuous scale, a difference between liraglutide and placebo of 0.7 kg could be detected, which would also not be considered clinically relevant.

It seems that the trial was actually powered on a fourth primary endpoint of progression from pre-diabetes to diabetes (of relevance to FDA requirements) but is of only secondary importance

regarding EMA guidance (guideline CPMP/EWP/281/96 Rev.1 – 2007) and therfore this trial could be considered to be over-powered.

Trial 1922

With respect to 10% weight loss responders, the sample size would be adequate to detect a difference between 10% for placebo and 20% for liraglutide that is of questionable clinical relevance. The mentioned difference of 1.7 kg is below the level of clinical relevance.

Trial 3970

As no clinically relevant difference in sleep apnoea parameters is established in literature, the sample size was adapted to the expected difference in weight loss of 6 kg, based on previous trials. It is not clear whether this results in a clinically relevant change in sleep apnoea.

Trial 1923

The trial would be powered to detect a doubling of the number of subjects who maintain their weight after diet-induced weight loss compared to placebo. This endpoint is not defined as such in guideline (CPMP/EWP/281/96 Rev.1 – 2007). Instead, the guideline recommends looking at patients who lose >10% of their baseline weight.

Randomisation

There are no concerns regarding randomisation using state-of the art systems (IVRS/IWRS). Stratification was appropriate to ensure proper distribution of baseline variables that are expected to be related to the outcomes; stratification by pre-diabetes status was recommended during the CHMP scientific advice (2008).

Blinding

Blinding was consistent with current practice in clinical trials. It must however be assumed that the (gastro-intestinal) adverse effects of liraglutide have unblinded active treatment in some cases.

Trial 1807 was single blind after 20 weeks and open label after 52 weeks. Orlistat treatment in trial 1807 was always given open-label.

Statistical methods

In general, the approach to statistical analysis and the use of ANCOVA are supported, as was confirmed in the 2008 CHMP scientific advice.

Populations

The Full Analysis Set (FAS) for the primary LOCF analysis only includes subjects with a valid post baseline efficacy measurement and as such is a modified intention-to-treat (ITT) analysis. An analysis of all randomised subjects with BOCF if no post-baseline assessment is available, was provided as a sensitivity analysis to better approach ITT.

The Safety Set is defined as usual.

Primary endpoint

As explained in the guideline (CPMP/EWP/281/96 Rev.1 - 2007), placebo-controlled trials for obesity usually have a high dropout rate; this is often explained by adverse events leading to withdrawal from active therapy and lack of efficacy leading to withdrawal from placebo. It is important to follow up patients who have discontinued treatment to facilitate intention to treat analysis. If this fails, imputation of missing data becomes necessary. The Applicant chose LOCF as imputation method.

The Applicant used two approaches for estimating the LS means, in the first two trials (1807 and 1923) the LS means were calculated using equal weights for each factor, for the later three trials (1839, 1922 and 3970) the Applicant calculated LS means weighing for the sample size. The change was driven by availability of appropriate software and resulted only in minor changes.

Sensitivity analyses

The Applicant also provided a BOCF sensitivity analysis in which subjects gaining weight were imputed using LOCF. The effect of this is difficult to predict, as this may apply to more subjects on placebo treatment than on active therapy.

The optimal treatment scenario is provided by the completers analysis which is also included.

Secondary endpoints

A large number of secondary endpoints were included in the trials, but multiplicity issues were not addressed for the individual trials. This was rectified by implementing a hierarchical testing procedure for some of these secondary endpoints which would be applied to the pooled analysis. In agreement with the FDA, the Applicant decided to accept these results as confirmatory only in the case in which statistical significance within trial 1839 alone was also achieved, to account for the fact that 2 (1807, 1923) of the 5 trials to be pooled were already unblinded at time of specification of the hierarchy.

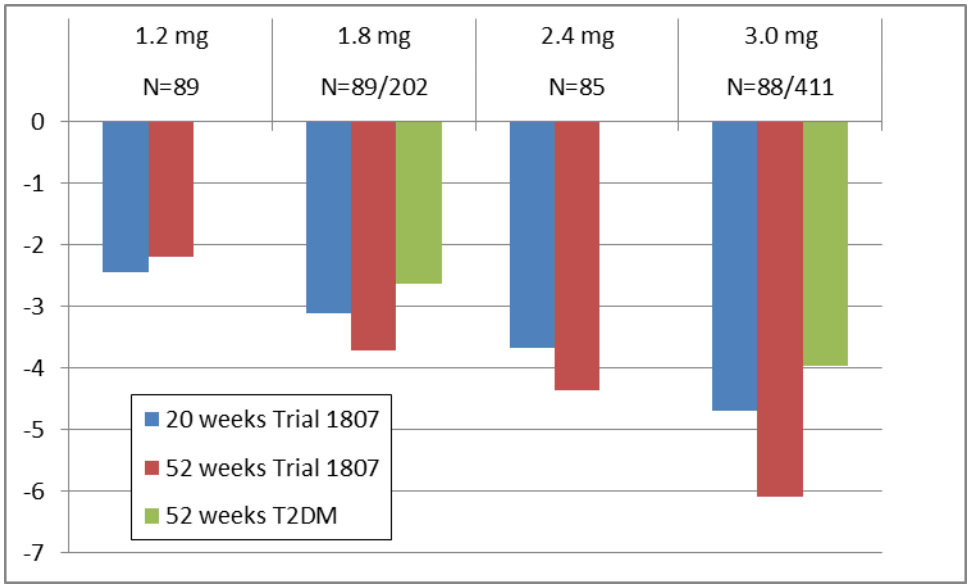
Change of primary endpoints during conduct of trial (trial 1923)

In trial 1923, 2 modifications to the endpoints of the trial were made to comply with FDA requests. These changes occurred well before unblinding and do no threaten the interpretation of the results from the trial.

Dose response studies

The dose selection for phase 3 is based on the results of trial 1807. However, because trial 1922 includes data on the comparison of the currently approved dose (for Victoza) and the proposed dose (for Saxenda), these data are included here also.

Figure E1 Mean weight loss (%) by liraglutide dose, difference to placebo – Trial 1807 and 1922 (T2DM) - 20 and 52 weeks



The results from trial 1807, supported by trial 1922, confirm that weight loss is dose dependent and that the highest dose tested is the most efficacious. Doses higher than 3.0 mg may be even more efficacious, but this is not discussed by the Applicant.

The comparison of safety (See safety section) between the various doses is more difficult, because the relatively small groups in trial 1807 (each <100 patients evaluable) are not very sensitive to rare adverse events that may still be important. While trial 1807 confirms that the safety of the 3.0 mg dose is acceptable for use in phase 3, the trial provides no evidence for equivalence of the 1.8 and 3.0 mg doses for safety.

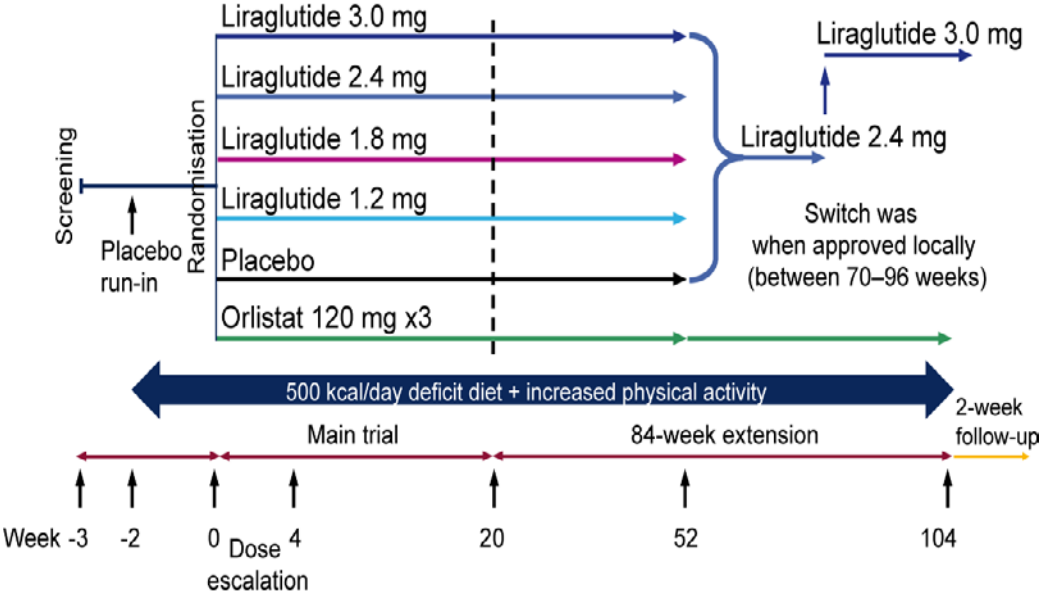
Results

The following sections summarise the efficacy results of the 5 main trials individually or across the trials, as appropriate

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table E3. Summary of efficacy for trial 1807

Title:	Effect of liraglutide on body weight in obese subjects without diabetes: a 20-week randomised, double-blind, placebo-controlled, six-armed parallel-group, multi-centre, multinational trial with an open label orlistat comparator arm.		
Study identifier	Trial ID: NN8022-1807 EUDRACT No.:2006-004481-13		
Design	This was a 20-week dose-finding trial, with 84-week extension and an interim analysis at 52 weeks, conducted in 564 subjects with BMI 30-40 kg/m^2, T2DM excluded. Randomisation was 1:1:1:1:1:1 (N=90-98 across treatment groups). The trial was performed at 19 sites in 8 European countries. This application focuses on the 52-week efficacy data. An evaluation of 20 and 52-week data is included with respect to liraglutide dose response. Data after 104 weeks are included in the evaluation of efficacy persistence.  Week 0-20 (double blind; orlistat open label): Main trial, stratification by gender. 2-week diet and exercise run-in with placebo injections for all subjects prior to randomisation. Weeks 20-52 (single-blind; subject and investigator blinded, sponsor unblinded): Extension. Subjects who chose to enrol provided new informed consent and continued on randomised treatment. Weeks 52-104 (open-label): Extension, liraglutide/placebo-treated subjects were initially treated with liraglutide 2.4 mg in the open-label extension period, but were all gradually (as sites received Ethics Committee approval) changed to treatment with liraglutide 3.0 mg based on discussion of the results of the planned 52-week interim analysis. Orlistat-treated subjects continued on orlistat. 2-week follow-up period after trial completion.		
	Duration	Main phase:	20 / 52 weeks
		Run-in phase:	2 weeks single-blind placebo
		Extension phase:	52 weeks
Hypothesis	Superiority		
Treatments	Placebo	Liraglutide-matching placebo	
	Liraglutide 1.2 mg	Liraglutide 1.2 mg once daily	
	Liraglutide 1.8 mg	Liraglutide 1.8 mg once daily	
	Liraglutide 2.4 mg	Liraglutide 2.4 mg once daily	
	Liraglutide 3.0 mg	Liraglutide 3.0 mg once daily	
	Orlistat	Orlistat (120 mg 3 times daily) open label	

Endpoints	Co-Primary endpoint	Body weight (kg)	
	Co-Primary endpoint	5% responders	Subjects with >5% weight loss
	Co-Primary endpoint	10% responders	Subjects with >10% weight loss
Database lock			

Primary Analysis (20 weeks)

Population	Intent to treat (LOCF)						
Time points	20 weeks						
	Treatment group	**Placebo**	**Liraglutide (mg)**				**Orlistat**
			1.2	**1.8**	**2.4**	**3.0**	
Descriptive statistics	Nr of subjects	98	95	90	93	93	95
	Body weight (kg) *	-2.76	-4.81	-5.52	-6.27	-7.15	-4.12
	5% responders	29.6	52.1	53.3	60.9	76.1	44.2
	10% responders	2.0	7.4	18.9	22.8	28.3	9.5
Effect estimate per comparison	**Body weight (kg)**						
	Difference		-2.06	-2.76	-3.51	-4.44	-1.36
	95% CI		-3.56; -0.56	-4.27; -1.26	-5.01; -2.01	-5.95; -2.92	
	P-value		0.0030	0.0000	0.0000	0.0000	
	5% responders						
To placebo	Difference @		22.5	23.7	31.3	46.5	14.6
	Odds		2.59	2.70	3.76	7.25	
	95% CI		1.19; 5.62	1.24; 5.88	1.71; 8.26	3.13; 16.83	
	P-value		0.0022	0.0015	0.0000	0.0000	
	10% responders						
	Difference @		5.4	16.9	20.8	26.3	7.5
Effect estimate per comparison	**Body weight (kg)**						
	Difference	1.36	-0.67	-1.39	-2.13	-2.96	
	95% CI		-2.22; 0.89	-2.96; 0.18	-3.69; -0.57	-4.54; -1.38	
	P-value		0.6769	0.0992	0.0033	0.0000	
	5% responders						
To orlistat	Difference @	-14.6	7.9	9.1	16.7	31.9	
	Odds		1.41	1.49	2.08	3.93	
	95% CI		0.66; 3.01	0.70; 3.18	0.96; 4.48	1.72; 8.96	
	P-value		0.2511	0.1914	0.0173	0.0000	
	10% responders						
	Difference @	-7.5	-2.1	9.4	13.3	18.8	

* Change from baseline (LSMeans) @ assessor's calculation

Extension interim Analysis 52 weeks

Population	Intent to treat LOCF						
Time points	52 weeks						
	Treatment group	**Placebo**	**Liraglutide mg**				**Orlistat**
			1.2	**1.8**	**2.4**	**3.0**	
Descriptive statistics	Number of subjects	98	94	90	92	92	95
	Body weight kg *	-2.7	-4.6	-6.2	-7.0	-8.9	-4.7
	SD	4.9	4.9	6.5	6.9	6.4	5.9
	5% responders	27.6	45.7	53.3	53.3	75.0	45.3
	10% responders	10.2	18.1	26.7	29.3	37.0	15.8
Effect estimate per comparison	**Body weight kg**						
	Difference		-1.76	-3.36	-4.14	-5.82	
	95% CI		-3.87; 0.35	-5.48; -1.23	-6.25; -2.02	-7.95; -3.68	
	P-value		0.1322	0.0005	0.0000	0.0000	
	5% responders						
To placebo	Difference @		18.1	25.7	25.7	47.4	17.7
	Odds		2.20	3.01	3.05	7.82	
	95% CI		0.99; 4.85	1.36; 6.67	1.37; 6.76	3.35; 18.28	
	P-value		0.0132	0.0006	0.0005	0.0000	
	10% responders						
	Difference @		7.9	16.5	19.1	26.8	5.6
Effect estimate per comparison	**Body weight kg**						
	Difference		0.17	-1.47	-2.21	-3.80	
	95% CI		-2.01; 2.35	-3.67; 0.73	-4.40; -0.02	-6.01; -1.59	
	P-value		0.9990	0.2946	0.0468	0.0001	
	5% responders						
To orlistat	Difference @	-17.7	0.4	8.0	8.0	29.7	
	Odds		1.02	1.43	1.44	3.67	
	95% CI		0.48; 2.18	0.67; 3.05	0.67; 3.09	1.62; 8.33	
	P-value		0.9409	0.2450	0.2281	0.0001	
	10% responders						
	Difference @	-5.6	2.3	10.9	13.5	21.2	

* Change from baseline LSMeans @ assessor's calculation

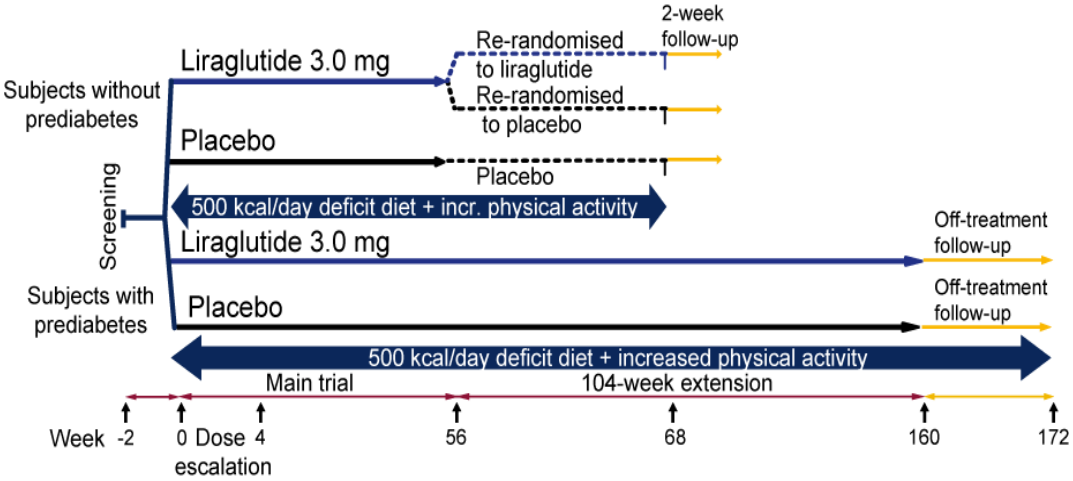
Extension Analysis 104 weeks

Population	Intent to treat LOCF					
Time points	104 weeks					
	Treatment group	**Placebo**	**Liraglutide mg**			**Orlistat**
			1.2	**1.8**	**2.4**	**3.0**	
Descriptive statistics	Number of subjects	98	94	90	92	92	95
	Body weight kg *	-5.4	-4.9	-5.6	-6.4	-8.2	-3.8
	SD	5.9	5.8	6.5	7.2	7.1	6.4
	5% responders	45.9	44.7	46.7	46.7	64.1	32.6
	10% responders	21.4	18.1	25.6	25.0	30.4	16.8
Effect estimate per comparison	**Body weight kg**						
	Difference @		0.5	-0.2	-1.0	-2.8	1.6
	95% CI						
	P-value						
	5% responders						
To placebo	Difference @		-1.2	0.8	0.8	18.2	-13.3
	Odds						
	95% CI						
	P-value						
	10% responders						
	Difference @		-3.3	4.2	3.6	9.0	-4.6
Effect estimate per comparison	**Body weight kg**						
	Difference @	-1.6	-1.1	-1.8	-2.6	-4.4	
	95% CI						
	P-value						
	5% responders						
To orlistat	Difference @	13.3	12.1	14.1	14.1	31.5	
	Odds				**2.55**		
	95% CI				**1.48; 4.37**		
	P-value				**0.0007**		
	10% responders						
	Difference @	4.6	1.3	8.8	8.2	13.6	

* Change from baseline LSMeans @ assessor's calculation # 2.4 and 3.0 mg groups combined

All patients were changed to active treatment.

Table E4. Summary of efficacy for trial 1839

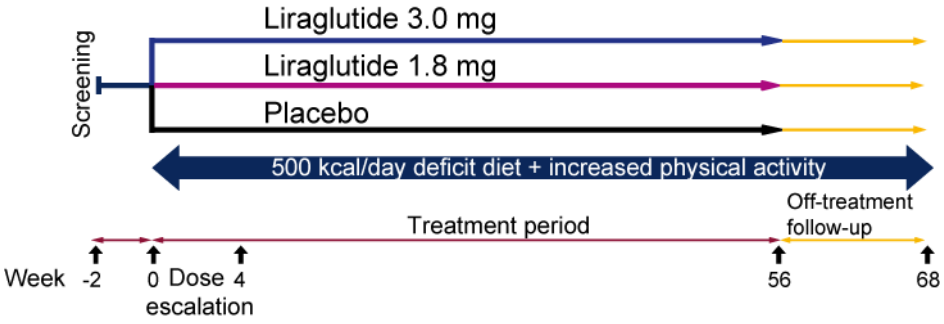
Title:	SCALE™ – Obesity and pre-diabetes. Effect of liraglutide on body weight in non-diabetic obese subjects or overweight subjects with comorbidities: A randomised, double-blind, placebo controlled parallel group, multi-centre, multinational trial with stratification of subjects to either 56 or 160 weeks of treatment based on pre-diabetes status at randomisation.		
Study identifier	Trial ID: NN8022-1839 EudraCT No.:2008-001049-24		
Design	This was the largest trial in the development programme and was designed to assess weight loss and the course of pre-diabetes associated with obesity. This trial represented approximately 70% of the total phase 3 population. The trial was conducted in 3731 subjects with or without pre-diabetes with BMI ⩾30 kg/m^2 or ⩾27 kg/m^2 with dyslipidaemia and/or hypertension, T2DM excluded. Randomisation was 2:1 (liraglutide N=2487: placebo N=1244). The 56-week main trial is completed; the 104-week extension for subjects with pre-diabetes at randomisation is on-going. The trial was performed at 191 sites in 27 countries in Europe, North and South America, Canada, Asia, South Africa and Australia. This application includes data from an analysis of the main period of 56 weeks (including both subjects with and without pre-diabetes at screening, as well as the 12-week re-randomisation period (for subjects without pre-diabetes at randomisation).  Stratification to 56 weeks of treatment for subjects without pre-diabetes at screening (with 12-week re-randomised treatment period) or 160 weeks (with 12-week observational off-treatment follow-up period) for those with pre-diabetes, and also by BMI. Subjects on liraglutide completing 56 weeks were re-randomised to continue on liraglutide or switch to placebo. Those on placebo remained on placebo. Week 0-56 (double blind): Main study for subjects with or without pre-diabetes. Week 56-160 (single-blind; sponsor unblinded): Extension for subjects with pre-diabetes. All subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial, including 12-week re-randomised period. Subjects with pre-diabetes continue in the ongoing 160-week phase of the trial.		
	Duration	Main phase:	56 weeks
		Run-in phase:	not applicable
		Extension phase:	12 weeks follow up; 104 weeks, only in subjects with pre-diabetes, not yet submitted

Hypothesis	Superiority		
Treatments	Lira	Liraglutide 3.0 mg/d (titrated in 4 weeks, full dose 52 weeks	
	Pbo	Matching placebo	
Endpoints	Co-primary endpoint	Body weight	Change (%) in fasting body weight from baseline to week 56
	Co-primary endpoint	5% responders	Proportion of 5% responders from baseline to week 56
	Co-primary endpoint	10% responders	Proportion of 10% responders from baseline to week 56
	Co-primary endpoint	N/A	delaying the onset of type 2 diabetes in subjects with pre-diabetes (104 week extension) Not yet reported
Database lock	02 May 2013		

Primary Analysis

Population	Full analysis set (Modified Intent to treat with LOCF)		
Time points	56 weeks		
Descriptive statistics	Treatment group	Lira	Pbo
	Number of subjects	2481	1242
	Body weight (%)	-7.98	-2.62
	SD	6.67	5.74
	5% responders (N)	1536	331
	%	63.2	27.1
	10% responders (N)	805	129
	%	33.1	10.6
Effect estimate per comparison	Endpoint	Comparison groups	Lira - Pbo
	Body weight	Difference	-5.39
		95% CI	-5.82; -4.95
		P-value	<0.0001
	5% responders	Odds	4.80
		95% CI	4.12 ; 5.60
		P-value	<0.0001
	10% responders	Odds	4.34
		95% CI	3.54 ; 5.32
		P-value	<0.0001

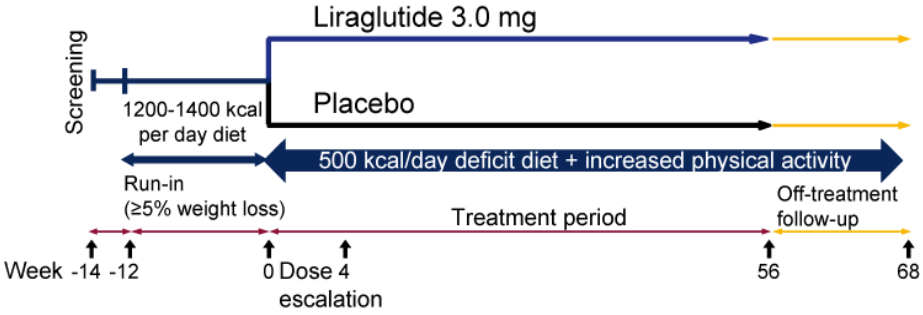
Table E5. Summary of efficacy for trial 1922

Title:	SCALE™ – Diabetes. Effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes - A 56 week randomised, double-blind, placebo-controlled, three armed parallel group, multi-centre, multinational trial with a 12 week observational follow-up period.		
Study identifier	Trial ID: NN8022-1922 EudraCT No.: 2008-002199-88		
Design	This trial was designed to investigate weight loss in obese or overweight individuals with diagnosed T2DM. In addition, this trial afforded the opportunity to compare the 3.0 mg dose of liraglutide to the 1.8 mg dose approved for the treatment of T2DM as Victoza. The trial was a 56-week double-blind weight loss trial conducted in 846 subjects with BMI ⩾27 kg/m^2 and with an established diagnosis of T2DM. Randomisation was 2:1:1 (liraglutide 3.0 mg N=423: 1.8 mg [Victoza] N=211: placebo N=212). The trial was performed at 126 sites in 9 countries in the US, Europe and South Africa. This application includes data from the main period of 56 weeks and the 12-week off-treatment follow-up period, as well as an evaluation of liraglutide dose response.  Stratification by background treatment and also by baseline HbA_{1c} (<8.5% or ⩾8.5%). 628 subjects (74%) completed the 56-week trial (N=324 (77%) for liraglutide 3.0 mg, N=164 (78%) for liraglutide 1.8 mg, N=140 for placebo). A 12-week observational off-treatment follow-up period was included, in order to assess the effects of drug cessation on weight control, and possible withdrawal side-effects. All subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial, including the 12-week follow-up period.		
	Duration	Main phase:	56 weeks
		Run-in phase:	not applicable
		Extension phase:	12 weeks follow up
Hypothesis	Superiority		
Treatments	Lira 3.0	Liraglutide 3.0 mg/d (titrated in 4 weeks, full dose 52 weeks)	
	Lira 1.8	Liraglutide 1.8 mg/d (titrated in 2 weeks, full dose 54 weeks)	
	Pbo	Matching placebo	
Endpoints	Co-primary endpoint	Body weight	Change (%) in fasting body weight from baseline to week 56
	Co-primary endpoint	5% responders	Proportion of 5% responders from baseline to week 56
	Co-primary endpoint	10% responders	Proportion of 10% responders from baseline to week 56
Database lock	23 May 2013		

Primary Analysis

Population	Full analysis set (Modified Intent to treat with LOCF)			
Time points	56 weeks			
Descriptive statistics	Treatment group	Lira 3.0	Lira 1.8	Pbo
	Number of subjects	411	202	210
	Body weight (%)	-5.9	-4.6	-2.0
	SD	5.5	5.5	4.3
	5% responders (N)	205	72	29
	%	49.9	35.6	13.8
	10% responders (N)	96	29	9
	%	23.4	14.4	4.3
Effect estimate per comparison	Endpoint	Comparison groups	Lira 3.0-Pbo	Lira 3.0-Pbo
	Body weight	Difference	-3.97	-2.62
		95% CI	-4.84; -3.11	-3.63; -1.62
		P-value	<0.0001	<0.0001
	5% responders	Odds	6.81	3.69
		95% CI	4.34 ; 10.68	2.24 ; 6.09
		P-value	<0.0001	<0.0001
	10% responders	Odds	7.10	3.84
		95% CI	3.48 ; 14.48	1.75 ; 8.41
		P-value	<0.0001	0.0008

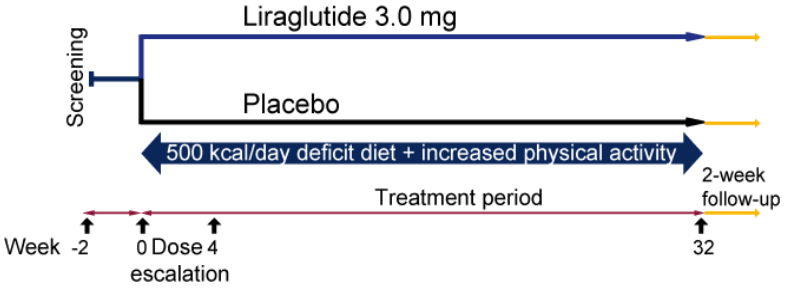
Table E6. Summary of efficacy for trial 1923

Title:	SCALE™ – Maintenance. Effect of liraglutide on long-term weight maintenance and additional weight loss induced by a 4 to 12 week low calorie diet in obese subjects; A 56 week randomised, double-blind, placebo controlled, parallel group, multi-centre trial with a 12 week follow-up period.		
Study ID	Trial ID: NN8022-1923; EudraCT No.: N/A		
Design	Trial 1923 was distinct among the trials in this development programme as it was designed to determine if liraglutide 3.0 mg could maintain weight loss compared to placebo in subjects who lost at least 5% of their baseline body weight through a low calorie (1200 kCal) diet. In addition, liraglutide 3.0 mg was evaluated in regard to its ability to induce additional weight loss after the 1200 kCal diet was liberalised to a net 500 calorie deficit compared to the subject's baseline diet. This was a 56-week double-blind weight loss and weight maintenance trial conducted in 422 subjects with BMI ⩾30 kg/m^2 or ⩾27 kg/m^2 with dyslipidaemia and/or hypertension, T2DM excluded. Randomisation was 1:1 (liraglutide N=212: placebo N=210). Only subjects achieving ⩾5% weight loss during the 4 – 12 week run-in period on LCD were randomised. The trial was performed at 36 sites in the US and Canada. This application includes data from the main 56 week period and the 12-week off-treatment follow-up period.  Stratification by comorbidity status (presence or absence of treated or untreated hypertension or dyslipidaemia) and also by BMI (⩾30 kg/m^2 or <30 kg/m^2). 305 subjects (72%) completed the 56-week trial (N=159 [75%] for liraglutide 3.0 mg, N=146 [70%] for placebo). A 12-week observational off-treatment follow-up period was included, in order to assess the effects of drug cessation on appetite and weight control, and possible withdrawal side-effects. All subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial from randomisation, including the follow-up period.		
	Duration	Main phase:	56 weeks
		Run-in phase:	4-12 weeks
		Extension phase:	12 weeks follow up
Hypothesis	Superiority		
Treatments	Lira	Liraglutide 3.0 mg/d (titrated in 4 weeks, full dose 52 weeks	
	Pbo	Matching placebo	
Endpoints	Co-primary endpoint	Body weight	Percentage change in body weight from randomisation to week 56;
	Co-primary endpoint	5% responders	The proportion that maintained the ⩾ 5% reduction in body weight achieved during the LCD run-in period;
	Co-primary endpoint	10% responders	The proportion of subjects achieving ⩾5% reduction of randomisation body weight.
Database lock	25-Apr-2012		

Primary Analysis

Population	Full analysis set (Modified Intent to treat with LOCF)		
Time points	56 weeks		
Descriptive statistics	Treatment group	Lira	Pbo
	Number of subjects	194	188
	Body weight (%)	-6.11	-0.05
	SE	0.66	0.63
	5% responders (N)	96	43
	%	46.4	20.9
	10% responders (N)	54	13
	%	26.1	6.3
Effect estimate per comparison	Endpoint	Comparison groups	Lira - Pbo
	Body weight	Difference	-6.06
		95% CI	-7.50 ; -4.62
		P-value	<.0001
	5% responders	Odds	4.82
		95% CI	3.01 ; 7.71
		P-value	<.0001
	10% responders	Odds	5.30
		95% CI	2.79 ; 10.08
		P-value	<.0001

Table E7. Summary of efficacy for trial 3970

Title:	SCALE™ – Sleep apnoea. Effect of Liraglutide in Obese Subjects with Moderate or Severe Obstructive Sleep Apnoea - A 32 week randomised, double-blind, placebo-controlled, parallel group, multi-centre and multinational trial		
Study identifier	Trial ID: NN8022-3970 UTN: U1111-1126-6260 EudraCT No.: not applicable		
Design	Trial 3970 was designed to determine if liraglutide 3.0 mg could reduce disease severity in obese subjects with moderate or severe sleep apnoea. The analysis of the results included investigation of the impact of weight loss on OSA and other sleep-related end points. This was the only trial where the primary endpoint addressed a co-morbidity of obesity (weight loss was a secondary end point) and the only trial of 32 weeks duration. Trial 3970 was a 32-week double-blind trial conducted in 359 subjects with BMI ⩾30 kg/m^2 with moderate or severe OSA, T2DM excluded. Randomisation was 1:1. The main aim was to investigate liraglutide's effects on severity of OSA in subjects unwilling or unable to use treatment with continuous positive airway pressure (CPAP). The trial was performed at 35 sites in the US and 5 in Canada. This application includes data from the full 32-week trial period.  		
	Duration	Main phase:	32 weeks
		Run-in phase:	not applicable
		Extension phase:	not applicable
Hypothesis	Superiority		
Treatments	Lira	Liraglutide 3.0 mg/d (titrated in 4 weeks, full dose 28 weeks	
	Pbo	Matching placebo	
Endpoints	Primary endpoint	AHI	Change from baseline in AHI events per hour
	Secondary endpoint	Body weight	Change (%) in fasting body weight from baseline to week 32
	Secondary endpoint	5% responders	Proportion of 5% responders from baseline to week 32
	Secondary endpoint	10% responders	Proportion of 10% responders from baseline to week 32
Database lock	11 September 2013		

Primary Analysis

Population	Full analysis set (Modified Intent to treat with LOCF)		
Time points	56 weeks		
Descriptive statistics	Treatment group	Lira	Pbo
	Number of subjects	175	178
	AHI (Mean)	-12.22	-6.08
	SD	23.34	25.90
	Body weight (%)	-5.72	-1.59
	SD	5.59	4.46
	5% responders (N)	81	32
	%	46.4	18.1
	10% responders (N)	39	3
	%	22.4	1.5
Effect estimate per comparison	Endpoint	Comparison groups	Lira - Pbo
	AHI	Difference	-6.10
		95% CI	-11.0 ; -1.19
		P-value	0.0150
	Body weight	Difference	-4.15
		95% CI	-5.21 ; -3.09
		P-value	<.0001
	5% responders	Odds	3.92
		95% CI	2.41 ; 6.38
		P-value	<.0001
	10% responders	Odds	18.96
		95% CI	5.69 ; 63.14
		P-value	<.0001

Analysis performed across trials (pooled analyses and meta-analysis):

Subject disposition

Across all the trials, 5813 subjects were exposed to treatment: 3872 to liraglutide (including 3384 to the 3.0 mg dose) and 1941 to placebo. In addition, 95 subjects were randomised and exposed to orlistat in trial 1807. Approximately 70% of subjects completed the phase 3 trials: 72% treated with liraglutide and 66% treated with placebo. (Table E8)

More subjects on liraglutide 3.0 mg discontinued due to AEs (9–11%) compared with those on placebo (3–4%); the proportions were similar between both groups in trial 1923 (~8.5%). Fewer subjects on liraglutide 3.0 mg (0-1% across the phase 3 trials) than placebo (1-3%) withdrew due to ineffective therapy, and fewer on liraglutide (6-11%) than placebo (11-20%) withdrew their consent to remain in the trial.

In the pooled dataset, the rate of withdrawals is high, 29.6%. This number is consistent over all trials and expected for placebo-controlled trials of one-year duration in obesity. To investigate what happened to the withdrawn subjects after withdrawal, these subjects were asked to come in for a measurement at the nominal time point of their 56 week visit in the 56-week phase 3 trials (trials

1923, 1922 and 1839). Only 26.8% of withdrawn subjects came in for this visit and may potentially not be representative for all withdrawn subjects.

Table E8 Subject disposition – summary – all 5 trials pooled

	Lira 3.0 mg N (%)	Total lira N (%)	Placebo N (%)	Total N (%)
Screened				8479
Screening failures				2652 (45.5)
Randomised	3395 (100.0)	3884 (100.0)	1943 (100.0)	5827 (100.0)
Exposed	3384 (99.7)	3872 (99.7)	1941 (99.9)	5813 (99.8)
Full analysis set	3328 (98.0)	3808 (98.0)	1919 (98.8)	5727 (98.3)
Safety analysis set	3384 (99.7)	3872 (99.7)	1941 (99.9)	5813 (99.8)
Completer*	2471 (72.8)	2809 (72.3)	1291 (66.4)	4100 (70.4)
Withdrawn	924 (27.2)	1075 (27.7)	652 (33.6)	1727 (29.6)
Adverse event	324 (9.5)	366 (9.4)	80 (4.1)	446 (7.7)
Ineffective therapy	48 (1.4)	52 (1.3)	88 (4.5)	140 (2.4)
Non-compliance with protocol	95 (2.8)	111 (2.9)	64 (3.3)	175 (3.0)
Withdrawal criteria**	340 (10.0)	371 (9.6)	307 (15.8)	678 (11.6)
Withdrawn consent	296 (8.7)	319 (8.2)	284 (14.6)	603 (10.3)
Target dose not tolerated	3 (0.1)	6 (0.2)	0 (0.0)	6 (0.1)
Pregnancy or pregnancy intent	32 (0.9)	33 (0.8)	14 (0.7)	47 (0.8)
Use of insulin, GLP1RA or DPP4i 1)	0 (0.0)	2 (0.1)	2 (0.1)	4 (0.1)
Unacceptable hyperglycaemia 2)	5 (0.1)	7 (0.2)	9 (0.5)	16 (0.3)
Unacceptable hypoglycaemia 2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pancreatitis 3)	6 (0.2)	6 (0.2)	0 (0.0)	6 (0.1)
Psych disorder (INV/MHP opinion) 3)	1 (0.0)	1 (0.0)	2 (0.1)	3 (0.1)
Calcitonin >=50 ng/L (France) 4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosis of type 1 diabetes or type 2 diabetes 5)	1 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Other	107 (3.2)	125 (3.2)	101 (5.2)	226 (3.9)
Lost to follow-up	67 (2.0)	74 (1.9)	59 (3.0)	133 (2.3)
Did not participate in the extension	10 (0.3)	50 (1.3)	12 (0.6)	62 (1.1)
Adverse event inclusive target dose not tolerated, pancreatitis and psychiatric disorder ***	334 (9.8)	379 (9.8)	82 (4.2)	461 (7.9)

Baseline data

In general, the baseline characteristics of the trials are consistent with the expected target population (Table E9). However, the representation of some subpopulations is limited:

- Males were 28.8%.
- Subjects with BMI <30 kg/m2 were only 5.4% of the population
- Subjects ≥65 years of age were only 6.6% of the population and only 0.4% of the participants were ≥75 years. The oldest patient was 82 years.
- Other races than White or Black (African American) represented 4.9% of participants.

Table E9 Demographics and baseline characteristics – summary – primary dataset (weight management pool) - safety analysis set

	Lira 3.0 mg	Total lira	Placebo	Total
Number of subjects	3384	3872	1941	5813
Age (yrs)				
N	3384	3872	1941	5813
Mean (SD)	46.6 (12.2)	47.0 (12.2)	46.6 (11.8)	46.9 (12.0)
Median	47.0	48.0	47.0	47.0
Min ; Max	18.0; 79.0	18.0; 82.0	18.0; 78.0	18.0; 82.0
Age Group (yrs)				
];65[	3152 (93.1)	3604 (93.1)	1825 (94.0)	5429 (93.4)
[65;75[	215 (6.4)	249 (6.4)	113 (5.8)	362 (6.2)
[75;[	17 (0.5)	19 (0.5)	3 (0.2)	22 (0.4)
Sex				
Female	2449 (72.4)	2763 (71.4)	1374 (70.8)	4137 (71.2)
Male	935 (27.6)	1109 (28.6)	567 (29.2)	1676 (28.8)
Race				
White	2845 (84.1)	3294 (85.1)	1651 (85.1)	4945 (85.1)
Black or African American	348 (10.3)	378 (9.8)	202 (10.4)	580 (10.0)
Asian	115 (3.4)	119 (3.1)	53 (2.7)	172 (3.0)
American Indian or Alaska Native	9 (0.3)	9 (0.2)	4 (0.2)	13 (0.2)
Native Hawaiian or Other Pacific Islander	5 (0.1)	5 (0.1)	4 (0.2)	9 (0.2)
Other	62 (1.8)	67 (1.7)	27 (1.4)	94 (1.6)
Height (m)				
N	3384	3872	1941	5813
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Median	1.7	1.7	1.7	1.7
Min ; Max	1.1; 2.0	1.1; 2.0	1.4; 2.0	1.1; 2.0
Body weight (kg)				
N	3384	3872	1941	5813
Mean (SD)	106.1 (21.4)	105.5 (21.0)	106.2 (22.2)	105.7 (21.4)
Median	102.7	102.1	102.6	102.3
Min ; Max	60.1; 234.3	60.1; 234.3	62.5; 244.9	60.1; 244.9
BMI at baseline (kg/m^2)				
N	3384	3872	1941	5813
Mean (SD)	37.9 (6.4)	37.6 (6.3)	37.8 (6.5)	37.7 (6.3)
Median	36.8	36.4	36.7	36.6
Min ; Max	27.0; 77.2	27.0; 77.2	25.7; 75.3	25.7; 77.2
History of CV disease				
Yes	311 (9.2)	351 (9.1)	172 (8.9)	523 (9.0)
History of psychiatric disorder	454 (13.4)	501 (12.9)	307 (15.8)	808 (13.9)
SMQ Depression (excl suicide and self-injury)	309 (9.1)	346 (8.9)	206 (10.6)	552 (9.5)
SMQ Suicide and self-injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety#	243 (7.2)	258 (6.7)	151 (7.8)	409 (7.0)
Glycaemic status				
Normo-glycaemia	1129 (33.4)	1264 (32.6)	676 (34.8)	1940 (33.4)
Pre-diabetes	1833 (54.2)	1976 (51.0)	1053 (54.3)	3029 (52.1)
Diabetes	422 (12.5)	632 (16.3)	212 (10.9)	844 (14.5)
Dyslipidaemia				
Yes	1166 (34.5)	1340 (34.6)	618 (31.8)	1958 (33.7)
Hypertension				
Yes	1296 (38.3)	1511 (39.0)	755 (38.9)	2266 (39.0)
Both dyslipidaemia and hypertension				
Yes	716 (21.2)	843 (21.8)	376 (19.4)	1219 (21.0)
Renal function				
Normal	1758 (52.0)	2015 (52.0)	1044 (53.8)	3059 (52.6)
Mild	1461 (43.2)	1670 (43.1)	830 (42.8)	2500 (43.0)
Moderate	161 (4.8)	181 (4.7)	63 (3.2)	244 (4.2)
Severe	3 (<0.1)	4 (0.1)	2 (0.1)	6 (0.1)

Outcomes and estimation

Primary endpoints related to weight loss

The development over time in body weight is similar in the various efficacy trials (Figure E2). The treated group shows a continuous weight decline with reaches a plateau after about 40 weeks. In the mITT pooled analyses using LOCF, weight loss was 7.5% (7.8 kg) with liraglutide 3.0 mg vs. 2.3% (2.5 kg) with placebo, a placebo-subtracted weight loss of 5.2% [-5.53 ; -4.83]. The mean treatment difference in trials 3970 (4.15%) and 1922 (3.95%) was less than in the pooled dataset (5.24%). Trial 3970 had a shorter treatment duration of 32 weeks and subjects may not have reached the full

treatment effect. Trial 1922 was executed in T2DM patients, which are known to respond less to weight reduction attempts.

Figure E2 Body weight (%) change from baseline – All trials pooled, Lira 3.0 N=3301; Pbo, N=1890

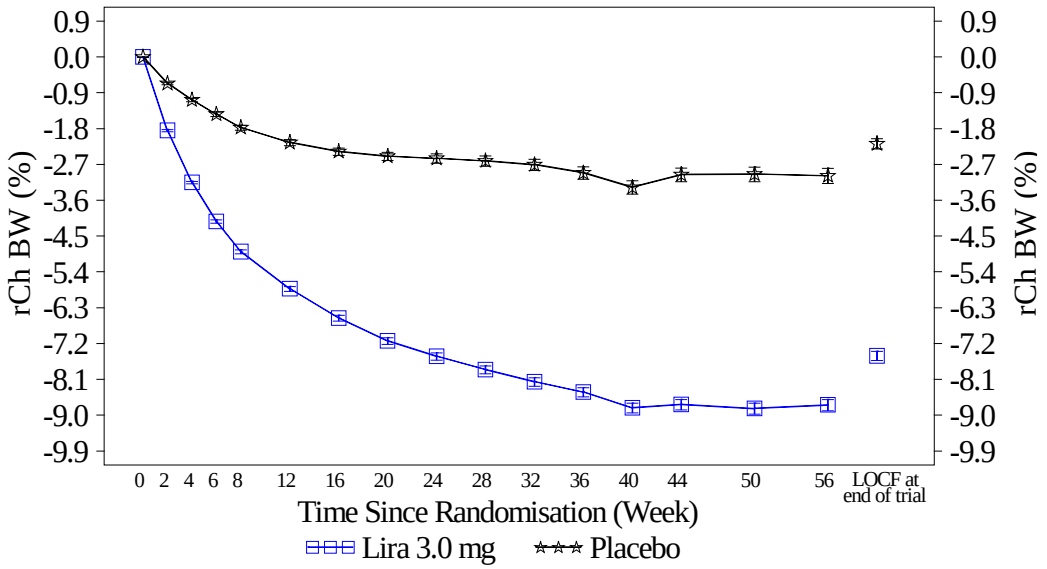
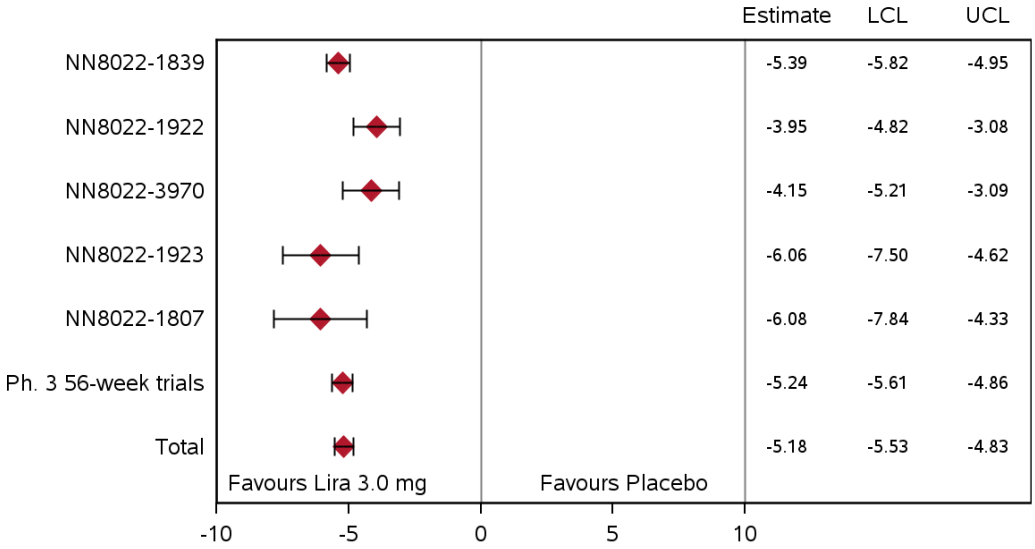


Figure E3 Treatment differences for fasting body weight change (%) by trial and pools



Data are LS means with 95% CI for the FAS with LOCF. P-value for interaction: 0.0196

The data are supported by a range of sensitivity analyses. The most favourable scenario is represented by the Completers analysis. In this analysis the placebo-subtracted treatment effect for weight loss was 5.6%. As discussed before, no clean BOCF analysis was provided as possibly least favourable scenario; the modified BOCF analysis (weight gain imputed with LOCF) resulted in a placebo-subtracted treatment effect for weight loss of 4.5%.

The likelihood of achieving a predefined response with liraglutide is greater for any weight loss in the range from -25% to +5%. The likelihood for achieving 10% weight loss was 30.5% for liraglutide

3.0 mg v 8.4% for placebo in the pooled 56-week trials. The estimates for completers were 38.2% and 12.7%; the estimates counting early withdrawals as non-responders were 28.6 and 8.52% respectively.

Secondary endpoints

A large number of secondary endpoints were included in the trials. As discussed before, these are interpreted primarily in an exploratory sense. Most parameters changed in a favourable way, consistent with changes usually seen with weight loss. Only "pulse" (heart rate) showed an unfavourable change, which is discussed under safety.

The results for the pooled analyses that were hierarchically tested are shown in Table E10.

Table E10 Confirmatory secondary endpoints tested in hierarchical manner– estimated treatment differences/odds ratios

Parameter	1839	1922	3970	1923	1807	All trials pooled est. mean (95% CI)
Waist circumference (cm)	-4.20*	-3.21*	-3.22*	-3.49*	-4.72*	-3.98 (-4.4; -3.6) *
HbA_{1c} (%-points)	-0.23*	-0.93*	-0.19*	-0.27*	-0.26*	-0.23 [a] (-0.25; -0.21) *
Fasting plasma glucose (mmol/L)	-0.38*	-1.77 *	-0.30*	-0.38*	-0.48*	-0.38 [a] (-0.41; -0.35) *
(mg/dL)	-6.90*	-31.92*	-5.42*	-6.84*	-8.57*	-6.88 [a] (-7.43; -6.32) *
Systolic blood pressure (mmHg)	-2.82*	-2.58*	-4.12*	-2.72*	-3.43*	-2.93 (-3.54; -2.31) *
Triglycerides (ratio)#	0.907*	0.863*	0.945	0.914*	0.891*	0.904 (0.885; 0.923) *
LDL cholesterol (ratio)#	0.976*	0.978	0.958	0.967	0.961	0.973 (0.96; 0.99) *
Total cholesterol (ratio)#	0.977*	0.964*	0.975	0.979	0.971	0.975 (0.967; 0.983) *
SF-36 (physical function score)	1.57 *	NA	0.45	NA	NA	1.40 (0.91; 1.89) *
IWQoL-Lite (physical function)	4.80*	4.92*	NA	NA	4.45*	4.81 (3.83; 5.79)*
SF-36 (general health score)	1.87*	NA	1.41*	NA	NA	1.77 (1.27; 2.27)*
HDL cholesterol (%)#	1.019*	1.028*	0.999	1.006	1.014	1.017 (1.008; 1.026)*
Use of antihypertensive drug§	1.59*	1.31	NA	1.97*	NA	1.61 (1.31; 1.97)*
Use of lipid lowering drug§	1.50*	2.16*	NA	2.14	NA	1.59 (1.19; 2.11)*
Use of oral anti-diabetic drug§	NA	5.08*	NA	NA	NA	5.08 (3.25; 7.94)*
Diastolic blood pressure (mmHg)	-0.89*	-0.37	-0.97	-0.33	-2.55*	-0.84 (-1.27; -0.41)*

Data are estimated treatment differences/ratios (ANCOVA) or odds ratios§ (logistic regression), *p<0.05.
#Treatment ratios. a) Excluding trial 1922 in T2DM.
CI: confidence interval. HDL: high-density lipoprotein. IWQoL-Lite: Impact of Weight on Quality of Life-Lite version. LDL: low-density lipoprotein. SF-36: 36-item Short-Form health status survey.

Ancillary analyses

Persistence of efficacy and effect of treatment discontinuation

In trial 1839, subjects without pre-diabetes at screening were re-randomised 1:1 to either continue treatment with liraglutide (liraglutide/liraglutide, 351 subjects) or to switch to placebo (liraglutide/placebo, 350 subjects). The placebo group continued on placebo (304 subjects), and diet and exercise continued for all groups.

Subjects who switched from liraglutide to placebo regained a mean 2.91% (2.63 kg) of body weight compared to 0.69% (0.61 kg) in those who continued on liraglutide (treatment difference: -2.18% [2.60; 1.75], p<0.0001). After three months, weight loss in subjects who switched from liraglutide to placebo (6.77% [6.73 kg]) was greater than that achieved with diet and exercise alone (3.11% [3.29 kg]).

It would be expected that weight would return to baseline after treatment discontinuation. These data are consistent with that expectation, albeit that the baseline weight has not been reached yet after three months.

As described before, the maximum effect with treatment occurs around 40 weeks. After that, small increases in weight are noticed. This may reflect the natural cause of obesity; from trial 1839 (after re-randomisation) it is evident that weight regain is worse with placebo compared to liraglutide.

Early prediction of response

The Applicant at the time of the submission of the dossier was of the opinion that a firm stopping rule is not clinically indicated for liraglutide, for reasons described below. Rather, it was proposed to let the physician make this evaluation based on the totality of the clinical effects observed after 12 weeks treatment with liraglutide 3.0 mg (16 weeks including dose escalation).

To support the above recommendation, the pooled data from the 2 largest phase 3 56-weeks trials (trials 1839 and 1922) were used to identify those subjects unlikely to achieve and sustain a weight loss of at least 5% of initial body weight after 56 weeks of treatment ('non-responders'). Several 'early response' criteria were evaluated (3, 4 and 5% weight loss at 8, 12 and 16 weeks). Only subjects with a valid body weight measurement at the specific time point were included in the analyses. Missing data were imputed using the LOCF method (primary analyses), or counted as 'non-responders' (sensitivity analysis).

The number and proportion of responders identified by the various criteria are shown in Table E11. The 'overall correctly predicted' number and proportion is shown in the far right column (number of correctly predicted responders plus number of correctly predicted non-responders). In evaluation of possible prediction criteria, equal weight will be put on positive and negative predictive value. With a low positive predictive value, a large number of subjects will be continued who would not in the end achieve response. While with a low negative predictive value, a large number of subjects would be stopped who would eventually have achieved response. Both are undesirable and it is not obvious which should be given most weight. From the results it can be seen that when requiring both good positive and negative predictive values the maximum values obtainable are just over 75% which can be achieved when using criteria of 3% weight loss at week 12 or 16 or 4% weight loss at week 16, with the 4% criteria by week 16 being marginally better, Table E11. Based on these results, the Applicant has agreed to include a stopping rule in section 4.1 of the SmPC. The stopping rule states that 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.

Table E11 Response criteria used to identify subjects unlikely to achieve clinically meaningful weight loss – Trials 1839 and 1922

Week	Early response criteria	N	Early response N (%)	Positive predictive value(a) N (%)	Early non-response N (%)	Negative predictive value(b) N (%)	Correctly predicted N (%)
8	3%	2653	2035 (76.7%)	1544 (75.9%)	618 (23.3%)	439 (71.0%)	1983 (74.7%)
	4%		1644 (62.0%)	1373 (83.5%)	1009 (38.0%)	659 (65.3%)	2032 (76.6%)
	5%		1245 (46.9%)	1096 (88.0%)	1408 (53.1%)	781 (55.5%)	1877 (70.8%)
12	3%	2578	2084 (80.8%)	1601 (**76.8%**)	494 (19.2%)	389 (**78.7%**)	1990 (77.2%)
	4%		1821 (70.6%)	1485 (81.5%)	757 (29.4%)	536 (70.8%)	2021 (78.4%)
	5%		1515 (58.8%)	1312 (86.6%)	1063 (41.2%)	669 (62.9%)	1981 (76.8%)
16	3%	2519	2099 (83.3%)	1609 (**76.7%**)	420 (16.7%)	338 (**80.5%**)	1947 (77.3%)
	4%		1893 (75.1%)	1541 (**81.4%**)	626 (24.9%)	476 (**76.0%**)	2017 (80.1%)
	5%		1637 (65.0%)	1411 (86.2%)	882 (35.0%)	602 (68.3%)	2013 (79.9%)

Missing week 56 responses are imputed using last observation carried forward. (a) Positive predictive value is defined as the percentage week 56 responders out of the early responders. (b) Negative predictive value is defined as the percentage week 56 non-responders out of the early non-responders. Correctly predicted, N= 'positive predictive value' + 'negatively predicted value' Pooled data from trials 1839 and 1922.

Comparison of results in sub-populations

The results regarding weight loss were consistent in most subgroups. However, the treatment estimate for females (-5.83%) was better compared to males (-3.56%).

When comparing subgroups based on baseline BMI, efficacy (% weight change) seems best in the lowest BMI subgroup. However, absolute weight loss is still higher in the high BMI subgroups. This discrepancy suggests that the effect is artificial. Surprisingly the results are slightly different for the genders. For males in the lowest BMI subgroup [27.0 ; 29.9 kg/m2] the LS Means outcome estimates were Lira 3.0 mg: n=56 baseline 90.90 kg; change -4.94 kg and Placebo: n=31 baseline 91.65 kg; change-1.83. The Treatment Contrast was only -3.19 kg [95% CI: -5.69 ; -0.69].

As discussed before, treatment effect in T2DM as assessed in trial 1922 was less than in the other 1-year trials. Also in this trial the results for males (-2.93%) were worse than for females (-4.84%).

Clinical studies in special populations

n/a

Supportive study(ies)

n/a

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The relevant CHMP guideline for Saxenda is the "Guideline on clinical investigation of medicinal products used in weight control" (CPMP/EWP/281/96 Rev.1 - 2007). According to the guideline, confirmatory phase III trials should be randomised, placebo controlled and double blinded, as done by the Applicant. The Applicant designed 4 different but similar trials which together provide an adequate overview of the benefits (and risks) that can be expected from treatment with Saxenda. The clinical programme (including the focus on 1-year efficacy data) is consistent with the guideline and acceptable.

The use of re-randomisation to assess the effect of treatment discontinuation (part of trial 1839) is considered a strong feature along with 3-months follow up in several other trials.

Population

The population in the trials based on obesity or overweight with additional risk factors is consistent with the guideline and representative of the target population. A large number of participants were included, such that several trials were powered to detect differences that are too small for clinical relevance (e.g. a treatment effect of 0.7 kg in trial 1839); these trials are considered somewhat over-powered. Of course, this reduces the width of the confidence intervals and provides welcome additional information with respect to safety.

Subjects with obesity that is secondary to endocrinologic disorders (e.g. Cushing's Syndrome) or to treatment with drugs that may cause weight gain (e.g. insulin, psychotropic drugs) or eating disorders were not included in the trials. The lack of data about these patients has been included in Section 4.4 of the SmPC.

Imputation of the primary endpoint

In the pooled dataset, the rate of withdrawals is high, 29.6%. This number is consistent over all trials and as expected for placebo-controlled trials of one-year duration in obesity. Only 26.8% of withdrawn subjects came in for the visit at the nominal end-of-trial. This emphasizes the relevance of the method for imputation of missing data, because 21.7% of subjects have missing endpoint data. The low follow up at 56 weeks is a major shortcoming of the trials; post-hoc correction seems not possible.

The Applicant chose LOCF as imputation method for these data; however, this is not considered conservative; it can be expected that after treatment discontinuation, baseline weight will be reached again after a few weeks or months. Using LOCF will carry the nadir of the weight to the analysis, where BOCF is more conservative.

The Applicant provided a BOCF sensitivity analysis in which subjects gaining weight were imputed using LOCF. The effect of this is difficult to predict, as this may apply to more subjects on placebo treatment than on active therapy. Therefore an unmodified BOCF sensitivity analysis on the randomised population was asked additionally and provided.

Secondary endpoints

A large number of secondary endpoints were included in the trials, but multiplicity issues were not addressed for the individual trials. Therefore the results of the individual trials can only be interpreted in an exploratory sense. The Applicant decided to accept these results as confirmatory only in the case in which statistical significance within trial 1839 alone was also achieved, to account for the fact that 2 (1807, 1923) of the 5 trials to be pooled were already unblinded at time of specification of the hierarchy. Although this approach is a bit artificial, it can be accepted in the end.

Trial 1807 extension data

Trial 1807 is the only source of 2-years data in this MAA. The analysis of these data is hampered by several factors:

- There was no placebo group. Treatments with orlistat and liraglutide were open label.
- The initial dose in the extension was 2.4 mg liraglutide, which was later adapted to 3.0 mg liraglutide. About 1/3 of the time described is related to the lower dose.
- Subjects that do not tolerate the treatments do not participate in the extension.
- Only 47 subjects completed the second year of treatment with high-dose liraglutide.

Thus the usefulness of these 2-year data is very limited.

Efficacy data and additional analyses

Dose

In the dose range that was investigated, the highest dose that was investigated in phase 2 (3.0 mg) was also the most effective dose, although the differences in the PD trials had seemed small. This dose was chosen for further evaluation in the phase 3 program.

In T2DM patients, not only weight-related measures, but also parameters of glycaemic control are better with the new 3.0 mg dose compared to the established 1.8 mg dose (marketed as Victoza). However, no data are available on switching from Victoza (liraglutide 1.8 mg) to Saxenda (3.0 mg), hence this cannot be recommended. Thus, if T2DM is the major clinical consideration and weight management (or weight loss) is a secondary consideration, then the 1.8 mg dose is appropriate. In liraglutide-naïve overweight/obese subjects with T2DM where weight management is the major clinical consideration, the Applicant recommends liraglutide at 3.0 mg as the treatment dose, which is acceptable (and in accordance with the indication).

Primary endpoint: weight loss

The liraglutide-treated group shows a continuous weight decline with reaches a plateau after about 40 weeks. In the mITT pooled analyses using LOCF, weight loss was 7.5% (7.8 kg) with liraglutide 3.0 mg v 2.3% (2.5 kg) with placebo, a placebo-subtracted weight loss of 5.2% [-5.53 ; -4.83].

The data are supported by a range of sensitivity analyses. The most favourable scenario is represented by the Completers analysis. In this analysis the placebo-subtracted treatment effect for weight loss was 5.6%. The unmodified BOCF analysis was provided as the least favourable scenario and resulted in a placebo-subtracted treatment effect for weight loss of 4.28%. Using the weight regain imputation method, the treatment effect was estimated as -5.05%.

The likelihood of achieving a predefined response with liraglutide is greater for any weight loss in the range from -25% to +5%. The likelihood for achieving 10% weight loss was 30.9% for liraglutide 3.0 mg v 9.0% for placebo in the pooled 56-week trials. The estimates for completers were 38.2% and 12.7%; the estimates counting early withdrawals as non-responders were 28.6 and 8.52% respectively.

The results regarding weight loss were consistent in most subgroups. However, the treatment estimate for females (-5.83%) was better compared to males (-3.56%) (a statistically significant interaction, $p<.0001$). The difference can be attributed to lower exposure in males. Treatment effect in T2DM as assessed in trial 1922 (-3.95%) was less than in all 1-year trials (-5.24%). This is explained by the high participation of males in this trial. After correction for gender effects, the interaction is no longer statistically significant ($p=0.1762$) and is not considered to pose any clinical problems.

Secondary endpoints

In T2DM patients, the HbA1c level was decreased by 0.93% compared to placebo. This result could be expected based on the known efficacy of liraglutide as an anti-diabetic product. This also resulted in a net reduction of use of oral anti-diabetic drugs; for such reductions, the protocol provided guidance. Counting both increase and decrease in use in the liraglutide and placebo groups, this affected about 30% of the participants. Parameters of glycaemic control were also improved in non-diabetes patients (e.g. HbA1c by 0.23%), but the clinical relevance of this change (within the normal range) is doubtful.

Both SBP (-2.9 mmHg) and DBP (-0.8 mmHg) were decreased compared to placebo. The decrease in SBP for each weight change category was larger with liraglutide than with placebo; this could be explained by an effect of liraglutide on SBP that is independent of weight loss, but is likely also partly explained by different mean changes in each category between liraglutide and placebo. This change in BP could be clinically relevant, but is offset by the increase in pulse rate; the outcome of the combination of these effects is not clear. There were no protocol rules for change in anti-hypertensives; the net change was favourable for liraglutide, but the difference was only 4%.

Small changes were also seen in lipid parameters. The treatment ratio that is provided for LDL (0.973 or 2.7% reduction) corresponds to an absolute change of 0.07 mmol/L (based on a baseline of 2.77 mmol/L). Also use of lipid-lowering medications was reduced, but the net difference was 3.3%.

The interpretation of the sleep-apnoea related parameters is difficult, as there is no established margin for clinical relevance. The decrease in AHI was closely correlated to weight loss, as was known from literature. The decrease in 'episodes' was accompanied by statistically non-significant changes in the patient-reported outcomes.

Pending clear evidence of outcome benefits attributable to liraglutide, patient-reported outcomes are relevant. The favourable change over time may be biased by the burden of daily injections ('with these injections, it must be effective'). The injections weigh in equally at end of trial for both active and placebo treatment. Therefore, the Quality of Life scales did not measure the burden of therapy caused by the injections as it is experienced by the patient. Of course, adverse effects like nausea do come up in the questionnaires.

Although statistical significance was achieved on all these measures, it is important if these changes in the pooled secondary parameters that were hierarchically tested are clinically relevant. The improvements in glycaemic control and systolic blood pressure fulfill these criteria. On the contrary, the effects on the Quality of Life scales are not considered relevant for the SmPC and should be excluded.

Stopping rule

As requested in the Day 120 LoQ, the Applicant investigated possible stopping rules, resulting in a proposal:

Treatment effects with Saxenda should be evaluated after 12 weeks on the 3.0 mg/day dose. If patients have not lost at least 5% of their initial body weight, treatment should be discontinued as clinically indicated.

To justify this rule, they have considered:

- weight loss after 8, 12 or 16 weeks of treatment
- gender
- baseline glycaemic status (trial 1922 in diabetic subjects vs. trial 1839 in subjects without diabetes)

According to the Applicant's analysis, there were no major differences between the data at weeks 8, 12 or 16. This is indeed confirmed by the ROC curves that do not show any clear point for best predicting the weight loss responders. Based on these data and the similarity with orlistat, it is agreed to use the 5% cut-off-margin and the Applicant and the CHMP has agreed on the following wording for the stopping rule included in section 4.1 of the SmPC:

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.

2.5.4. Conclusions on the clinical efficacy

After treatment with liraglutide 3.0 mg, mean weight loss was 7.5% (7.8 kg) with liraglutide 3.0 mg vs. 2.3% (2.5 kg) with placebo, a placebo-subtracted weight loss of 5.2%. When applying more conservative methods than LOCF imputation for missing data, a treatment effect of -4.28% is estimated. Efficacy is less in males and in patients with T2DM.

In the revised target population and for subjects meeting the criteria of the stopping rule, the expected mean weight change is -10.82% after one year (not corrected for placebo). A response of at least 10% is achieved by 50.1%.

2.6. Clinical safety

The analysis of safety is based on a pooled analysis of the phase 2 and 3 trials. Data from the clinical development program for Victoza (EMEA/H/C/001026) for the use of liraglutide in T2DM are used supplementary and for comparison, which was found to be acceptable by CHMP.

Patient exposure

The exposure as documented in the weight management pool includes 3872 patients exposed to liraglutide for the proposed indication. Exposure for at least one year to the proposed dose is documented in 2341 patients. (Table S1)

Table S1 Exposure – weight management pool

	Lira 3.0 mg	Total lira	Placebo	Total
Number of subjects	3384	3872	1941	5813
Years of exposure	2974.3	3372.7	1600.9	4973.6
Exposure (yrs)				
Mean (SD)	0.88 (0.3)	0.87 (0.3)	0.82 (0.3)	0.86 (0.3)
Median	1.07	1.07	1.06	1.07
Min ; Max	0.00 ; 1.22	0.00 ; 1.22	0.00 ; 1.22	0.00 ; 1.22
Subjects with >= 12 months exposure	2341	2567	1139	3706

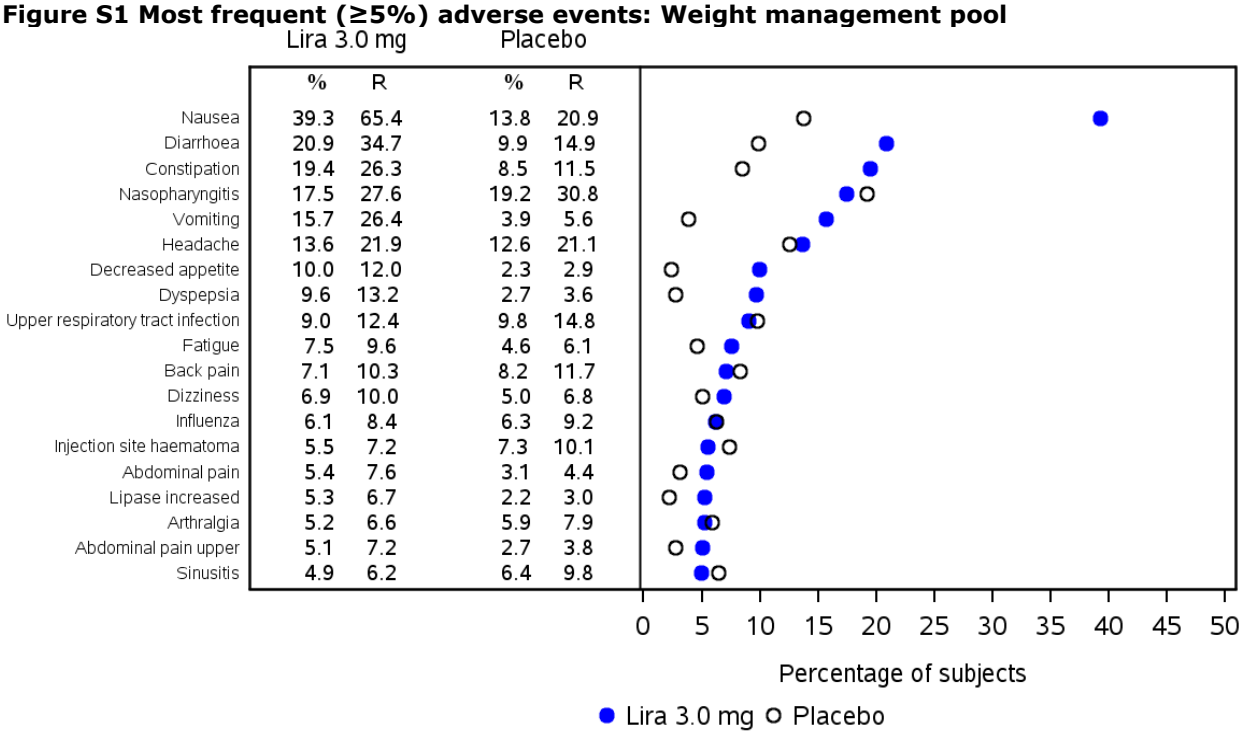
N: Number of subjects, SD: Standard deviation

During assessment, interim data from the placebo controlled extension of trial 1839 were provided. In total, in trial 1839 and its extension up to 1 Oct 2014, 903 subjects were exposed to liraglutide 3.0 mg for ≥2 years and 694 patients were exposed for 3 years.

Adverse events

AEs reported by at least 5% of subjects in either treatment group are shown in Figure S1.

Figure S1 Most frequent (≥5%) adverse events: Weight management pool



%: Percentage of subjects experiencing at least one event; R: event rate per 100 PYE. Please note that AEs of hypoglycaemia are not included in this figure.

The general AE profile is in line with the experience with Victoza. The most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders. Most patients experience nausea already in the first weeks of treatment, during dose titration. Other patients express decreased appetite, which is in line with the pharmacology of liraglutide. Also asthenic conditions like fatigue occur early and in increased incidence with liraglutide.

The efficacy of dose titration to reduce GI side effects and to improve tolerability is not analysed in this dossier. Dose titration was implemented throughout the program.

Hypoglycaemia

High levels of GLP-1 have been implicated as potential mediators of hypoglycaemia in fasting patients after glucose administration (reactive hypoglycaemia) and after Roux-en-Y Gastric Bypass surgery. Therefore, hypoglycaemia was observed carefully in the program.

In subjects without T2DM, no severe hypoglycaemic events were reported. The proportion of subjects reporting AEs of hypoglycaemia outside the fasting FPG and OGTT visits was low, both with liraglutide 3.0 mg (1.6% of subjects) and placebo (1.1% of subjects). Many hypoglycaemic episodes occurred after OGTT in these patients and were recognised by glucose measurement rather than symptoms. The circumstances of an OGTT can be considered non-physiologic and therefore, these events are less important. This is supported by the lack of hypoglycaemic AEs when tolerance to a mixed meal was tested instead of pure glucose.

In subjects with T2DM, severe hypoglycaemia was reported by 0.7% of subjects treated with liraglutide 3.0 mg (3 subjects with 5 events, 13 events per 1000 PYE) and 1.0% of subjects treated

with liraglutide 1.8 mg (2 subjects with 3 events, 16 events per 1000 PYE) and occurred only in patients taking concomitant SU therapy. Subjects taking SUs were more likely (3–4 times) to experience a minor hypoglycaemic episode in any category compared with subjects not taking SUs. The Applicant has proposed a warning in Section 4.4 of the SmPC regarding concomitant use with SUs, which is agreed.

Cardiovascular safety

Cardiovascular safety is an important issue in the assessment of this product. The relevant guideline (CPMP/EWP/281/96 Rev.1 - 2007) states that in view of the goals of treatment of obesity, drugs used to treat it should be shown to have no deleterious effects on cardiovascular risk factors. Yet, the consistent finding that GLP-1 analogues increase the pulse rate has caused concern in this respect.

Mechanism

The mechanism behind the increase in pulse rate is not elucidated, however the Applicant suggests that GLP-1 receptors are present in the cardiac pacemaker and exert a direct effect. It seems unlikely that the increase in pulse is the result of adrenergic stimulation based on the clinical pharmacology data.

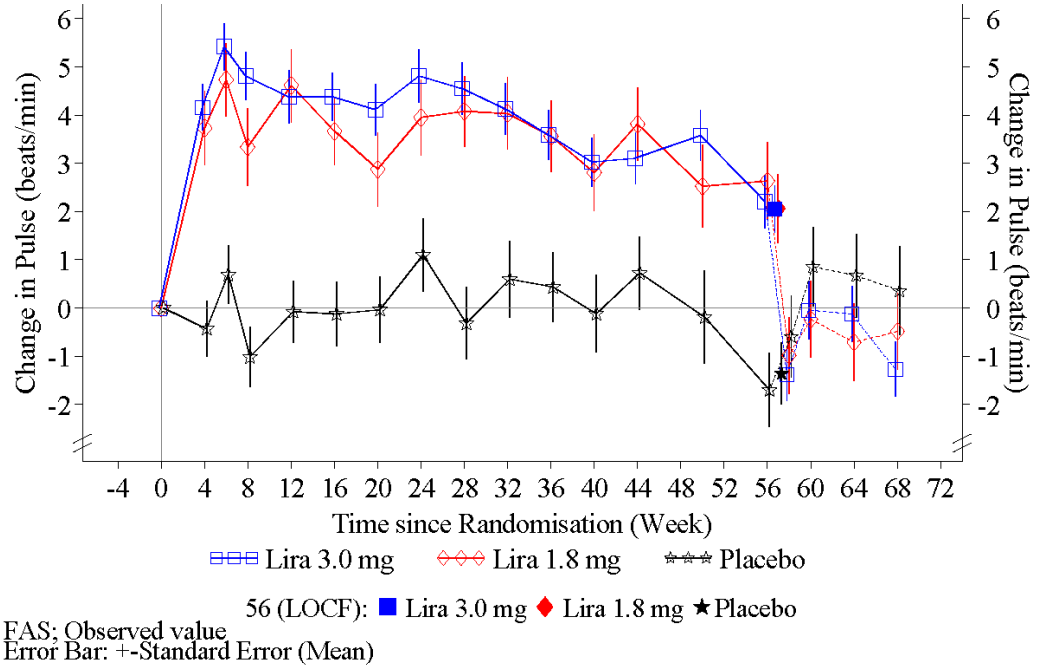
Pulse observations

Based on the pool of 5 trials, mean resting pulse increased after treatment initiation in the liraglutide 3.0 mg group and peaked after approximately 6 weeks (Mean change from baseline: liraglutide 4.5 bpm, placebo 1.1 bpm), and gradually declined thereafter. The effect persists until end-of-trial and is then 2.8 bpm above placebo.

Dose response

According to the Applicant, there is no dose response for the effect on pulse. This is supported by data from trial 1922 in T2DM visualised in Figure S2. The data from Trial 1807 are somewhat less convincing, but a dose response, if any, must be small.

Figure S2 Pulse rate in Trial 1922



Major Adverse Cardiac Events (MACE)

The Applicant has provided an extensive cardiovascular meta-analysis to assess the risk of MACE (cardiovascular death or non-fatal stroke or myocardial infarction). The pre-specified MACE meta-analysis returned a hazard ratio for the weight management pool of 0.40 [95% CI: 0.15; 1.05] for total liraglutide vs. total comparator (primary analysis, 17 events). The individual trials and a meta-analysis of the diabetes programme with liraglutide 1.8 mg show similar results.

In the response to the Day120 LoQ, meta-analyses of adjudicated MACEs in the weight management pool updated with data from the ongoing 1839-ext until the cut-off date 11 Nov 2013 were provided. The analyses gave the following hazard ratios and 95% CIs:

- 0.40 [0.16; 1.01] for total liraglutide versus total comparator (weight management pool including 1839-ext, primary analysis, total number of events = 19)
- 0.33 [0.12; 0.90] for liraglutide 3.0 mg versus placebo (weight management pool including 1839-ext, sensitivity analysis, total number of events = 16)

Adverse events in SOC "Cardiac Disorders"

The rate of events in the SOC "Cardiac disorders" was 4.5 events/100 PYE for liraglutide 3.0 mg, 4.7 events/100 PYE for total liraglutide and 4.3 events/100 PYE for placebo. The 'MedDRA search for cardiac arrhythmia' identified a total of 132 treatment-emergent events reported in 113 subjects with liraglutide 3.0 mg (3.3%, 4.4 event per 100 PYE) and 64 events in 58 subjects with placebo (3.0%, 4.0 event per 100 PYE)

Pancreatitis

Incretin based therapies, including liraglutide, have been brought in relation with events of pancreatitis. The Applicant cites literature showing that obesity itself is associated with an increased risk of pancreatitis. A study reported 2-year incidence of pancreatitis for obese individuals opting or

not opting for gastric bypass surgery. The incidence in the non-operated controls was low, 0.1 events/100 PYE for males and 0.2 for females but much higher after surgery (0.6 and 0.4% respectively), suggesting an effect of weight loss. T2DM, a common comorbidity of obese individuals, independently increases the risk of acute pancreatitis by 50%, compared to controls without T2DM. The incidence of acute pancreatitis in individuals with T2DM ranges between 0.05–0.42 events per 100 PYE.

In a recent perspective (N Engl J Med 2014; 370:794-797 February 27, 2014DOI: 10.1056/NEJMp1314078), regulators from Europe and FDA have stated that both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. In accordance to this, a warning has been included in the SmPC (section 4.4) and likewise, pancreatitis has been included in the RMP.

Adjudicated events of acute pancreatitis occurred in greater number with liraglutide compared to placebo: 7 (0.2% of subjects; 0.2 events per 100 PYE) with liraglutide 3.0 mg versus 1 (<0.1% of subjects; <0.1 events per 100 PYE) with placebo during the main treatment periods. The numbers within the weight management programme are too small to allow analysis of a possible dose-response.

In the weight management trials, events sent for adjudication were 17 (0.5% of subjects, 0.6 events per 100 PYE) for total liraglutide and 3 (0.2% of subjects, 0.2 events per 100 PYE) for comparator. Adjudication confirmed 8/20 (40%) of the cases. The 20 pancreatitis events identified in the main period and sent for adjudication combined investigator reported events (MESI) and database searches performed to identify any potential additional pancreatitis cases not already reported by investigators as MESI, based on (1) AEs of pancreatitis or (2) events of increased lipase/amylase with concomitant abdominal pain as an AE within a time window of +/- 30 days).

A MedDRA search in the safety database from the T2DM indication identified 9 treatment-emergent events of pancreatitis in 9 subjects treated with liraglutide (0.1%, 0.2 events per 100 PYE) and 2 treatment-emergent events in 2 subjects treated with comparator (<0.1%, <0.1 events per 100 PYE). In both treatment groups, the majority (5 of 9 events) were reported as ‘pancreatitis acute’ or ‘pancreatitis’. In this program, no adjudication was implemented for pancreatitis.

In the weight management program, some cases were not primarily identified as AE, thus the search may have been more sensitive than in the T2DM programme. Comparing non-adjudicated events, the rate of pancreatitis may be higher in the weight management programme (0.6 events per 100 PYE) than in the T2DM programme (0.2 events per 100 PYE), which could be related to the indication or the dose or overly sensitive inclusion of events. This occurred although T2DM is an independent risk factor for pancreatitis.

All in all, comparison of the (adjudicated) data from the weight management programme to the (unadjudicated) data from the T2DM programme is not reliable.

All but two of the confirmed events were reported as SAEs by the investigator, and subjects with treatment-emergent events were withdrawn from any on-going liraglutide treatment. Two of the cases would likely have been classified as moderately severe (defined by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure) according to the revised Atlanta criteria. For the majority of cases, the duration was short (2-15 days). Gall stones were reported in only one of these cases.

With liraglutide at doses up to 3.0 mg, lipase elevations and fluctuations were common and unaccompanied by pancreatitis in 99.8% of cases (values ≥2×UNR in subjects with T2DM), indicating a low predictive value of pancreatic enzyme activity elevation in this context. Two subjects had lost >20% of their original weight. No other factors were identified as risk factors for pancreatitis; occurrence seems not related to duration of use.

Mean amylase and lipase values were higher with liraglutide 3.0 vs placebo (e.g. LOCF at end of trial: [amylase] 61.1 vs 57.4 U/L, baseline corrected difference 4.5 [lipase] 48.4 vs 36.7 U/L, baseline corrected difference 12.1). There was no clear trend during treatment.

During the 1-year treatment period, more subjects on liraglutide 3.0 mg than on placebo experienced amylase activity ≥UNR (4.5% vs. 2.3%), the majority of which were <2 ×UNR. Few subjects (0.3% with liraglutide 3.0 mg and 0.2% with placebo) experienced amylase levels of ≥2×UNR, and just 2 subjects on liraglutide 3.0 mg and 1 on placebo had amylase ≥3×UNR, at any time during treatment. Hence, the mean increase in amylase with liraglutide during trials was attributable to small increases within the normal range in many subjects, rather than to large increases in a few subjects.

During the 1-year treatment period, more subjects on liraglutide 3.0 mg than subjects on placebo experienced lipase activity ≥UNR (21-27% vs. 6-7%), the majority of which were <2×UNR. Lipase levels of ≥2×UNR occurred in 5.7% of subjects with liraglutide 3.0 mg and 2.6% with placebo; lipase levels of ≥3×UNR occurred in 2.1% with liraglutide 3.0 mg and 1.0% with placebo), at any time during treatment.

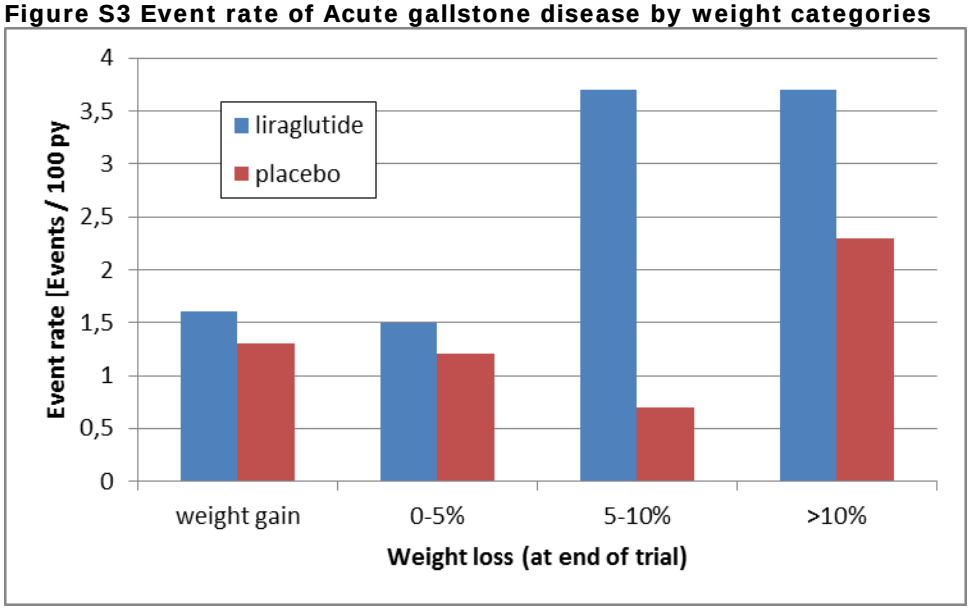
Acute gallstone disease

There were no prior safety concerns with respect to gallbladder events based on clinical trial or post-marketing pharmacovigilance data with liraglutide for T2DM (Victoza). An increased risk of gallstone formation, induced by weight loss, has been proposed as a potential mediator of the observed greater frequency of acute pancreatitis cases seen with GLP-1 based therapies. A recent publication showing reduced gallbladder emptying following acute administration of exenatide (a GLP-1 analogue) provides an alternative potential mechanism.

In the weight management pool, the proportion of subjects reporting acute gallstone disease events was higher with liraglutide 3.0 mg (2.3%) than with placebo (0.9%) The imbalance was mainly driven by events of cholelithiasis and cholecystitis ('cholelithiasis': 1.5% vs. 0.5%; 'cholecystitis acute': 0.4% vs. <0.1%; 'cholecystitis': 0.2% vs. <0.1%, respectively, for liraglutide 3.0 mg vs. placebo).

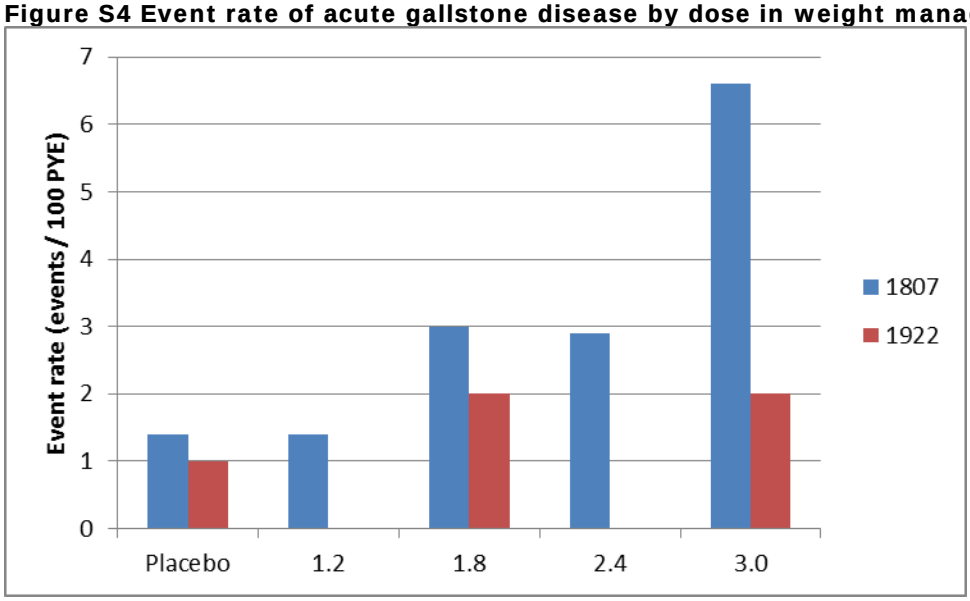
The risk of acute gall stone disease is related to the weight loss that was achieved. Nevertheless, an increased incidence of gallbladder-related events was consistently observed across weight-loss categories, indicating that other factors than weight loss may be involved.

Figure S3 Event rate of Acute gallstone disease by weight categories



AEs of "Acute gallstone disease" as identified by a MedDRA search in the weight management pool were 79 (2.3% or 3.1 events/100 PYE) vs 17 (0.9% or 1.2 events/100 PYE) for liraglutide 3.0 mg vs placebo respectively. In supplementary pool II - excluding NN8022 trials, describing mainly diabetes trials at the liraglutide dose of 1.8 mg, the corresponding numbers were 55 (0,8% or 1,3 events / 100 PYE) and 28 (0,8% or 1,3 events / 100 PYE). Accordingly, in the T2DM, the dose of 1.8 mg liraglutide does not signal gall stone events. The higher frequency in the weight management pool could be attributed to dose or indication. In dose-finding trial 1807, Figure S4 is suggestive of a dose response, but in T2DM trial 1922, the (low) numbers of events were not. Gallbladder events have been adequately addressed in the SmPC.

Figure S4 Event rate of acute gallstone disease by dose in weight management trials



Neoplasms

The proportion of subjects in the weight management trials with neoplasms confirmed by the external EAC and the corresponding event rates were in general similar with liraglutide 3.0 mg (1.9%, 2.3 events per 100 PYE) and placebo (1.5%, 2.2 events per 100 PYE), as were the distribution (benign, malignant or pre-malignant) and type (tissue or organ of origin) of neoplasm. The overall incidence rate of confirmed malignant neoplasms was low, and all cases of malignant neoplasms with liraglutide occurred at the 3.0 mg dose, consistent with its relative contribution to overall exposure.

Breast

Breast cancer and breast carcinoma in situ occurred more frequently in females treated with liraglutide 3.0 mg as compared with placebo in the weight management trials. Based on treatment-emergent external EAC-confirmed events in the main treatment period, the proportion of females with events and the corresponding rates were: for breast cancer: 0.29% (0.4 events per 100 PYE) vs. 0.08% (0.1 per 100 PYE), breast cancer in situ: 0.13% (0.1 events per 100 PYE) vs. 0.08% (0.1 events per 100 PYE) for liraglutide 3.0 mg and placebo, respectively. Breast cancer was too infrequent to make any firm conclusions regarding a potential effect of liraglutide treatment. Human breast carcinomas do not express the GLP-1 receptor, which is detected at very low amounts in non-neoplastic human breast ducts and lobuli. The Applicant attributes these findings to chance. At present this can be neither confirmed nor rejected. Breast cancer is included in the RMP as an important potential risk.

Pancreas

In the weight management trials, there were no reports of exocrine pancreas cancer. A single subject was diagnosed with multiple endocrine neoplasia Type 1 (MEN1) during treatment with liraglutide 3.0 mg, but this subject had been under investigation for the disorder prior to trial enrolment.

Thyroid

Medullary thyroid carcinoma (MTC), an extremely rare form of cancer in humans, was a focus of discussion in the original regulatory review of liraglutide for the treatment of T2DM and a number of post-approval commitments have been completed (non-clinical) or are underway (pharmacoepidemiology and case series registry). Based on all available clinical data, there is no evidence that the rodent findings translate into increased risk in humans.

The overall incidence of thyroid cancers in the weight management trials was low, with no apparent differences between liraglutide 3.0 mg and placebo; all but one thyroid cancers were of non C-cell origin. One MTC event occurred in a placebo subject shortly after randomisation. This is the second event of MTC diagnosed in clinical development programmes with liraglutide; none of the events were in subjects exposed to liraglutide

Calcitonin is a specific biological marker of MTC and all elevated levels (≥20 ng/L) were subject to on-going blinded review by an independent external group of thyroid experts. Patients with MTC usually have calcitonin values >50 ng/L. The clinical significance of fluctuations below this level in patients without MTC is unknown. Consistent with findings in all completed trials with liraglutide for T2DM to date, there was no indication of a liraglutide effect on blood calcitonin concentration with either 1.8 mg (T2DM) or 3.0 mg (weight management).

Colon

Colorectal carcinomas do not express the GLP-1 receptor and in the normal colon, only myenteric plexus cells express the receptor. Malignant colorectal neoplasms occurred at very low rate in weight management trials, with no imbalances between liraglutide and placebo More subjects treated with liraglutide 3.0 mg (11 with 11 events, 0.3%, 0.4 events per 100 PYE) than with placebo (4 subjects with 4 events, 0.2%, 0.3 events per 100 PYE) reported benign colorectal neoplasms, mainly colon adenomas in males aged above 50 years with a relevant medical history. The majority of the events were diagnosed during routine screening colonoscopy. Based on a lack of biological plausibility and no imbalances in completed trials with liraglutide in T2DM, the Applicant attributes the imbalance to chance. At present this can be neither confirmed nor rejected. Neoplasm is included in the RMP as an important potential risk.

Skin

Skin fibrosarcoma is of interest because of preclinical findings. No cases of skin fibrosarcoma were observed in the weight management trials. The proportion of subjects diagnosed with skin cancers appeared to be lower with liraglutide than with placebo (0.2%, 0.2 events per 100 PYE vs. 0.3%, 0.4 events per 100 PYE, respectively).

Renal failure

Events related to renal failure are discussed in Section 4.4 of the SmPC of Victoza under the subject dehydration; a similar statement is proposed for Saxenda. It is likely that investigators were aware of this issue during their participation in the trial, either based on their experience with Victoza or on specific information from the trial. Based on similar adverse event rates and similar rates of subjects with abnormal clinical chemistry values (e.g. creatinin values above normal range, Table S2), the precautionary strategy is considered adequate.

Table S2 Serum creatinine above normal range – weight management pool

Serum creatinine > normal range	Liraglutide 3.0 mg	Placebo
Baseline	3.4% of subjects	3.4% of subjects
3 months	4.2% of subjects	4.3% of subjects
6 months	3.3% of subjects	3.9% of subjects
End of trial (LOCF)	3.2% of subjects	3.8% of subjects
Shifts from normal at baseline to high at end of trial (LOCF)	1.4% of subjects	1.5% of subjects

Medication errors related to the device

The trials were done with the Novo Nordisk FlexPen, which is also in use for insulin products. For Saxenda a different device is proposed. The Saxenda pen is similar to the FlexTouch pen, which is approved for insulin products. Thus, the information related to the device from the trials does not apply to the proposed product. However, the performance of the Saxenda pen is expected to be similar to the FlexTouch pen.

Thyroid disease

Thyroid disease raises no concern in this development program.

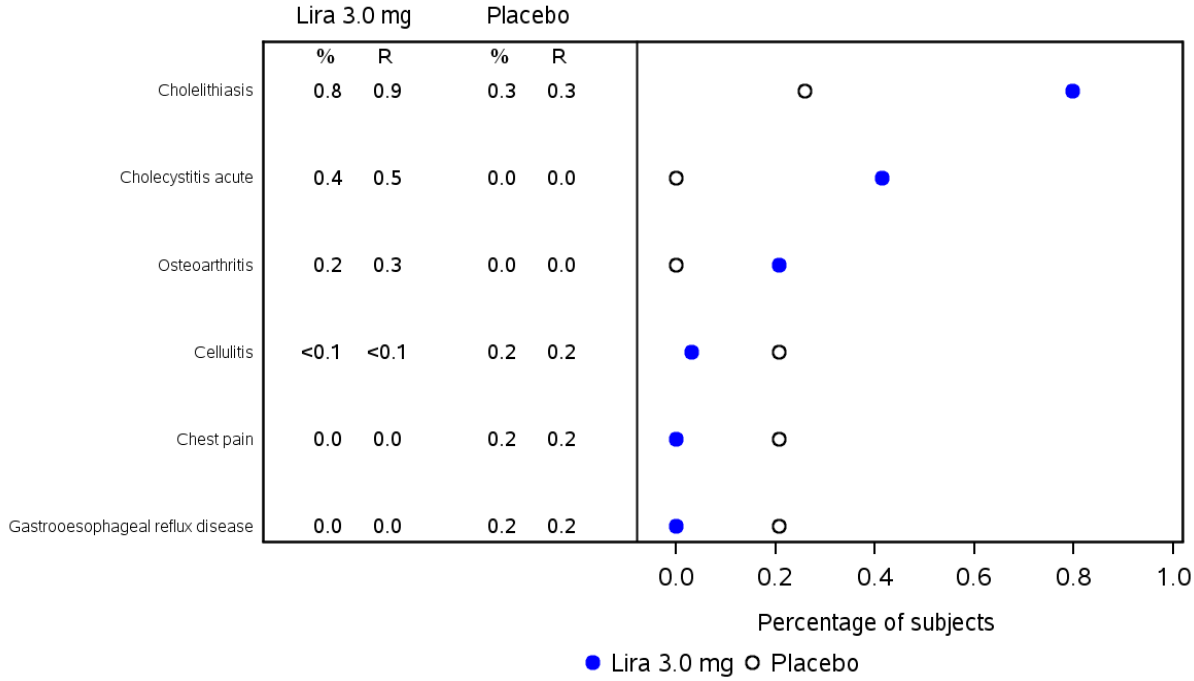
Psychiatric disorders

Current data do not suggest that Saxenda causes depression or stimulates suicidal behaviour.

Serious adverse events and deaths

In the weight management pool, the proportion and rate of subjects reporting SAEs was higher in the liraglutide 3.0 mg group (6.3%, 9.3 events per 100 PYE) than in the placebo group (4.6%, 7.1 events per 100 PYE). This is partly explained by a difference in acute gallstone events (Figure S5).

Figure S5 Most frequent SAEs (≥0.2%) – treatment-emergent – weight management pool



%: Percentage of subjects experiencing at least one event, R: event rate per 100 patient years of exposure.

For SAEs, the comparisons in the dose-finding trial 1807 and T2DM trial 1922 are underpowered to assess the rates of rare events such as pancreatitis, cardiovascular events and neoplasms.

Mortality was rare in the clinical development programme (liraglutide n=3, placebo: n=3, with many more patients exposed to liraglutide) and no new concerns are identified by analysis of deaths.

Laboratory findings

Based on laboratory findings, physical examination and ECG, no safety concerns were identified.

Safety in special populations

Older patients

Exposure in older patients above 75 years is extremely limited. Only 17 patients aged ≥75 years were included in the SCALE program, of whom 7 (41%) discontinued treatment due to AEs (See Table S3). Consequentially this resulted in a "non recommendation" (Section 4.4) pending more reassuring data. The Applicant's proposal to address this in Section 4.2 of the SmPC is acceptable:

No dose adjustment is required based on age. Therapeutic experience in patients ⩾75 years of age is limited and use in these patients is not recommended (see sections 4.4 and 5.2).

Table S3: **Frequency of AEs (and subjects withdrawn due to AEs) in the SCALE programme by age group, liraglutide 3.0 mg only**

	Age group			
	<65 years	65-74 years	75-84 years	≥85 years
Total subjects	3182	217	17	0
Total AEs (E, %)	18705 (91.5)	1580 (94.5)	61 (88.2)	0
Fatal (E, %)	2 (<0.1)	0	0	0
Serious adverse events (E, %)	248 (5.9)	27 (10.6)	3 (11.8)	0
Withdrawals due to AEs (N, %) a	284 (8.9)	32 (14.7)	7 (41.2)	0
Drug withdrawal(SMQ)	0	0	0	0
Psychiatric disorders (SOC)	336 (8.7)	23 (7.4)	0	0
Nervous system disorder (SOC)	1339 (26.0)	78 (24.0)	3 (11.8)	0
Accident and injuries (SMQ)	439 (10.7)	48 (11.5)	0	0
Cardiac disorders (SOC)	126 (3.1)	9 (3.2)	0	0
Vascular disorders (SOC)	186 (5.0)	12 (5.5)	2 (5.9)	0
Cerebrovascular disorders (SMQ)	7 (0.2)	0	0	0
Infections and infestations (SOC)	2965 (50.1)	186 (48.4)	4 (23.5)	0

Renal impairment

Renal impairment seems to have no special impact on AEs due to liraglutide, although more AEs are seen in both liraglutide and placebo groups. However, exposure of severely renally impaired patients is extremely limited to only 3 patients on active treatment, resulting in not recommending the use of the product in that population in the SmPC sections 4.2 and 4.4.

Hepatic impairment

The Applicant only provided data with respect to baseline AST and ALT values and AEs. No specific analysis is provided with regard to baseline Child-Pugh class, although impaired hepatic function apparently was no specific exclusion criterion, resulting in not recommending the use of the product in severe hepatic impairment in the SmPC sections 4.2 and 4.4.

Pregnancy

The data in unintended pregnancies during the clinical development of Saxenda are limitted but reassuring. Still, given the teratogenic potential of the product in preclinical investigations, liraglutide

should not be used during pregnancy. Also weight reduction, either by non-pharmacological or pharmacological means, is usually not recommended during pregnancy.

This is refelcted accordingly in section 4.6 of the SmPC and is in line with a similar text of the SmPC of Victoza, which is supported.

Immunological events

Liraglutide is a protein-based drug and accordingly, immunological events were more frequent with liraglutide than with placebo.

Although allergic reactions were similar between liraglutide and placebo, cases of **anaphylaxis** were only reported with liraglutide. Both in the proposed SmPC of Saxenda and the SmPC of Victoza , anaphylactic reactions are categorised as 'rare', which is supported.

Injection site reactions

The placebo treatment used the same device as active treatment and the placebo formulation contained the same excipients as active treatment.

Injection site reactions were frequently reported in the weight management pool, more so with liraglutide 3.0 mg (13.9%, 22.9 events per 100 PYE) than with placebo (10.5%, 15.7 events per 100 PYE). This incidence rate was higher than that observed in completed trials with liraglutide for T2DM (2.9%, 5.6 events per 100 PYE vs. 1.5%, 2.7 events per 100 PYE, for liraglutide and comparator).

The incidences of injection site reactions reported in the weight management pool were higher than those reported with liraglutide 1.8 mg in subjects with T2DM in trial 1922. Indeed, in trial 1922 the rate of injection site reactions with lira 3.0 mg was about twice the rate with lira 1.8 mg; although the rates for lira 1.8 mg and placebo were similar. Both rates were higher than in the Victoza program.

Table S4 Injection site reactions (predefined SMQ search) by system organ class, high level group term and preferred term - treatment emergent (weeks 0 to 58) - summary - Safety Analysis Set Trial 1922

	Lira 3.0 mg				Lira 1.8 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	422				210				212			
Events	39	(9.2)	94	25	17	(8.1)	22	12	18	(8.5)	20	11
e.g. injection site …												
erythema	4	(0.9)	4	1	3	(1.4)	3	2				
haematoma	19	(4.5)	33	9	4	(1.9)	4	2	12	(5.7)	14	8
haemorrhage	1	(0.2)	27	7	1	(0.5)	1	1				
pain	5	(1.2)	5	1	4	(1.9)	4	2				
pruritus	1	(0.2)	1	0	4	(1.9)	4	2				
reaction	5	(1.2)	6	2	4	(1.9)	5	3				

Source 1922 CSR, Table 14.3.1.109

Data from trial 1922 (Table S5) suggest that also for liraglutide antibodies a dose response is possible. It is agreed that the rates were low and antibody formation seems to have no clinically relevant impact.

Table S5 Liraglutide antibodies in treatment week 58 - Safety Analysis Set Trial 1922

	Lira 3.0 mg		Lira 1.8 mg		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	422		210		632	
Positive …						
Liraglutide Antibody	9	(2.1)	3	(1.4)	12	(1.9)
Cross Reacting Effect	1	(0.2)	0	(0.0)	1	(0.2)
Neutralising Effect	2	(0.5)	0	(0.0)	2	(0.3)

Safety related to drug-drug interactions and other interactions

No new data with respect to safety of interactions, beyond what has been provided from the Victoza development program, was presented ; the Applicant's approach to interactions is therefore based on the assumption of equivalence with Victoza. According to trial 3630, gastric emptying after 5 hours is equivalent between liraglutide doses of 1.8 and 3.0 mg. Furthermore, it is unlikely that the potential for interactions is significantly different between obesity and T2DM. Therefore, the Applicant's reasoning was accepted by CHMP.

Accordingly, the paragraphs on interaction in the SmPCs of Saxenda and Victoza are similar.

Discontinuation due to AES

There are no safety concerns related to discontinuation of liraglutide 3.0 mg.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions (i.e. attributable to liraglutide) reported in clinical trials have been included in the Summary of Product Characteristics.

The safety database includes 5813 patients. Of these, 2341 were on the target dose for at least 1 year. This exposure is sufficient based on guidance in ICH-E1.

Adverse events

The **general AE** profile is in line with the experience with Victoza. The most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders. Most patients experience nausea already in the first weeks of treatment, during dose titration. Other patients express decreased appetite, which is in line with the pharmacology of liraglutide. Also asthenic conditions like fatigue occur early and in increased incidence with liraglutide.

In subjects without T2DM, no severe **hypoglycaemic events** were reported. The proportion of subjects reporting AEs of hypoglycaemia outside the fasting FPG and OGTT visits was low, both with liraglutide 3.0 mg (1.6% of subjects) and placebo (1.1% of subjects). Many hypoglycaemic episodes occurred after OGTT in these patients and were recognised by glucose measurement rather than symptoms. The circumstances of an OGTT can be considered non-physiologic and therefore, these events are less important.

In subjects with T2DM, severe hypoglycaemia was reported by 0.7% of subjects treated with liraglutide 3.0 mg (3 subjects with 5 events, 13 events per 1000 PYE) and 1.0% of subjects treated with liraglutide 1.8 mg (2 subjects with 3 events, 16 events per 1000 PYE) and occurred only in

patients taking concomitant SU therapy. The Applicant has proposed a warning in Section 4.4 of the SmPC regarding concomitant use with SUs, which is agreed.

The consistent finding that GLP-1 analogues increase the pulse rate has caused concern with respect to **cardiovascular safety**. There are data that GLP-1 receptors are present in the cardiac pacemaker suggesting a direct effect of liraglutide on the heart. The maximum increase in pulse rate is 4.5 bpm for liraglutide (compared to placebo 1.1 bpm, treatment effect 3.4 bpm) after 6 weeks and slightly declined thereafter. The effect persists until end-of-trial and is then 2.8 bpm above placebo. There is no indication of a dose response.

The period of maximum effect on pulse rate is well covered by the safety database; however less information is available with respect to (very) long term effects of the increase in pulse. Because the effect on pulse is not strongly related to dose and seems to be a class effect, information from the large cardiovascular safety trials with liragutide (LEADER) and other GLP-1 analogues is relevant. This LEADER trial (investigating liraglutide 1.8 mg) is on-going and no data are available, although it is somewhat reassuring that the safety monitoring board recommended trial continuation. Long-term extensions of trials in this application will also provide 2-years data by 2015. Currently some uncertainty remains around this issue.

The data from the MACE analysis strongly suggest that liraglutide 3.0 mg has no deleterious effect on CV safety as required by the guideline.

In the weight management pool, the proportion of subjects reporting **acute gallstone disease** events was higher with liraglutide 3.0 mg (2.3%) than with placebo (0.9%) The imbalance was mainly driven by events of cholelithiasis and cholecystitis ('cholelithiasis': 1.5% vs. 0.5%; 'cholecystitis acute': 0.4% vs. <0.1%; 'cholecystitis': 0.2% vs. <0.1%, respectively, for liraglutide 3.0 mg vs. placebo).

The risk of acute gall stone disease is related to the weight loss that was achieved. Even within these categories, weight loss for liraglutide may have been more than for placebo. Nevertheless, an increased incidence of gallbladder-related events was consistently observed across weight-loss categories, indicating that other factors than weight loss may be involved. The higher frequency in the weight management pool could be attributed to dose or indication.

Uncertainty of a possible link of the use of GLP-1 analogues with **acute pancreatitis** still exists. Adjudicated events of acute pancreatitis occurred in greater number with liraglutide compared to placebo: 7 (0.2% of subjects; 0.2 events per 100 PYE) with liraglutide 3.0 mg versus 1 (<0.1% of subjects; <0.1 events per 100 PYE) with placebo during the main treatment periods. The numbers within the weight management programme are too small to allow analysis of a possible dose-response.

Comparing non-adjudicated events, the rate of pancreatitis may be higher in the weight management programme (0.6 events per 100 PYE) than in T2DM (0.2 events per 100 PYE), which could be related to the indication or the dose.

It is conceivable that the events of acute pancreatitis and acute gallstone disease are related, but the low number of pancreatitis events precludes further analysis at present.

There is no evidence of an increased number of **malignancies** in the weight management program. However, the numbers of events were too low for sound statistical analysis and some types of neoplasms show a numerical disadvantage for liraglutide 3.0 mg (breast, colon). The Applicant commits to detailed follow-up of relevant cases.

Injection site reactions were frequently reported in the weight management pool, more so with liraglutide 3.0 mg (13.9%, 22.9 events per 100 PYE) than with placebo (10.5%, 15.7 events per

100 PYE). This incidence rate was higher than that observed in completed trials with liraglutide for T2DM (2.9%, 5.6 events per 100 PYE vs. 1.5%, 2.7 events per 100 PYE, for liraglutide and comparator).

Renal failure is addressed in the SmPC of Victoza as a risk, which is likely related to dehydration caused by GI adverse events. In the weight management program, rates were similar for liraglutide and placebo, suggesting this risk is adequately managed by creating awareness.

Medication errors related to the device cannot be adequately addressed as the proposed commercial device is different from the device used in the trials. This issue is discussed in the Pharmacovigilance section.

Thyroid disease and psychiatric disorders caused no concern in the weight management program.

Relation of AEs to dose

Overall, the higher liraglutide dose in comparison to Victoza seems to have little effect on the AE rate, except for gastrointestinal events which are more frequent. However, the comparisons in the dose-finding trial 1807 and T2DM trial 1922 are underpowered to assess the rates of rare events such as pancreatitis, cardiovascular events and neoplasms.

Safety beyond 1 year of treatment

In the extension of dose-finding trial 1807, AE rates for subjects using liraglutide for weight management were compared to event rates with orlistat. As the AE profile of both liraglutide and orlistat is mostly gastrointestinal, it is not surprising that event rates were generally comparable between treatments.

With the day 120 and 180 responses, additional interim data from the extension of trial 1839 have been added, which confirm the safety profile established during the main trials. In total, in trial 1839 and its double blind, placebo controlled extension up to 1-Oct-2014, 903 subjects were exposed to liraglutide 3.0 mg for ≥2 years and 694 patients were exposed for 3 years. Important event rates of MACE, gall bladder events and pancreatitis did not increase over time; however the number of events was too low for more robust conclusions.

Special populations

Renal impairment seems to have no special impact on AEs due to liraglutide, although more AEs are seen in both liraglutide and placebo groups. However, exposure of severely renally impaired patients is extremely limited to only 3 patients on active treatment. Saxenda is proposed to be “not recommended” in these patients.

Data on subjects with **hepatic impairment** are limited, the Applicant only provided data with respect to baseline AST and ALT values and AEs. No specific analysis is provided with regard to baseline Child-Pugh class, and such data were not captured in the phase 3 program. Impaired hepatic function apparently was no specific exclusion criterion. Based on PK-data, exposure is lower in subjects with hepatic impairment compared to subjects with normal liver function. Therefore, treatment is expected to be safe. Efficacy may be reduced, but the stopping rule will protect subjects from long-term use of a non-effective therapy. In subjects with mild/moderate hepatic impairment, cautions should be used because of the very limited therapeutic experience and the potentially more severe impact of gall bladder events.

The Applicant suggests that the lower liraglutide exposure observed in subjects with severe hepatic impairment is likely because liraglutide is highly bound to plasma albumin and clearance partly determined by albumin binding. This might be a part of the explanation. In patients with severe hepatic impairment, the exposure is decreased with 44% and the benefit of treatment to this population is seriously questioned. Therefore treatment of this special patient population is not recommended, which is adequately addressed in section 4.2 of the SmPC.

The data in unintended **pregnancies** during the clinical development of Saxenda are limited but reassuring. Still, given the teratogenic potential of the product in preclinical investigations, liraglutide should not be used during pregnancy. Also weight reduction, either by non-pharmacological or pharmacological means, is usually not recommended during pregnancy. This is adequately addressed in the SmPC.

Interactions

No new data with respect to safety of interactions are discussed; the Applicant's approach to interactions is based on equivalence with Victoza. According to trial 3630, gastric emptying after 5 hours is equivalent between liraglutide doses of 1.8 and 3.0 mg. It is unlikely that the potential for interactions is significantly different between obesity and T2DM. Therefore, the Applicant's reasoning is accepted. Accordingly, the (proposed) interaction paragraphs in the SmPCs of Saxenda and Victoza are similar.

Comparison with the clinical trial program of Victoza

The mean age in the pooled trials for the weight management programme was 46.9 years (range 18-82) In the clinical trial program for Victoza , mean age was approximately 55 years, ranging from 19–80 years. Mean body weight was 105.7 kg, while in the Victoza trials it ranged from approximately 80–100 kg. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001026/WC500050016.pdf).

The rates of cardiac disorders (SOC) were 4.5, 4.7 and 4.3 events / 100 PYE for liraglutide 3.0, total and placebo respectively. This can be compared to the initial MAA for Victoza where the rates were liraglutide 0.6 mg: 8.3, liraglutide 1.2 mg: 7.3, liraglutide 1.8 mg: 5.7, placebo: 6.8 and active comparator: 4.9 events per 100 SYE.

In conclusion, the population for Saxenda was younger and weightier but had a lower rate of cardiac events.

2.6.2. Conclusions on the clinical safety

The general AE profile is in line with the experience with Victoza. However, current data are insufficient to assess if uncommon events (pancreatitis, neoplasms) occur more frequently with Saxenda's higher dose (3.0 mg) compared to the dose in T2DM (1.8 mg). It seems that the increase in pulse rate is not dose dependant. Gall bladder events occur more frequently with 3.0 mg compared to 1.8 mg.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 7 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hypoglycaemia in combination with other anti-glycaemic agents (T2DM patients only) Gastrointestinal adverse events Altered renal function Allergic reaction Acute gallstone disease Pancreatitis
Important potential risks	Hyperglycaemia due to discontinuation of insulin Medullary thyroid cancer Neoplasm (including breast cancer) Pancreatic cancer Cardiovascular disorders Immunogenicity – Anti-liraglutide antibody formation Immunogenicity – Immune complex disorders
Missing information	Children and adolescents < 18 years Pregnant and lactating women Patients with severe hepatic impairment Patients with severe renal impairment Patients with congestive heart failure NYHA III-IV Patients with a history of major depression or other severe psychiatric disorders Concomitant use of other weight lowering products Off-label use

Abbreviations: NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus.

Pharmacovigilance plan

Study / activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
EX2211-3748 LEADER® Category 3	A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events.	Cardiovascular disorders, neoplasms, pancreatic cancer, pancreatitis, anti-liraglutide antibody formation, congestive heart failure,	Ongoing	Final study report 30 Mar 2016
NN8022-1839 SCALE Category 3	Effect of liraglutide on body weight in non-diabetic obese subjects or overweight subjects with co-morbidities	Neoplasms (including breast cancer)	Ongoing	Final report 27 Aug 2015
NN8022-1839 SCALE Category 3	Collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in NN8022-1839 (including prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status and age at menopause)	Neoplasms (including breast cancer)	Planned	27 Aug 2015
EX2211-3748 LEADER® Category 3	Collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in LEADER® (including prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status and age at menopause)	Neoplasms (including breast cancer)	Planned	30 Mar 2016
MTC registry MTC- 22341 Category 3	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the U.S. and to identify any increase related to the introduction of Victoza® injection into the marketplace.	Medullary thyroid cancer	Ongoing	Final report 15 Sep 2026
NN2211-3784,	Post-marketing safety surveillance to observe the	Neoplasms (including thyroid	Ongoing	Final study report

Study / activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Optum Database study Category 3	safety profile of liraglutide when used in a real-life setting in the U.S. To describe and monitor the safety profile of liraglutide and compare the incidence of adverse events with other antidiabetic medications commonly in use	cancer, MTC, pancreatic cancer and overall malignant neoplasms [including breast cancer]), serious hypoglycaemia, acute pancreatitis, acute renal failure, macrovascular conditions, microvascular conditions, thyroid events and hypersensitivity reactions		31 Jan 2016
NN2211-3880, CPRD study Category 3	To evaluate the safety of liraglutide in the U.K. population To compare safety outcomes during current use of liraglutide with the safety outcomes during the use of other non-insulin antidiabetic drugs (NIADs). ***Addendum study in 3880:*** A substudy evaluating the potential risk of neoplasms in patients treated with liraglutide in combination with metformin and insulin	Neoplasms (including malignant neoplasms, pancreatic cancer and thyroid cancer, including MTC), acute pancreatitis and macrovascular conditions	Ongoing	Final study report 30 Jun 2015
NN8022-4192 Category 3	A mechanistic study to assess effects of liraglutide on gallbladder emptying & pancreatic enzymes	Acute gallstone disease	Planned	Protocol submission : 3 months after approval in the EU
NN8022-XXXX Category 3	Drug utilisation study: CPRD (with questionnaires) in the United Kingdom	Off-label use (Victoza® used for treatment of weight management and Saxenda® not used correctly according to approved label)	Planned	Protocol submission : 3 months after approval in the EU

Study / activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
NN8022-XXXX Category 3	Drug utilisation study: Retrospective chart review of medical records in Germany and Italy.	Off-label use (Victoza® used for treatment of weight management and Saxenda® not used correctly according to approved label)	Planned	Protocol submission : 3 months after approval in the EU

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypoglycaemia in combination with other anti-glycaemic agents (T2DM patients only)	Text included in Section 4.2, Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Gastrointestinal AEs	Text included in Section 4.2, Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Altered renal function	Text included in Section 4.2, Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Allergic reaction	Text included in Section 4.3, Section 4.8 and listed in Section 4.8 of the SmPC	None
Acute gallstone disease	Text included in Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Pancreatitis	Text included in Section 4.4 and listed in Section 4.8 of the SmPC	None
Hyperglycaemia due to discontinuation of insulin (T2DM patients only)	Text included in Section 4.4 of the SmPC	None
Medullary thyroid cancer	Text included in Section 4.4 of the SmPC	None
Neoplasms (including breast cancer)	None proposed	None
Pancreatic cancer	None proposed	None
Cardiovascular disorders	Text included in Section 4.4 and listed in Section 4.8 of the SmPC	None
Immunogenicity – Anti-liraglutide antibody formation	Text included in Section 5.1 of the SmPC	None
Immunogenicity – Immune complex disorders	None proposed	None
Children and adolescents < 18 years	Text included in Section 4.1 and 4.2 of the SmPC	None
Pregnant and lactating women	Text included in Section 4.6 of the SmPC	None
Patients with severe hepatic	Text included in Section 4.2 and Section	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
impairment	4.4 of the SmPC	
Patients with renal impairment/end-stage renal disease	Text included in Section 4.2 and 4.4 of the SmPC	None
Congestive heart failure NYHA III–IV	Text included in Section 4.4 of the SmPC	None
Major depression or other severe psychiatric disorders	None proposed	None
Concomitant use of other weight lowering drugs	Text included in Section 4.4 of the SmPC	None
Off-label use	Text included in Section 4.1 of the SmPC Text included in patient leaflet.	None

Abbreviations: AE = adverse event; NYHA = New York Heart Association; SmPC = summary of product characteristics; T2DM = type 2 diabetes mellitus.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Saxenda (liraglutide 3.0 mg once daily, SC) is proposed for chronic weight management in adult obese patients (BMI ≥30 kg/m²) or overweight patients (27≤ BMI <30 kg/m²) with weight related comorbidity. The active substance is already authorised as Victoza for use in Type 2 Diabetes (T2DM) with a lower dose (1.8 mg). Liraglutide regulates appetite by increasing feelings of satiety, leading to a lower caloric intake of approximately 140 kcal/meal as assessed in PD trial 3630.

Benefits

Beneficial effects

The clinical development programme for liraglutide in weight management includes one phase 2 dose-finding trial (trial 1807) and four confirmatory phase 3 trials (trials 1839, 1922, 3970 and 1923), which were conducted worldwide and involved 5813 subjects in the originally proposed target population (BMI ≥30 kg/m² or BMI ≥27 kg/m² with weight related comorbidity).

In the **dose** range that was investigated, the highest dose investigated (3.0 mg) was also the most effective. This dose was chosen for further evaluation in the phase 3 programme and was proposed for authorisation.

The Applicant executed 5 separate trials which together provide an adequate overview of the benefits (and risks) that can be expected from treatment with Saxenda. The clinical programme (including the focus on 1-year efficacy data) is consistent with the "Guideline on clinical investigation of medicinal products used in weight control" (CPMP/EWP/281/96 Rev.1 - 2007). In all trials, liraglutide or placebo was given on top of counselling to improve diet and exercise throughout the trial. All 5 trials investigated the proposed dose in (subsets of) the target population and evaluated the effect on

weight, usually after 56 weeks, thus allowing pooling of the main results. The population in the trials together is representative of the target population.

The **primary analysis** estimated the weight loss and the proportion of responders defined as subjects achieving a 5- or 10% weight loss. A hierarchical testing procedure was applied. In the pooled dataset, treatment with liraglutide 3.0 mg resulted in weight loss of 7.5% (7.8 kg) vs. 2.3% (2.5 kg) with placebo, a placebo-subtracted weight loss of 5.2% [95% CI: 4.83; 5.53]. The results were highly statistically significant. The data were robust across a range of sensitivity analyses. The placebo-subtracted treatment effect in the most favourable scenario (the Completers analysis), was 5.6% and in the least favourable scenario (BOCF, but subjects with weight gain imputed with LOCF) 4.5%.

The responders achieving > 10% weight loss were 30.5% for liraglutide 3.0 mg v 8.4% for placebo in the pooled 56-week trials. Also these results were highly statistically significant and supported by sensitivity analyses. The (favourable) estimates looking at completers only were 38.2% and 12.7% respectively; the (unfavourable) estimates counting early withdrawals as non-responders were 28.6% and 8.52% respectively.

In general, the results were consistent over the various trials and relevant subgroups with statistically significant results, e.g. normoglycaemic (n=1780, -5.26%) and pre-diabetic (n=2844, -5.41%) study participants. During the assessment, a more restricted target population was discussed by CHMP, i.e. adults with BMI ≥30 kg/m^2 and at least one weight related comorbidity. However, when comparing subgroups based on baseline BMI, although the absolute weight loss was higher in the high BMI subgroups, the efficacy as % weight change was less than in the lowest BMI subgroup. The treatment estimate for females (n=3759; -5.83%) was better compared to males (n=1488; -3.56%). Treatment effect in T2DM as assessed in trial 1922 (-3.95%) was less than in all 1 year trials (-5.24%). This is partly explained by the high participation of males in this trial, as the results for males (-2.93%) was worse than for females (-4.84%). After correction for gender effects, the interaction is no longer statistically significant and is not considered to pose any clinical problems.

During assessment, a stopping rule was proposed and accepted for the SmPC section 4.1, stating that treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose (16 weeks including the titration phase) if patients have not lost at least 5% of their initial body weight. For subjects who pass the stopping rule (N=1637, 65.0%), the expected weight change is -11.2% after one year. A response of at least 10% is achieved by 51.2%. Also, effects on risk factors are at least as good as in the overall population.

The **secondary endpoints** were (related to) body composition and weight (e.g. waist circumference), glycaemic control (e.g. HbA1c), cardiometabolic risk, concomitant medications and patient reported outcomes. This is consistent with the guideline. Sleep apnoea was the primary endpoint in trial 3970. To control the Type I error caused by the multitude of endpoints, a hierarchical testing procedure was defined for the pooled analyses of the secondary endpoints. The results from this analysis can be used in a confirmatory way. Statistically significant effects were observed on waist circumference (-3.98 cm), HbA1C (-0.93% in T2DM patients), SBP (-2.9 mmHg), DBP (-0.8 mmHg), and LDL (2.7%). The effects on SBP and HbA1c are largely independent from the effect on weight.

There were beneficial treatment effects in the patient reported outcomes for the following domains: SF-36 physical function score: 1.40 (0.91; 1.89), SF-36 general health score: 1.77 (1.27; 2.27) and IWQoL-Lite physical function: 4.81 (3.83; 5.79).

The **pharmacokinetic properties** of liraglutide 3.0 mg in obese or overweight subjects were overall similar to those for liraglutide at doses up to 1.8 mg in healthy subjects and subjects with T2DM. Liraglutide 3.0 mg generally resulted in higher exposure than liraglutide 1.8 mg in obese and overweight subjects and the exposure increased in an approximately dose-proportional manner.

Subjects with obesity that is secondary to **endocrinologic disorders** (e.g. Cushing's Syndrome) or to **treatment with drugs** that may cause weight gain (e.g. insulin, psychotropic drugs) or **eating disorders** were not included in the trials and use of liraglutide in these patients are not recommended in the SmPC.

The Applicant recognised several factors that influenced the exposure to liraglutide for instance gender and weight, and also (but to a lesser extent) T2DM and the injection site, albeit that these two are considered not clinically relevant when evaluated separately. Between extreme scenarios, an up to 5 fold exposure difference can occur. Especially in high-weight males, exposure may be too low for therapeutic efficacy. The Applicant argues, that therapy will be discontinued by the stopping rule in these cases, which is agreed.

Uncertainty in the knowledge about the beneficial effects

In the pooled dataset, the rate of withdrawals is high, 29.6%. This number is consistent across all trials. This withdrawal rate is not unexpected for placebo-controlled trials of one-year duration in obesity. Only 26.8% of subjects who withdrew came in for the visit at the nominal end-of-trial, causing **missing endpoint data** for 21.7% of subjects.

The interpretation of the **sleep-apnoea** related parameters is difficult, as there is no established margin for clinical relevance. The mean apnoea-hypopnoea index (AHI) was the primary endpoint in trial 3970. AHI at baseline (49.2 events/hour) reflected a severely diseased study population and decreased after 32 weeks with both liraglutide 3.0 mg and placebo, but the improvement was greater with liraglutide (-12.2 vs. -6.1 episodes/hour, p=0.015). The decrease in AHI was closely correlated to weight loss, as was known from literature. The decrease in 'episodes' was accompanied by statistically non-significant (but beneficial) changes in the sleep-related patient-reported outcomes.

It is not clear if and how long the benefits will **persist** after treatment discontinuation; in fact, it is likely that weight would return to baseline. In trial 1839, subjects treated with liraglutide who had completed 1 year of treatment were re-randomised to 3-months treatment with liraglutide or placebo. Subjects who switched from liraglutide to placebo gained a mean 2.91% (2.63 kg) of body weight compared to 0.69% (0.61 kg) in those who continued on liraglutide (treatment difference: -2.18% [-2.60; -1.75], p<0.0001). However, weight change in subjects who switched from liraglutide to placebo (-6.77% [-6.73 kg]) still remained greater than patients initially randomised to placebo (plus diet and exercise) (-3.11% [-3.29 kg]).

No estimate is shown about the results in the whole target population before application of the stopping rule; such an analysis is complicated by the fact that the stopping rule was not applied in the trials and treatment of all subjects was continued. Thus the results in this population are presented for subjects complying to the stopping rule.

Risks

Unfavourable effects

The safety database includes 5813 patients. Of these, 2341 were on active treatment with the target dose for at least 1 year. The extent of exposure is adequate based on guidance in ICH-E1.

The **general AE** profile is in line with the experience with Victoza. The most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders like nausea (liraglutide: 65.4 v placebo 20.9 events/100 PYE), diarrhoea (34.7 v 14.9), constipation (26.3 v 11.5), vomiting (26.4 v 5.6). Most patients experience such events already in the first weeks of treatment, during dose titration. Other patients express decreased appetite (12.0 v 2.9), which is in line with the pharmacology of liraglutide. Also asthenic conditions like fatigue (9.6 v 6.1) occur more frequently with liraglutide

In subjects without T2DM, no severe **hypoglycaemic events** were reported. The proportion of subjects reporting AEs of hypoglycaemia outside the FPG and OGTT visits was low, both with liraglutide 3.0 mg (1.6% of subjects) and placebo (1.1% of subjects). In subjects with T2DM, severe hypoglycaemia was reported by 0.7% of subjects treated with liraglutide 3.0 mg (3 subjects with 5 events, 13 events per 1000 PYE) and 1.0% of subjects treated with liraglutide 1.8 mg (2 subjects with 3 events, 16 events per 1000 PYE) and occurred only in patients taking concomitant SU therapy.

The consistent finding that GLP-1 analogues increase the pulse rate has caused concern with respect to **cardiovascular safety**. There are data, that GLP-1 receptors are present in the cardiac pacemaker suggesting a direct effect of liraglutide on the heart. In the large trials from the weight management programme, the maximum increase in pulse rate was 4.5 bpm for liraglutide (compared to placebo 1.1 bpm, treatment effect 3.4 bpm) after 6 weeks and slightly declined thereafter. The effect persists until end-of-trial and is then 2.5 bpm above placebo. There is no indication of a dose response. In the PD trials, the difference in pulse rate was 6-9 bpm during the night. In response to FDA regulations, the Applicant has provided an extensive cardiovascular meta-analysis to assess the risk of **MACE** (CV death or non-fatal stroke or myocardial infarction). The pre-specified MACE meta-analysis returned a hazard ratio for the weight management pool of 0.40 [95% CI: 0.15; 1.05] for total liraglutide vs. total comparator (primary analysis, 8 v 9 events).

In the weight management pool, the proportion of subjects reporting **acute gallstone disease** events was higher with liraglutide 3.0 mg (2.3%) than with placebo (0.9%) The imbalance was mainly driven by events of cholelithiasis and cholecystitis ('cholelithiasis': 1.5% vs. 0.5%; 'cholecystitis acute': 0.4% vs. <0.1%; 'cholecystitis': 0.2% vs. 0.1% , respectively, for liraglutide 3.0 mg vs. placebo).

Uncertainty of a possible link of the use of GLP-1 analogues and **acute pancreatitis** still exists. Adjudicated events of acute pancreatitis occurred in greater number with liraglutide compared to placebo: 7 (0.2% of subjects; 0.2 events per 100 PYE) with liraglutide 3.0 mg vs. 1 (<0.1% of subjects; <0.1 events per 100 PYE) with placebo during the main treatment periods. Events of acute pancreatitis were usually reason for hospitalisation, although most subjects recovered within 2 weeks. Non-adjudicated pancreatitis events were more frequent in this MAA dossier (0.6 events per 100 PYE) than in the T2DM MAA dossier (0.2 events per 100 PYE). In the T2DM trials, no adjudication was implemented; also, the methods of data-collection in this weight management dossier were different (more sensitive).

Injection site reactions were frequently reported in the weight management pool, more so with liraglutide 3.0 mg (13.9%, 22.9 events per 100 PYE) than with placebo (10.5%, 15.7 events per 100 PYE). This incidence rate was higher than that observed in completed trials with liraglutide for T2DM (2.9%, 5.6 events per 100 PYE vs. 1.5%, 2.7 events per 100 PYE, for liraglutide and comparator).

Renal failure is addressed in the SmPC of Victoza as a risk, which is likely related to dehydration caused by gastro intestinal adverse events. In the weight management programme, rates were similar for liraglutide and placebo.

Thyroid disease and psychiatric disorders caused no concern in the weight management programme. Patients at risk for suicidality or with eating disorders were excluded from the trials.

No new data with respect to safety of **interactions** beyond what has been provided from the Victoza development program, were presented; the Applicant's approach to interactions is based on equivalence with Victoza. According to trial 3630, gastric emptying after 5 hours is equivalent between liraglutide doses of 1.8 and 3.0 mg. It is unlikely that the potential for interactions is significantly different between obesity and T2DM.

In the Victoza programme, no effect of liraglutide on **QTc** was observed. This was confirmed for Saxenda by an analysis of ECGs from a subset of patients in the phase-3 programme in weight management.

Uncertainty in the knowledge about the unfavourable effects

Overall, the higher liraglutide **dose** in comparison to liraglutide used in T2DM (Victoza) seems to have little effect on the AE rate, except for gastrointestinal events which are more frequent. However, the comparisons in the dose-finding trial 1807 and T2DM trial 1922 are underpowered to assess the rates of rare events such as pancreatitis, cardiovascular events and neoplasms.

There is no evidence of an overall increased number of **malignancies** in the weight management program. However, the numbers of events were too low for sound statistical analysis and some types of neoplasms show a numerical disadvantage for liraglutide 3.0 mg (breast).

Medication errors related to the device cannot be adequately addressed based on the phase 3 trials as the proposed commercial device is different from the device used in these trials. However, the results of the usability study are reassuring.

For the T2DM indication, a large cardiovascular safety study (**LEADER**) is on-going. Although the extrapolation of data from LEADER to Saxenda is not straightforward (different indication, different population, different dose), the trial is expected to provide additional valuable information. However, as the trial is on-going, data are not available to maintain the blind. The Data Monitoring Committee supervises the trial regularly and has recommended normal continuation of the trial. The final report of this trial is expected in 2016.

Data in **special populations** are sparse. Exposure in older patients above 75 years is very limited (n=17 for liraglutide 3.0 mg) and “not recommended” in the SmPC. Similarly, exposure of severely renally impaired patients is limited to only 3 patients on active treatment and is not recommended. Exposure in subjects with hepatic impairment is reduced based on the PK trial. Use in severe hepatic impairment is “not recommended” because exposure is reduced by 44%. Use in mild or moderate hepatic impairment should be with caution, as efficacy and safety in this population are not investigated.

Data with regard to **safety beyond 1 year of treatment** were primarily available from the extension of dose-finding trial 1807, where AE rates for subjects using liraglutide for weight management could be compared to event rates with orlistat (the only comparator used in the second year of trial 1807). With the day 120 and 180 responses, additional interim data from the extension of trial 1839 have been added, which confirm the safety profile established during the main trials. In total, in trial 1839 and its double blind, placebo controlled extension up to 1-Oct-2014, 903 subjects were exposed to liraglutide 3.0 mg for ≥2 years and 694 patients were exposed for 3 years.

Balance

Importance of favourable and unfavourable effects

According to the weight reduction guideline (CPMP/EWP/281/96 - 2007) an important goal of treatment of obesity is to prevent associated morbidity and mortality. The over-all effect on **weight loss** by Saxenda is considered clinically relevant. After treatment with liraglutide 3.0 mg, weight loss was 7.5% with liraglutide 3.0 mg vs. 2.3% with placebo, a placebo-subtracted weight loss of 5.2%, with narrow confidence intervals. 10%-Responders were 30.5% for liraglutide 3.0 mg v 8.4% for placebo. This is also in accordance with the requirement of the guideline. Saxenda is at least as efficacious as Victoza for glucose regulation. This may be important for patients with treatment targets related to both diabetes and weight loss. The other **secondary endpoints** related to cardiovascular risk that were included in the testing hierarchy all tested statistically significant.

However, the actual treatment benefits were small and often directly related to weight loss. Thus, these endpoints validate the weight loss, but the clinical relevance of most of these endpoints is limited. The effects on glycaemic control and SBP are independent on weight loss.

The **low follow up** at 56 weeks is a major shortcoming of the trials; post-hoc correction seems not possible. Missing endpoint data were imputed for 21.7% of participants. Based on the sensitivity analyses that are provided, the impact of imputations on the estimate of the treatment effect may be around 1%. Also, the effect is not consistent in all subgroups. The estimates of the treatment effect in **males** (-3.56%) and in patients with **T2DM** (-3.95%) and in male T2DM (-2.93%) patients are below the overall estimate (-5.2%). The proposed stopping rule performs acceptably in all subgroups, leading to more expected discontinuations in males and T2DM patients when applied.

Treatment **discontinuation** is associated with weight regain. The Applicant provided data of 3-months re-randomised follow up. In these 3 months, with continued counselling, weight regain was +2.91%; obviously. This was in a completers population, therefore after these 3 months the difference with the original placebo group was still -3.66% to their original baseline weight. It is likely that the treatment effect will continue to decrease after the 3 months that were investigated. The prospect of lifelong treatment for weight management may concern potential users.

A favourable change over time in **patient-reported outcomes (PROs)** occurred in both treatment groups. The Applicant did not show the clinical relevance of the differences between treatment groups. The outcome of the PROs may be biased by the burden of daily injections as these may foster the opinion that the medicine is strong and effective. The injections weigh in equally at end of trial for both active and placebo treatment. Therefore, the Quality of Life scales did not measure the burden of therapy caused by the injections as also the control patients got injected (sham injections). Of course, adverse effects like nausea did come up in the questionnaires.

The interpretation of the **sleep-apnoea** related parameters is difficult, as there is no established margin for clinical relevance.

Regarding **unfavourable effects**, the use (and dose) of liraglutide is limited by GI-symptoms. Gastrointestinal adverse events are very frequent with Saxenda, especially early during therapy, leading to a high number of withdrawals for AEs (9.5%). As with Victoza, the dose is gradually titrated over 4 weeks that mitigates this problem somewhat. Saxenda is administrated as subcutaneous injections and associated with many injection site reactions (22.9 events per 100 PYE). Most issues of long-term effects resemble those with GLP-1 analogues as seen in T2DM, but now within the context of the indication of weight control. In a population of overweight/obese, risks are more important than when treating a disease like T2DM.

The risks of **pancreatitis and gallbladder** events do not increase over time and can thus be accurately estimated from the phase 3 data. The rate of **pancreatitis** was numerically higher in the weight management programme (0.6 events per 100 PYE) than in T2DM (0.2 events per 100 PYE), which could be related to different methods of data collection, the indication, the weight loss, the dose, or a combination hereof. It is also conceivable that some of the events of acute pancreatitis are related to acute gallstone disease that was identified as a new adverse drug reaction in this programme. The low number of pancreatitis events precludes further analysis. Although these pancreatitis events usually lead to hospitalisation, recovery is often quick and without sequelae. The risk of acute **gall stone disease** is related to the weight loss that was achieved. However, even when correcting for weight loss, a further contribution of liraglutide is likely.

There is limited information about **long-term (>1 year) safety**. Dose-responsiveness for **rare events** cannot be excluded based on current data. This implies that other uncertain risks such malignancies cannot be judged accurately with use of the T2DM data. Such events are of relevance because they are associated with severe morbidity and mortality (see discussion of the RMP). Some

types of **neoplasms** show a numerical disadvantage for liraglutide 3.0 mg (breast cancer and benign colon neoplasms), which could be a chance finding but needs follow-up in the RMP, similar to GLP-1 analogues in general.

Important events of **hypoglycaemia** only occurred in subjects taking other hypoglycaemic treatments for T2DM, in particular SU derivatives. This is consistent with liraglutide's mode of actions, which stimulates insulin secretion only during hyperglycaemia. When liraglutide is used in T2DM, glucose lowering therapy must be adapted, which is addressed in the SmPC.

The final major issue is the increase in **heart rate** and its implications for the cardiovascular risk. The Applicant has put forward some valid issues regarding this uncertainty. Although related to its mechanism of action, it is not accompanied by an increase of activity of the sympathetic nervous system, it appears not to be dose-related and data so far with GLP1-analogues including several meta-analyses do not suggest a signal of a deleterious effect on cardiovascular outcome. Also, as indicated above, other risk factors may be favourably altered. Data on Saxenda so far appear reassuring, but it should be recognised that the studied population is a low risk population with a low number of events. More convincing data will have to be obtained from the LEADER study. To address the concern relating to the increase in pulse rate, it is recommended as a precaution in SmPC section 4.4 to discontinue the drug when a clinically relevant sustained increase in heart rate occurs.

No separate analysis is shown for safety after application of the stopping rule. Safety is likely in line with the overall population. Based on larger weight loss, the risk of gall bladder events may be relatively higher.

Benefit-risk balance

The overall B/R of Saxenda is positive, provided that the Applicant commits to perform a number of post authorisation measures.

While the risks of gall bladder disease and pancreatitis have been established and discussed in the SmPC, the acceptability of these risks in an overweight but otherwise healthy population should be considered on an inidividual basis, especially if the primary goal of therapy is a reduction in the cardiovascular risk. The data on breast cancer and colon neoplasms currently do not prove or disprove a tumour promoting effect of Saxenda.

Saxenda's efficacy is moderate, in particular in men, but is still considered clinically relevant when viewing the results on primary and secondary endpoints in totality.

According to the Applicant, the ongoing post-authorisation commitments for Victoza (liraglutide 1.2 and 1.8 mg for T2DM) will provide information regarding the long-term safety of Saxenda pertaining to the concerns raised by the CHMP (risks associated with increase in pulse, pancreatitis, malignant breast and benign colon neoplasms).

Based on phase 2 and 3 data, there is no dose response relationship for the increase in heart rate. As discussed before, gall bladder events are likely dose related. The number of pancreatitis and malignancy events is too low to allow assessment of dose-responsiveness. Therefore, the commitments from the Victoza programme are of limited value for the assessment of pancreatitis, gall bladder events and neoplasms.

LEADER includes 5500 subjects with BMI >30 kg/m^2 and T2DM, which could be candidates for Saxenda (if weight reduction would be selected as treatment target). These subjects represent a group with high CV risk as a result of atherosclerotic disease. LEADER is designed as a CV safety trial, but in fact measures the net result of CV efficacy and safety. In general, the weight management population (younger, more females) has lower CV risk and thus lower expected benefits than the

LEADER population. A dedicated CV outcome trial of Saxenda, with an 'enriched population' to improve feasibility would mimic LEADER except for the dose.

It is not known, if LEADER participants would also be at higher risk for any adverse long-term effect of the increase in pulse rate, although they are likely susceptible. As LEADER is designed as a non-inferiority trial, no confirmatory evidence for any benefits is expected. Effects in subjects with hypertension, dyslipidaemia or mobility disorders (but without T2DM) are not assessed with LEADER. Thus, the position of the Applicant that the results of the studies included in the pharmacovigilance plan for Victoza will be fully applicable to Saxenda, is not supported due to differences in patient population and dosage. If the results of LEADER would be ambiguous in this high risk population a need for a separate CV outcome study with Saxenda cannot be excluded, whereas this would likely be not the case if results would suggest a beneficial effect on CV outcome. Therefore, it will be important to assess the data from LEADER also with respect to Saxenda once the results are available.

Discussion on the benefit-risk assessment

The fact that Saxenda is to be injected and may cause nausea in a substantial number of patients can be an obstacle for many patients, but this is not a major issue in terms of benefit-risk; it is more a choice that speaks for the patient's motivation.

Benefits have been shown on weight and weight-related co-morbidities, in particular on blood pressure that are considered surrogate for cardiovascular outcome. Also, an effect on obstructive sleep-apnoea has been demonstrated, although the relevance is still questioned. In terms of risks, pancreatitis and cholecystitis are identified risks, but in the context of their low incidence and the population at risk for CV disease, they can be accepted. The uncertainty regarding the occurrence of neoplasms is addressed further in the RMP and thus this is not considered a remaining issue. The increase in heart rate is assessed in the context of the overall effect on CV outcome.

As indicated above, available evidence at the moment shows a lack of deleterious effect on cardiovascular outcome, with even a suggestion of a beneficial effect, and the mechanism of action has been studied extensively. It is agreed with the Applicant that 1-year safety of Saxenda is covered by the clinical trials. As indicated by the Applicant, the report for the LEADER trial will be finalised and provided to the CHMP in 2016 and its results are expected to further characterise the safety profile of liraglutide also with regard to Saxenda.

During the assessment, an alternative, more restricted target population was discussed, i.e. adults with BMI ≥30 kg/m^2 and at least one weight related comorbidity in whom, based on the assumption of a higher baseline CV risk, possibly more benefits could be expected on CV outcome in the long term. However efficacy in terms of weight loss was similar to the original target population and no data is available to show such a differential long-term CV benefit. During the assessment, a stopping rule was proposed that treatment with Saxenda should only continue after 12 weeks on the 3.0 mg/day dose in those patients who have lost at least 5% of their initial body weight; the stopping rule will protect subjects from long-term use of a non-effective therapy. After discussion, the CHMP concluded that the B/R is positive on the available data in the original target population subject to adherence to such a stopping rule.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Saxenda 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/m² (obese), or
- ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes 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.

is favourable and 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.

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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 agreeed 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.