EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/705417/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eperzan

International non-proprietary name: albiglutide

Procedure No. EMEA/H/C/002735/0000

Note

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

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Product information

Name of the medicinal product:	Eperzan
Applicant:	GlaxoSmithKline Trading Services Limited 6900 Cork Airport Business Park Kinsale Road Cork IRELAND
Active substance:	albiglutide
International Nonproprietary Name/Common Name:	albiglutide
Pharmaco-therapeutic group (ATC Code):	A10BX13
Therapeutic indication(s):	Eperzan is indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control as: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance. <u>Add-on combination therapy</u> In combination with other glucose-lowering medicinal products including basal insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 4.4 and 5.1 for available data on different combinations).
Pharmaceutical form:	Powder and solvent for solution for injection in pre-filled pen
Strengths:	30 mg and 50 mg

Route of administration:	Subcutaneous use
Packaging:	Cartridge (DDC)
Package sizes:	1 pre-filled pen and 4 pre-filled pens

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List of abbreviations

AE	adverse event
ADA	anti-drug antibodies
ANCOVA	analysis of covariance
AUC	area under the plasma concentration-time curve
BE	bioequivalence
BMI	body mass index
CHF	congestive heart failure
CFB	change from baseline
CI	confidence interval
CLr	renal clearance
CL/F	apparent clearance
Cmax	maximum observed plasma concentration
CV	cardiovascular
DDI	drug-druginteraction
DPP-IV	dipeptidyl peptidase IV
EC50	concentration to elicit half maximal effect
ECG	electrocardiography
ECLIA	electrochemiluminescent immunoassay
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FTIH	first-time-in-human
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
h	hour(s)
HAS	human serum albumin
hERG	human ether-à-go-go related gene
ICH	International Conference on Harmonization
INR	International normalized ratio
ITT	intent-to-treat
kg	kilogram
l	liter
LOCF	last observation carried forward
LoQ	list of questions
LS	least squares
MAA	Marketing Authorization Application
MACE	major adverse cardiac events
MAD	multiple ascending dose
MET	metformin
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OC	observed case
OL	open label
PD	pharmacodynamic(s)
pio	pioglitazone
PIP	Paediatric investigational plan
PK	pharmacokinetic(s)
PPN	pre- and post-natal
QTc	QT interval corrected for heart rate

SAD	single ascending dose
SC	subcutaneous
SD	standard deviation,
SE	standard error
sita	sitagliptin
STZ	streptozotocin
SU	sulfonylurea
TK	toxicokinetic
tQT	thorough QT
T1/2	Terminal phase half-life
Tmax	Time of occurrence of Cmax
T2DM	type 2 diabetes mellitus
TZD	thiazolidinedione
V/F	Apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services Limited submitted on 7 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eperzan, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 April 2012.

The applicant applied for the following indication:

Eperzan is indicated for the treatment of type 2 diabetes mellitus in adults, as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin or other first-line agents are inappropriate due to contraindications or intolerance.
- in combination with oral glucose-lowering medicinal products and/or insulin when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).

The legal basis for this application refers to:

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

The applicant indicated that albiglutide was considered to be a new 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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included the EMA Decision P/0130/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0130/2012 was not yet completed as some measures were deferred.

The PDCO issued a letter on partial compliance for the PIP P/0130/2012.

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.

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 December 2010, 17 March 2011 and 21 June 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Eperzan has not been given a Marketing Authorisation in any country yet.

A new application was filed in the following countries: United States, Canada, Switzerland.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

GLAXO OPERATIONS UK LTD
(TRADING AS GLAXO WELLCOME OPERATIONS)
HARMIRE ROAD
BARNARD CASTLE
Durham, DL12 8DT
United Kingdom

Manufacturer responsible for import and batch release in the European Economic Area

N/A

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 7 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members

on 14 June 2013.

- During the meeting on 25 July 2013, 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 25 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2013.
- The summary report of the inspection carried out at the following sites: Investigator site Crest Clinical Trials: 5 August 2013 – 9 August 2013, Investigator site Madras Diabetes Research Foundation: 10 September 2013 – 13 September 2013 and CRO: PPD Sorrento South Corporate Center: 12 August 2013 – 16 August 2013 was issued on 11 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 October 2013.
- During the CHMP meeting on 21 November 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 December 2013.
- During the meeting on 23 January 2014, 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 Eperzan.

2. Scientific discussion

2.1. Introduction

Problem statement

Type 2 diabetes mellitus (T2DM) is a major global public health problem given its association with significant microvascular and macrovascular complications and a reduced life span. Appropriate management of the metabolic syndrome, including hyperglycaemia, hypertension, dyslipidaemia, and obesity, which co-exist in patients with T2DM, is critical to reducing future patient morbidity and mortality. Achievement of a target glycosylated haemoglobin (HbA1c) level of <7% is viewed as an important glycaemic goal, but for many patients this is not achievable due to the presence of co-morbidities, the need for multiple anti-diabetic drugs, poor compliance with treatment, or adverse reactions associated with established anti-diabetic therapies. For these reasons, there remains an unmet need for new antidiabetic therapies that allow further personalization of diabetes regimens based on efficacy, safety and tolerability.

Incretin-based therapies are a new class of agents with clinically relevant advantages over other available therapies. In a healthy individual, glucagon-like peptide-1 (GLP-1) plays an important role regulating postprandial blood glucose concentrations by stimulating glucose-dependent insulin secretion resulting in increased glucose utilization by tissues. GLP-1 also suppresses

glucagon secretion at normal and elevated glucose levels, leading to reduced hepatic glucose output. In addition, GLP-1 suppresses appetite, delays gastric emptying time and slows small bowel motility, delaying food absorption and decreasing the rate of glucose absorption. In patients with T2DM, the postprandial rise in endogenous GLP-1 is reduced or absent, glucagon is inappropriately elevated, and obesity is common. Accordingly, the rationale for use of GLP-1 receptor (GLP-1R) agonists, such as exenatide, liraglutide and in this application, albiglutide, is to replace or supplement endogenous GLP-1 in patients with T2DM.

GLP-1R agonists have demonstrated improvements in glycaemic control and weight without the burden of hypoglycaemia and weight gain commonly associated with other anti-diabetic agents. However, increased rates of gastrointestinal (GI) symptoms, particularly nausea and vomiting, have been noted during the first months of treatment with both exenatide and liraglutide. Linkage of GI symptoms to progressive renal impairment in some patients has resulted in label restrictions and avoidance of the use of currently approved GLP-1R agonists in patients with various degrees of renal impairment. Marketed GLP-1R agonists often require frequent subcutaneous (SC) injections; exenatide is administered twice daily (although a once weekly formulation has now been approved) and liraglutide requires once daily administration. Both formulations of exenatide are associated with specific antibody formation and in 6% of patients this is associated with an attenuated glycaemic response. Therefore within the GLP-1 agonist class, there remains an unmet need for an effective once weekly administered agent.

About the product

Albiglutide is a GLP-1 receptor agonist which acts on pancreatic beta cells to increase insulin production and augment glucose-dependent insulin secretion. Albiglutide is generated through genetic fusion of two tandem copies of modified human GLP 1 (97% amino acid sequence homology to endogenous human GLP-1 fragment 7-36) to human albumin. The GLP-1 sequence has been modified to confer resistance to dipeptidylpeptidase IV (DPP-IV) mediated proteolysis. The human albumin moiety of the recombinant fusion protein, together with the DPP-IV resistance, greatly extends the half-life to 5 days allowing once weekly dosing.

The following indication is sought:

Eperzan is indicated for the treatment of type 2 diabetes mellitus in adults, as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin or other first-line agents are inappropriate due to contraindications or intolerance.
- in combination with oral glucose-lowering medicinal products and/or insulin when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).

The proposed posology is as follows:

The recommended dose of Eperzan is 30 mg once per week, administered subcutaneously.

The dose may be increased to 50 mg once weekly based on individual glycaemic response.

Albiglutide is to be administered by a new single use pen injector which has been evaluated in Phase III studies.

2.2. Quality aspects

2.2.1. Introduction

The active substance of the drug product is albiglutide, an agonist of the GLP-1 receptor and acts on pancreatic beta cells to increase insulin production and augment glucose-dependent insulin secretion.

Albiglutide is a recombinant fusion protein consisting of two copies of a 30-amino acid sequence of modified human glucagon-like peptide 1 genetically fused in series to human albumin. Albiglutide active substance is produced through fermentation of a genetically modified strain of *Saccharomyces cerevisiae* followed by purification. The human albumin moiety of the recombinant fusion protein, together with engineered resistance to dipeptidyl peptidase IV (DPP-IV), greatly extends the half-life to 5 days allowing once weekly dosing by subcutaneous injection.

Drug product manufacturing consists of thawing, pooling and mixing of bulk active substance, dilution to a target concentration using an excipient solution and aseptic filling of active substance in the front chamber of the dual chamber cartridge, lyophilisation and aseptic filling of WFI in the rear chamber and finally assembly into pen injectors.

The final pharmaceutical form of the product is powder and solvent for solution for injection in pre-filled pen (30 and 50 mg strength). The Dual Chamber Cartridge (DCC) is a Type 1 glass barrel with a sealed rubber stopper and a rubber closure disc encased in a snap on cap. The pen which houses the DCC is composed of a clear plastic cartridge holder and an opaque plastic pen mechanics sub-assembly and is supplied with a CE marked 29G, thin walled, 5-mm pen needle.

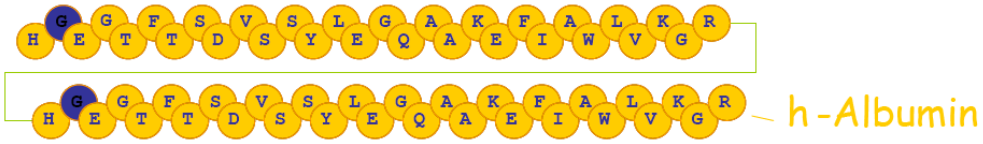
The indication applied for under this application is treatment of adult type 2 diabetes mellitus patients. The recommended applied dose is 30 – 50 mg weekly.

2.2.2. Active Substance

Albiglutide is a recombinant fusion protein consisting of two copies of a 30-amino acid sequence of modified human glucagon-like peptide 1 (GLP-1, fragment 7-36) genetically linked in series to human albumin. Specifically, the first modified GLP-1 copy is fused at its C-terminus to the N-terminus of the second copy. This peptide, in turn, is genetically fused at its C-terminus to the N terminus of human albumin. A schematic representation of albiglutide is shown in the Figure 1 below.

The GLP-1 sequence has been modified with a glycine substituted for the naturally-occurring alanine at position 8 in order to confer resistance to dipeptidylpeptidase IV (DPP-IV) mediated proteolysis. Albiglutide contains 35 cysteines in the albumin portion of the molecule, with 34 of them forming 17 disulfide bonds. Albiglutide is not glycosylated.

Figure 1: Schematic Representation of Albiglutide



The albiglutide molecule binds to the GLP-1 receptor and to the FcRn receptor, this binding protects albiglutide from degradation and extends its half life.

Manufacture

Manufacturing process and process controls

The albiglutide active substance manufacturing process has adequately been described. Main steps are fermentation, recovery and purification. Briefly, fermentation and harvest processes occur in several stages that expand the cells followed by a production scale bioreactor stage, wherein albiglutide accumulates in the bioreactor. After recovery of the albiglutide containing supernatant, albiglutide is purified by a series of chromatography and filtrations steps. Albiglutide is formulated and filtered into bulk active substance containers. No reprocessing strategy is described.

The ranges of critical process parameters and routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The process is considered acceptable.

Control of starting materials

All raw materials used in the active substance manufacturing process are either pharmacopoeia grade, American Chemical Society (ACS), or are tested according to internal GlaxoSmithKline (GSK) testing specifications. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of the cell substrate.

Albiglutide is expressed using a plasmid transformed into the host cell line, Saccharomyces cerevisiae. The stability of the plasmid is favoured by complementation of leucine deficiency in the host. The construction of the expression vector is adequately described. Furthermore, sufficient information has been provided regarding characteristics of the plasmid and the producer cell line.

A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

Development of Controls for the Commercial Manufacturing Process

The process control strategy for albiglutide active substance (DS) manufacture is part of an overall product control strategy which includes control of raw materials and excipients,

procedural controls, process parameter controls, process monitoring, in-process testing, release testing, and product characterization. The DS process control strategy was developed using risk assessment tools applied to product, process and facility knowledge, resulting in a combination of process controls and product testing, to ensure product quality and patient safety.

A broad range of critical quality attributes (CQAs) has been identified. Process characterisation has been made to explore the linkage between process parameters and CQAs to identify the critical process parameters for the fulfilment of CQA acceptance criteria as defined by prior knowledge, including historical in-process data from the clinical supply campaigns. The studies were made on a small scale, which was qualified by dedicated studies. Proven Acceptable Ranges were established by multifactorial studies or in certain cases, as acceptably justified, by univariate studies. Moreover, small-scale spiking studies were performed to further characterize the ability of the process to clear DNA. Repeated use of columns and extractable and leakage is also in general well addressed.

The applicant does not claim a full design space but merely a verification of PARs. Nevertheless, the process characterisation is considered, to a great extent, being in line with the requirements for "an enhanced, quality by design approach" as described in the ICH Q8 guideline for process development. In general, the approach of development of the process control strategy is endorsed. Moreover, as supported by further process development data submitted with the response to the LoQ the results are considered to be shown in sufficient detail to support the claim of a well-controlled process.

The down-scaling study showed in most cases similar or better performance at commercial scale compared to the small scale, however, sometimes the opposite was found. The scale differences have been acceptably accounted for in the development, and it has been acceptably addressed how the remaining source of uncertainty at full scale would be handled if ranges beyond those, qualified during PPQ would be applied.

Process validation

In summary, an adequate strategy for validation of each of the process phases (fermentation, recovery and purification) was established. The Process Performance Qualification (PPQ) campaign indicated process performance and consistency in control of critical process parameters (CPPs), process yields and microbial control throughout the purification process. Results of the PPQ campaign indicate that the levels of process residuals and impurities described met acceptance criteria.

Although the applicant does not explicitly refer to an "enhanced approach" in terms of "Quality by design" or "design space", proven acceptable ranges beyond the normal operational ranges are claimed. The strategy for validation of each of the process phases consists of both laboratory and manufacturing scale evaluations of critical process parameters, in-process controls, and in-process specifications. Studies were first performed using a validated small-scale model to establish the proven acceptable ranges of process parameters.

The PPQ was executed with four full scale batches from vial thaw through purification. Thereby, normal operational ranges were in general targeted. The dual lines of equipment in place for steps 1-5 were included in the validation. Extended cell age was established during the Clinical Campaign batches. The cell age for the PPQ batches were less than the maximum extended number of generations studied for in vitro cell age (IVCA).

The purification process was validated with the same four batches employed for the validation of the fermentation process. In addition to the routine critical process parameters and in-process controls, criteria for extended controls of CQAs analysed in eluates were included in the validation, along with monitoring of DNA and HCP and other process derived impurities. Consistency was moreover evaluated for the non-critical parameters and attributes, such as yield.

The numeric acceptance criteria for the outputs, including CQA were based on a statistical review and analysis of the data from clinical manufacturing batches and additional small-scale studies.

Results were shown compliant with the acceptance criteria. The normal operating ranges (NOR) and the proven acceptance ranges, (PAR) both as derived from the Process characterisation were indicated when relevant.

The validation of in-process hold times was determined based on microbial and biochemical hold studies, as assessed by incubation of samples withdrawn from fractions of commercial scale processing. Additional studies were completed to validate BDS freezing and shipping procedures.

Worst case scenarios based on small scale batches have set the upper limits for resin lifetime and UF/DF membranes reuse. The commercial scale resin lifetime studies will be used to determine the maximum number of cycles for each chromatography column based on product yield, microbial levels, and product purity when a sufficient number of cycles have been run on each column to assess data trends. Effective cleaning procedures used for the reuse of resins and membranes have been demonstrated.

It is declared by a short statement that, as part of continued process verification (CPV), ongoing monitoring, trending and review will be conducted to assure that during routine production the process remains in a state of control. It is stated that risk management, together with any continuous improvement opportunities, will be applied throughout the product lifecycle to maintain the control strategy to meet product quality requirements. The CPV is acknowledged as an appropriate measure in line with GMP, but it is not taken into account in the judgement of the process validation, as such.

In general the results are considered supportive for the claim of a well controlled process. Clarifications requested in the primary assessment in conjunction with the process development and characterisation, have been acceptably provided.

Characterisation

The extent of characterisation data provided is well within the standards for a recombinant product and also includes comparability data between process 2 (pivotal clinical batches) and process 3 (commercial product). Significant findings relevant for comparability have already been discussed in the section on process development above.

Specification

Specifications for albiglutide active substance are sufficiently justified. The applicant has provided extensive forced degradation/stress studies to demonstrate that appropriate release methods are in place. With the response to the LoQ D120, the active substance specifications were revised and several limits were tightened and the release and shelf life specifications are the same now. The 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 specifications include tests for appearance, identity, purity, potency, and quantity. The applicant sufficiently justified not to include specifications for some impurities.

Analytical methods

The analytical assays for active substance testing and their validation are deemed acceptable. Additional information was provided for some analytical assays upon request and was deemed sufficient.

Batch data

The batch analysis data presented for Process 3 batches (Commercial, Qualification, and Clinical/Stability) complies with the active substance specification in place at the time of testing, and demonstrates manufacturing consistency. In addition results from Process 2 batches and Process 1 batches are presented.

Reference material

There is no international reference standard for albiglutide. All reference standard batches manufactured to date are described by results from release and characterisation testing. In stability studies no significant changes were observed by any of the stability indicating assays at the recommended storage conditions.

Qualification of new reference standards are described in the dossier and are found acceptable. Every new reference standard will be qualified against RS-P3 which is considered the primary reference standard.

Container closure system

The container closure system for albiglutide active substance is a plastic bottle with a lined polypropylene screw cap closure. Compliance of components of the container closure system with EP, USP and FDA requirements is stated.

Stability

Sufficient stability data has been provided to support the proposed shelf life of the active substance. The stability data are obtained with tests which are a subset of the tests from the release specifications selected for stability indicating properties.

Comparability exercise for Active Substance

Manufacturing Process Development History

In summary, the development of albiglutide DS encompassed various site, scale, and manufacturing process changes to accommodate requirements for increased scale of manufacture and to optimize individual processing steps for improvement of product quality and manufacturing productivity. Changes have sufficiently been described.

Comparability

Overall, based upon biochemical, biophysical and clinical assessments, comparability has been established between the phase III product produced with process 2 active substance and the commercial product manufactured with Process 3 active substance.

The exercise for demonstration of comparability involves comparison of batch data of active substance and drug product, extended characterization, comparison of degradation profiles and clinical bioequivalence studies. The strategy chosen is considered well in line with the guideline ICH Q5E, "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process". A variety of characterization techniques were employed to elucidate the structure of the molecule and to compare Process 2 and Process 3. Most important, no new impurities were found. The results of structural characterization and functionality were assessed as highly similar for Process 2 and Process 3, albeit with a few differences.

In addition to analytical comparability, possible impact on pharmacokinetics or safety and efficacy of differences observed between Process 2 and Process 3 active substance has been clinically evaluated using Process 2 and Process 3 products. By reference to the assessment of the response to the clinical safety issue which was raised in this context, this comparability issue is considered as solved.

2.2.3. Finished Medicinal Product

Description and composition of drug product

Albiglutide drug product is presented as a lyophilized product in a 30 mg or 50 mg single use pen injector assembled with a dual chamber cartridge (DCC), the deliverable volume is 0.5 ml. The front chamber contains albiglutide in a lyophilised cake prepared from aqueous solution containing sodium phosphate, mannitol, trehalose andpolysorbate 80. The rear chamber is filled with the diluent water for injection. The DCC is assembled in the pen injector by an automated process.

The Dual Chamber Cartridge (DCC) is a Type 1 glass barrel with rubber stoppers and a rubber closure disc. The pen which houses the DCC is composed of a clear plastic cartridge holder and a plastic pen mechanics sub-assembly and is supplied with a CE marked 29G, thin walled, 5-mm pen needle.

Pharmaceutical Development

The data presented on pharmaceutical development is at large considered satisfactory. A comprehensive list of the manufacturing lineage of albiglutide drug product batches used in clinical studies and development is provided.

Formulation and process development

The applicant has decided to formulate the dose of albiglutide as strength (mg/DCC) and not by specific biological activity. A link has been established between biological activity (potency assay) and amount of protein. Formulation development studies have been presented and drug product overfill studies were performed to deliver 0.5 mL with a target protein concentrations of 62 and 103 mg/mL respectively.

The development of the lyophilisation cycle is well described.

Development results indicate that there is a direct relationship between protein concentration and reconstitution time and that a longer reconstitution time therefore is needed for the 50 mg strength compared to the 30 mg strength. Therefore, in the patient leaflet the patient is instructed to wait for 15 and 30 minutes respectively for the powder and water to fully mix. The applicant recommends that the drug product be administered within 8 hours after reconstitution. There are slight changes in purity observed after 8 hours under ambient light and temperature conditions which is consistent with the known effects of light exposure for liquid forms of albiglutide but all proposed acceptance criteria were met for all assays at 8 hours.

DCC and pen-injector

The pen injector is specially designed and developed for the albiglutide drug product. The albiglutide pen injector was designed in accordance with the Medical Device Directive (93/42/EEC) and ISO 13485:2003 "Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes". Operation of the pen is satisfactorily documented and the critical attribute is volume delivered.

The combination of the dual chamber cartridge and the pen injector forms a single integral product, and is not considered as separate medical device. However, the relevant essential requirements of Annex 1 to the Medical Device Directive (MDD) shall apply as far as the safety and performance-related device features are concerned.

The Applicant has provided a Human Factors study investigating the usability of the pen device and IFU. The study was well designed and the provided data are considered sufficient to conclude that the IFU provides adequate information for a correct handling of the pen and that the pen design is adequate and allows safe use. Adequate instructions for use are proved in the SPC and labelling.

Adventitious agents

No animal-derived materials are used in the commercial manufacturing process for albiglutide active substance or drug product, nor in the manufacture of the MCB or WCB. All media components used in the fermentation and purification process are synthetic, biosynthetic or plant derived. Salmon sperm DNA and Yeast extract/ Peptone Y were used early in the development of the production cell line, specifically the Accession Cell Bank (3610, Y1G9).

Since Albiglutide is produced in *Saccharomyces cerevisiae* and no human or animal derived components are used during the commercial manufacturing process the risk for transmission of adventitious agents is found to be negligible.

Manufacture of the product

Manufacturing process and process controls

Manufacture is overall adequately described and there are no intermediates during manufacture. Critical in-process controls were determined based on product and process understanding and utilisation of risk management principles. In process controls are well justified for all steps.

Briefly, drug product manufacturing consists of thawing, pooling and mixing of bulk active substance, dilution to a target concentration using an excipient solution and aseptic filling of active substance in the front chamber of the dual chamber cartridge, lyophilisation and aseptic

filling of WFI in the rear chamber and finally assembly into pen injectors. The sample volume for bioburden testing has been increased from 10 to 100 ml and a pre-filtration limit of 10 cfu/100 ml is applied.

All steps of pen assembly, including labelling, are fully automated and a flow diagram of the pen injector automated assembly and labelling processes is provided including information on holding times, temperatures etc. It has been verified that the applied conditions do not have a negative impact on the quality and integrity of the final drug product.

Process validation

For the process validation studies 6 batches, 3 of each strength, were produced at the commercial batch size. Hold times, mixing parameters, lyophilization parameters were not tested at their upper limits during PPQ as these were extensively characterized for development batches in the commercial facility. This is found acceptable. Pen assembly was validated using three lots representative of commercial production.

The validation studies have demonstrated that the sterilising filters are appropriate for their intended use. Results and requirements for the media fill validation cover the maximum duration of filling and are in line with current EU requirements.

It has been demonstrated during process development and validation that a homogenous solution is obtained prior to filling of the front chamber. All validation batches complied with the established in-process and release specifications. No critical deviations were observed. In conclusion, the drug product manufacturing process has sufficiently been validated.

Control of excipients

All excipients comply with the requirements in their respective pharmacopoeial monographs (Ph Eur or USP) and pharmacopoeial methods are used for testing. No excipients of human or animal origin are used in the manufacture of the drug product.

Product specification

The drug product release and shelf-life specifications are found suitable for control of the drug productand include tests for appearance, identity, purity, potency, quantity and pen injector functionality. Several limits have been tightened and acceptance criteria for sub-visible particles have been included as requested. Microbiological quality is adequately assured during manufacture. The methods used for routine control are deduced from the characterisation studies, and the specification limits are set in line with batch data, including batches used in clinical trials.

Batch data

The batch analysis data presented for commercial batches for the 30 mg and the 50 mg strength complies with the limits in the proposed drug product specification.

Container closure system

The container closure system is adequately described. Suitability of the glass cartridge as primary packaging is demonstrated with respect to container closure integrity, moisture

permeation and light exposure. Functionality of the chamber is adequately documented to deliver 0.5 ml for injection.

Stability of the product

The submitted stability data sufficiently justify the proposed shelf life of the drug product.

At time of CHMP opinion real time stability data for the commercial scale batches of the drug product, both for the 30 and 50 mg strengths (with process 3 active substance) cover 24 months storage at 2-8 ºC and several dual storage time points at 30°C. In accordance with the ICH Q5C guideline the expiration dating should be based on real-time/real-temperature data. Therefore, the data available at time of CHMP opinion support a shelf-life of 24 months at 2-8 ºC with up to 4 weeks at ≤ 30°C.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In summary, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrates consistent batch-to-batch production of Eperzan achieving a well-defined quality for the active substance and the drug product. The fermentation, recovery and purification of the active substance, albiglutide, are adequately controlled and validated. Appropriate active substance specifications have been set. The active substance has been well characterised using state-of the-art methods with regard to its physicochemical characteristics. The manufacturing process of the drug product has been described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications. The data presented support the shelf-life proposed for active substance or drug product. No excipients of human or animal origin are used in the product manufacture and therefore there is no risk of contamination with viral or TSE agents by these ingredients. Recommendations for future quality development are not given at time of positive opinion.

Although the applicant does not explicitly refer to an "enhanced approach" in terms of "Quality by design" or "design space", proven acceptable ranges, beyond the normal operational range, are claimed. In general the approach of development of the process control strategy for albiglutide active substance manufacture is endorsed. Moreover, additional data submitted during the procedure and the results shown are considered in sufficient detail to be supportive for the claim of a well-controlled process.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Eperzan 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.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

Albiglutide is a GLP-1R agonist generated through genetic fusion of two tandem copies of modified human GLP-1 to human albumin, developed by GlaxoSmithKline. The human albumin moiety of the recombinant fusion protein, together with engineered resistance to dipeptidyl peptidase IV (DPP-IV), greatly extends the half-life allowing once weekly dosing by subcutaneous (sc) injection. Albiglutide is produced in Saccaromyces cerevisiae by recombinant DNA technology.

During development, changes in the manufacturing process for albiglutide have been conducted. The majority of studies in the non-clinical development program were conducted using albiglutide manufactured by the initial small-scale production process that was used in phase I and phase II clnicial trials (Process 1). In support of phase III clinical trials, albiglutide manufacturing was modified (referred to as Process 2) and a selected number of non-clinical studies were conducted with this material. The product for commercial use is however manufactured in an improved process referred to as Process 3. Material from Process 3 has not been tested in the non-clinical program.

Safety pharmacology studies were GLP-compliant. Many of the pharmacokinetic studies are not in accordance with GLP. This is however not considered to have any negative impact on the results or assessment. Toxicokinetic data from the pivotal toxicology studies were analysed according to GLP. Pivotal studies on general and reproductive toxicity were conducted according to GLP regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Albiglutide is a recombinant fusion protein consisting of two copies of a 30-amino acid sequence of modified human glucagon-like peptide 1 (GLP-1, fragment 7-36) genetically linked in series to human albumin. The interaction of albiglutide with the human GLP-1R and activation of adenylate cyclase was assessed in human embryonic kidney epithelial cells expressing the human GLP receptor (HEK293-hGLP-1R). Albiglutide was less potent in the stimulation of cAMP accumulation (EC_{50} = 0.24 nM) than GLP-1 (EC_{50} = 0.019 nM).

Aggregate findings of in vitro and in vivo effects of albiglutide in nonclinical species are consistent with those observed with other GLP-1R agonists in humans and nonclinical species, and support a beneficial effect on fuel homeostasis in T2DM.

In vitro and in vivo pharmacology studies revealed:

- increased insulin secretion

- improved insulin sensitivity
- increased beta cell mass (albiglutide was comparable to exendin-4 regarding to stimulation of beta cell proliferation, inhibition of islet cell apoptosis, and degree of islet associated connective tissue
- reduced food consumption and body weight
- slowed gastric emptying

Secondary pharmacodynamic studies

Effects of albiglutide on cardiovascular and respiratory systems have been investigated in male cynomolgus monkeys following subcutaneous administration in a combined safety pharmacology study. Qualitative neurobehavioral assessment of central nervous system (CNS) has been performed as a part of a repeat dose toxicity study. Albiglutide had no apparent effects on cardiovascular function, heart rate, electrocardiographic intervals or respiratory function and did not produce any evidence of electrocardiographic waveform abnormalities or arrhythmias. Furthermore, there were no albiglutide-related effects on neurobehavioral functional assessments. Safety margin of 55-fold towards highest estimated steady state human plasma concentration at 50 mg dose was established.

2.3.3. Pharmacokinetics

Nonclinical studies were performed in mice and monkeys to study pharmacokinetics of albiglutide. There were no significant differences between the sexes. A higher systemic exposure was achieved in monkeys compared to mice. In mice, terminal half-life after intravenous injection was 8 hours. In the monkey half-life after sc injection was approximately 40-60 hrs. Together, the binding to the Fc receptor along with the DPP-IV resistance, greatly extends the half-life of albiglutide relative to native GLP-1 (1.5 to 5 minutes). The half-life in man is several days (3-10 days).

No studies were performed on distribution, metabolism or excretion, since such studies are not considered informative for a recombinant protein.

2.3.4. Toxicology

Mouse and cynomolgus monkey were selected as species for toxicology studies. Both species are pharmacologically relevant. Mouse was selected as the rodent species rather than rat because of the large body of GLP-1 related pharmacology data in mouse, and rat offered no advantages with regards to immunogenicity.

The majority of studies in the nonclinical development program were conducted using albiglutide manufactured by Process 1. A selected number of pivotal nonclinical studies, including a 52 week monkey study, were conducted with material from Process 2. Nonclinical studies have confirmed comparable efficacy and pharmacokinetics between Process 1 and 2. In anticipation of commercialization, the active substance manufacturing process was improved (referred to hereafter as Process 3). Biochemical and bioanalytical testing demonstrate that Process 2 and Process 3 material are comparable with the exception of approximately 2 times higher levels of

oxidized methionines in Process 3 material, a targeted reduction in Process 3 of the inactive 6-AA product-related impurity and a reduction in protease activity in Process 3. The higher levels of oxidized methionines in these albiglutide product-related substances are predominantly due to increased levels of oxidation at two of six methionines in the albumin portion of albiglutide.

Nonclinical studies with Process 3 active substance were not conducted since the oxidized methionine levels found in Process 3 were considered qualified in the 52 week monkey study, due to adequate margins of safety on a body weight basis for the oxidized methionines. Albumin is considered the major and predominant antioxidant in plasma. Methionine is particularly susceptible to oxidation, leading to methionine sulfoxide, and oxidation and reduction of methionine is proposed as a ROS scavenging system to protect proteins from modifications. Consequently, the added body burden of oxidized methionine by albiglutide is not considered a safety issue in itself. However, it has been postulated that oxidization of methionine in peptides/proteins may alter receptor affinities, pharmacodynamic effects, pharmacokinetics and potential toxicity.

Single dose toxicity

Single dose toxicity studies in mice and monkeys did not show any unexpected findings. High doses were tolerated, i.e. up to 1000 mg/kg subcutaneously and up to 500 mg/kg intravenously.

Repeat dose toxicity

Repeat-dose toxicity was studied up to 14 days duration in mice and monkey. Long-term toxicity was studied in the cynomolgus monkey only due to ADA, which limited duration of studies in mice to 14 days. Repeat dose toxicity studies with weekly sc administration for 4 weeks, 5 weeks, 26 weeks and 52 weeks were performed in cynomolgus monkeys The findings observed in the monkey were effects based on pharmacological effects of albiglutide, i.e. decreased food consumption and decreased body weight gain or body weight loss. High exposure multiples to clinical exposure were reached (~70-fold AUC at the highest dose 50 mg/kg). Since systemic exposure was high in the monkey, the general toxicity of albiglutide is appropriately studied, however, only in one species.

In the 52-week monkey study there was a tendency of increased pancreas weight at the 50 mg/kg dose group, more pronounced in males than in females. There were no significant differences in systemic exposure between males and females. A special investigative study was performed by the applicant to estimate cell number and volume of acinar, ductal and islet cells by using stereological methods. The high dose group 50 mg/kg given albiglutide and a control group given a vehicle were included in the analysis. The applicant's conclusion of the results was that "the quantitative assessment of islet, ductal and acinar cell number and compartment volume by stereology, in combination with qualitative Ki67 immunohistochemistry and routine microscopic evaluation of pancreas, indicate that the marginal pancreatic tissue weight increases observed in monkeys given 50 mg/kg/week albiglutide for 52 weeks were associated largely with increased volume of the acinar subcompartment and there was no evidence of ongoing proliferative events or morphologic abnormalities. Increased islet cell number noted in monkeys given 50 mg/kg/week was considered to be pharmacologically-mediated, not associated with ongoing proliferation and was not considered to be contributory to the overall increase in pancreatic weight."

In the investigative pancreas study (Study No I11223), immunohistochemical staining with a panel of markers for islet cells (insulin, glucagon, somatostatin, pancreatic polypeptide), ducts/ductules (AE1/AE3) and proliferation (Ki-67) was performed. The evaluation of these stainings was conducted by subjective assessment, without any quantitative or semi-quantitative analysis.

Carcinogenicity

No carcinogenicity studies have been conducted. Because of the emergence of clearing anti-albiglutide antibodies by 14 days in rodents, meaningful 2-year studies in rats or mice are not feasible.

The applicant has discussed the potential risk for thyroid tumours seen with other GLP-1R agonists. There were no thyroid findings in monkeys treated for 52 weeks. It is however, agreed that these negative findings in the monkey do not negate the C-cell proliferative effects seen in rodents with other GLP-1R agonists. To better understand how nonclinical rodent and monkey data extrapolates to human, studies are ongoing to examine GLP-1R distribution in thyroid (and pancreas) from healthy, untreated rodents and monkeys compared to humans.

In order to evaluate the potential for abliglutide to induce calcitonin increase and C-cell hyperplasia, feasibility tests were performed in immunocompromised (mu-deficient) mice. While the model was suitable for generating liraglutide related calcitonin release and C-cell hyperplasia, potential effects of albiglutide could not be addressed due to an unexpected decrease in albiglutide exposure between dosing day 7 and 21. The mechanism for this decrease is unknown, but the unpredictable toxicokinetic profile in this strain of mice indicates that they are not suitable for assessing potential effects of albiglutide on thyroid C-cell hyperplasia. However, a dose-dependent increase in plasma calcitonin levels was observed in male and female mice 24h post dose at dosing day 7, indicating that albiglutide, like other GLP-1R agonists, do have the potential to cause C-cell hyperplasia and thyroid tumours in rodents.

Reproduction Toxicity

Reproductive and developmental toxicity was studied in the mouse only. In the mouse embryofoetal developmental study, bent ribs were observed at the high dose level (50 mg/kg). According to the Applicant this is due to maternal toxicity. No toxicokinetics was performed on pregnant mice. Calculations on exposure margins were based on data from studies in nonpregnant mice. Safety margins to NOAEL was ≤5-fold compared to human exposure in terms of AUC at 50 mg human dose.

Peri and postnatal studies showed the following:

All reproductive capacity parameters for the F1 generation (mating, fertility, mating index, average number of days in cohabitation and estrous cycling) were comparable among all dose groups. The mean duration of gestation was comparable among all dose groups. There were no test article-related effects on litter size, pup survival and clinical observations or mean body weights in the F2 generation pups. The NOAEL for maternal (F0) reproductive function was 50 mg/kg/day and for the postnatal development of the offspring in F1 mice was <1 mg/kg/day based on slightly decreased pre-weaning body weight gain at all doses. There were no AUC based safety margins calculated by the Applicant.

2.3.5. Ecotoxicity/environmental risk assessment

Albiglutide is a recombinant protein. No risk to the environment from the use of albiglutide is expected.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The pharmacology program is considered sufficient. No issues for the safety evaluation have been identified.

Pharmacokinetics

The pharmacokinetics program is sufficient and there are no issues.

Toxicology

No toxicity studies with the commercial Process 3 active substance were performed. The oxidized methionine levels found in Process 3 were considered qualified in the 52 week monkey study, due to adequate margins of safety on a body weight basis for the oxidized methionines. Albumin is considered the major and predominant antioxidant in plasma. Methionine is particularly susceptible to oxidation, leading to methionine sulfoxide, and oxidation and reduction of methionine is proposed as a ROS scavenging system to protect proteins from modifications. Consequently, the added body burden of oxidized methionine by albiglutide is not considered a safety issue in itself. However, it has been postulated that oxidization of methionine in peptides/proteins may alter receptor affinities, pharmacodynamic effects, pharmacokinetics and potential toxicity.

Based on the fact that the methionines are situated on the albumine component and not on the GLP-1 receptor binding component, that albiglutide from Process 2 and 3 appears to be equally potent in a cAMP bioassay (provided that the applicant can verify the cAMP bioassay for Process 3), and that existing clinical data have demonstrated comparable clinical pharmacokinetic and efficacy properties between the two processes, the lack of non-clinical studies with albiglutide from process 3 is not considered as a major deficiency. Animal studies are not considered useful in terms of predicting potential immunogenicity of human or humanized proteins in patients, and the lack of non-clinical antigenicity studies with material from Process 3 is therefore acceptable. The potential for differences in immunogenic properties between materials from different manufacturing processes can only be determined in patients.

Chronic toxicity was only studied in monkeys, due to the emergence of clearing ADA in mice after two weeks. The findings observed in the monkey were effects based on pharmacological effects of albiglutide, i.e. decreased food consumption and decreased body weight gain or body weight loss. Since systemic exposure was high in the monkey, the general toxicity of albiglutide is appropriately studied, however, only in one species.

A safety concern regarding GLP-1 receptor agonists and potential increased risk of pancreatic neoplasias has recently been discussed by the CHMP. The outcome from this procedure was that there is no evidence for such risk based on available data. For albiglutide, a tendency of increased pancreaas weight and a significant increase in islet cell number was observed in

monkeys. These issues were further discussed by the Applicant. It is agreed that these minor findings, with no associated pathological changes, are of no concern for the safety evaluation.

No carcinogenicity studies have been conducted. It is agreed that 2-year studies in rats or mice are not feasible due to the emergence of ADA. As concluded by the applicant the absence of thyroid findings in monkeys do not negate the findings on thyroid C-cell neoplasia seen with other members of the class. Also for these, there were no findings in monkeys. The applicant has presented initial studies in immunocompromised (mu-deficient) mice to evaluate the potential of albiglutide to induce calcitonin increase and C-cell focal hyperplasia relative to liraglutided. These studies showed that these mice were not suitable for long-term studies due to an early decrease in systemic exposure. However, the finding of increased calcitonin levels after 7 days support the view that albiglutide shares the C-cell tumorigenic properties with other members of the class. A study on characterization of GLP-1R distribution in rodent, monkey and human thyroid is ongoing. When finalised, the data will be submitted.

Mouse was selected as rodent species for toxicology studies. While this is acceptable, mouse has some limitations for reproduction toxicity studies such as having fast metabolism, being stress sensitive, and foetuses are very small, making foetal evaluations difficult. In the mouse embryo-foetal developmental study, bent ribs were observed at the high dose level (50 mg/kg). According to the Applicant this is due to maternal toxicity, however, the picture of the finding is not entirely as typical caused by maternal toxicity (foetal weight was not decreased).

No toxicokinetics was performed on pregnant mice. Calculations on exposure margins were based on data from studies in nonpregnant mice. While initial exposure would be expected to result in high multiples to clinical exposure, the emergence of ADA will result in lower exposures in the later part of the study. As discussed by the Applicant in the response to the Day 120 LoQ, exposure throughout organogeneis could be demonstrated. However, due to the lack of complete toxicokinetic data in pregnant animals, and the uncertainities in extrapolating from data in non-pregnant animals, no clear figures on safety margins can be derived. Based on the available data it can however be concluded that such margins would be low or non-existing.

Embryofoetal development was only studied in mice. For other members of the class, there have been common findings likely to be related to the pharmacologically mediated effect on food intake. These findings were generally limited to skeletal variations. However, there are differences within the class. Thus, lixisenatide demonstrated a number of malformations in rats and rabbits, both skeletal and visceral, and it was concluded that there may be other mechanisms than maternal toxicity for embryofetal toxicity. As a result, the conclusions on the embryofoetal toxicity and the resulting recommendations on use during pregnancy and in women of child-bearing potential differ between the products. While a clearer picture of the teratogenic potential of albiglutide in relation to other members of this class could be acquired from a study in a second species, it is likely that the rabbit would not be suitable for this purpose since a strong immune response to albiglutide would likely develop in this species. Also, further studies in non-human primates cannot be justified. The conclusion drawn from the mouse study, and the information given in the product information is considered adequate (however, with no figures on safety margins). The strict recommendations for use during pregnancy and in women of childbearing potential (in line with the previously agreed text for another GLP-1 receptor agonist product, exenatide once weekly, and in both cases primarily based on the long wash-out period), are appropriate.

2.3.7. Conclusion on the non-clinical aspects

Some revisions in SmPC section 5.3 were implemented and all non-clinical issues raised had been satisfactorily addressed during the procedure.

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

Table 5 Overview of Study Design for Albiglutide Phase II and Phase III Efficacy Studies

Study	Design	Population	Number of Subjects Randomly Assigned[1]	Background Therapy	Treatment Arms	Primary Efficacy Endpoint	Duration of Follow-Up [Treatment Period][2]	Study Status/ Database Freeze (Completed Studies) or Data Cut-Off Date
GLP112753	Randomized, double-blind, placebo and active control	T2DM, inadequate glycemic control on current background therapy	1049 (315)	MET	1. Placebo. 2. Albiglutide (30 mg weekly, optional[3] uptitration to 50 mg weekly). 3. Glimepiride (2 mg daily, optional uptitration to 4 mg daily). 4. Sitagliptin (100 mg/day).	104 weeks	52 weeks; double-blind; [156 weeks]	All subjects completed at least 2 years of treatment Data cut-off date: 27 Feb 2012
GLP112754	Randomized, open-label, active control	T2DM, inadequate glycemic control on current background therapy	779 (516)	MET or MET + SU	1. Albiglutide (30 mg weekly, optional uptitration to 50 mg weekly). 2. Insulin glargine (10 units daily, optional uptitration per package insert).	52 weeks	104 weeks open-label; [156 weeks]	All subjects completed at least 2 years of treatment Data cut-off date: 01 Mar 2012
GLP112755	Randomized, double-blind, placebo control	T2DM, inadequate glycemic control on current background therapy	310 (155)	PIO or PIO + MET	1. Placebo. 2. Albiglutide (30 mg weekly, no uptitration).	52 weeks	104 weeks; double-blind; [156 weeks]	All subjects completed at least 2 years of treatment Data cut-off date: 20 Dec 2011
GLP112756	Randomized, double-blind, placebo control	T2DM, drug naïve and inadequate control on diet and exercise	309 (204)	Diet & Exercise	1. Placebo. 2. Albiglutide (30 mg weekly). 3. Albiglutide (30 mg weekly from Baseline to Week 12 with forced uptitration to 50 mg weekly at Week 12.	52 weeks	104 weeks; double-blind; [156 weeks]	All subjects completed at least 2 years of treatment Data cut-off date: 08 Mar 2012

Study	Design	Population	Number of Subjects Randomly Assigned[1]	Background Therapy	Treatment Arms	Primary Efficacy Endpoint	Duration of Follow-Up [Treatment Period][2]	Study Status/ Database Freeze (Completed Studies) or Data Cut-Off Date
GLP112757	Randomized, double-blind, placebo and active control	T2DM, inadequate glycemic control on current background therapy	685 (281)	MET + GLIM	1. Placebo. 2. Albiglutide 30 mg weekly, optional uptitration to 50 mg weekly). 3. PIO 30 mg weekly, optional uptitration to 45 mg weekly).	52 weeks	104 weeks; double-blind; [156 weeks]	All subjects completed at least 2 years of treatment. Data cut-off date: 22 Feb 2012
GLP108486	Randomized, open-label, active control	T2DM, inadequate glycemic control on current background therapy	586 (292)	Glargine or glargine + other oral agents	1. Albiglutide (30 mg weekly with optional uptitration to 50 mg weekly. 2. Lispro insulin.	26 weeks	26 weeks; open-label; [52 weeks]	Study complete[3] Database freeze[4] 12 Mar 2012
GLP114179	Randomized, open-label, active control	T2DM, inadequate glycemic control on current background therapy	841 (422)	MET, SU and TZD either alone or in combination	1. Albiglutide (30 mg once per week with forced uptitration to 50 mg weekly at Week 6). 2. Liraglutide (forced uptitration - 0.6 mg daily for the first week, 1.2 mg at Week 1, and 1.8 mg at Week 2 per package insert).	32 weeks	none	Study complete. Database freeze 28 Oct 2011
GLP114130	Randomized, double-blind, active control	T2DM, inadequate glycemic control, renal impairment	507 (254)	Diet & Exercise or other OAD therapy (MET, TZD and SU either alone or in combination	1. Albiglutide 30 mg weekly, optional uptitration to 50 mg weekly + sitagliptin placebo. 2. Sitagliptin 25, 50 or 100 mg/day per severity of renal impairment+ albiglutide placebo.	26 weeks	26 weeks; double-blind; [52 weeks]	Study complete. Database freeze: 15 June 2012

Study	Design	Population	Number of Subjects Randomly Assigned[1]	Background Therapy	Treatment Arms	Primary Efficacy Endpoint	Duration of Follow-Up [Treatment Period][2]	Study Status/ Database Freeze (Completed Studies) or Data Cut-Off Date
Phase IIB								
GLP110125	Randomized, double-blind, placebo control, with open-label active reference	T2DM, inadequate glycemic control on current background therapy	361 (326)	Diet & Exercise or MET	1. Exenatide 5 µg BID for 4 weeks, then 10 µg BID for 12 weeks. 2. Albiglutide 4 mg weekly. 3. Albiglutide 15 mg weekly. 4. Albiglutide 30 mg weekly. 5. Albiglutide 15 mg every other week. 6. Albiglutide 30 mg every other week. 7. Albiglutide 50 mg every other week. 8. Albiglutide 50 mg every 4 weeks. 9. Albiglutide 100 mg every 4 weeks. 10. Placebo weekly.	16 weeks	8 weeks [16 weeks]	Study complete.
GLP110932	Randomized, double-blind, placebo control	Japanese T2DM	215 (161)	Diet & Exercise or one OAD	1. Albiglutide 15 mg weekly. 2. Albiglutide 30 mg weekly. 3. Albiglutide 30 mg every other week. 4. Placebo weekly.	16 weeks	8 weeks [16 weeks]	Study complete.

MET = metformin; SU = sulfonylurea; PIO = pioglitazone; OAD = oral antidiabetic medications.
1. In parentheses is the number of subjects randomly assigned to treatment with albiglutide.
2. Planned total treatment period once the study is completed.
3. Optional uptitration occurred as a single event after a certain number of weeks on study, as needed based upon protocol-specified criteria (see Section 1.4.1) and physician judgement, and was treatment-masked in blinded studies. Uptitrated subjects were required to remain at the higher dose level for the remainder of study participation.
4. The GSK108486 database was originally frozen 23 Nov 2011. It was opened and re-frozen on 12 Mar 2012; see CSR GLP108486, Section 4.8.1.1 for details.

2.4.2. Pharmacokinetics

For an NCE, the Clinical Pharmacology program should aim at describing the disposition of the substance, identify sub-groups of patients in which exposure might be altered, and potential interactions with other medical products.

Albiglutide is a recombinant fusion protein with a molecular weight of approximately 73 kDa and is to be administered via subcutaneous injection. Therefore, the lack of mass-balance, food effect, absolute bioavailability and mechanistic drug-drug interaction studies are acceptable.

In general, the albiglutide bioanalytical methods are acceptable. However, a shift in albiglutide concentration was identified and subsequently could be attributed to switching from manual to robotic pipetting in the sample handling.

Clinical comparability, based on PK parameters, between process 2 and 3 albiglutide was shown in vivo. The comparability between active substance from process 1, used in the initial characterisation of albiglutide, and active substance from process 2 or 3 were based on quality and preclinical data.

Absorption

Albiglutide is administered subcutaneously and based on its molecular weight (73 kDa), the primary route of absorption is likely to be lymphatic circulation. Different injection sites (abdomen, leg and arm) did not impact the exposure of albiglutide.

Distribution

The apparent volume of distribution after a single dose of albiglutide was 8.2-18.5 L. Albiglutide steady state was reached after 3-4 weeks and was accumulated 1.5-2 times after repeated dosing. Albiglutide is dose proportional in the clinical relevant range (30-50 mg).

Elimination

The half-life of albiglutide was 3.6-6.8 days for subjects with type 2 diabetes and the mean population estimate of apparent clearance (CL/F) was 67 mL/hr, based on the population PK analysis (see below). The expected metabolic pathway of albiglutide is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes.

Dose proportionality and time dependencies

Population PK analysis

Population PK (PPK) analyses were conducted using non-linear mixed effects modelling methods implemented in NONMEM, version 7.2 to describe the PPK of albiglutide.

The PPK analysis of phase III albiglutide data included data pooled from four studies (GLP112754, GLP112756, GLP112757, GLP114130) in patients with T2DM receiving albiglutide either alone or in combination with other anti diabetic medications. GLP114130 was a study in renally impaired TD2M subjects. A total of 1113 subjects were included in the PK analysis (study 125754 n= 454, study 112756 n=184, study 223868 n=247, study 114130 n=247).

A one-compartment model with a first order absorption and elimination process was found to describe the PPK of albiglutide. Inter-individual variability was estimated for CL/F only. An assay shift factor (proportionality constant) was estimated to account for and quantifying the magnitude of the shift in bioanalytical assay. The estimated factor (0.61) was in accordance with the difference estimated by incurred sample reanalysis (0.67). For the effect of body weight, eGFR, race and co-administration of insulin see special populations section below.

The model predicted average albiglutide concentration at steady state in a typical individual receiving a dose of 30 and 50 mg was 2681 and 4469 ng/ml, respectively.

Special populations

The results of the renal impairment study were affected by the earlier described bioanalytical shift in albiglutide concentration and therefore the results are not consistent between the two stages included in the study. Recalculateddata suggested a 30-40% increase in exposure in subjects with severe renal impairment as compared to subjects with normal renal function. This is in line with the PPK data were CL/F was decreased approximately 30% (from normal) in severe renal impairment.

No formal studies of albiglutide have been performed in patients with hepatic impairment.

The effect of weight, gender, race and age on the PK of albiglutide was evaluated in the PPK analysis with weight and race identified as significant covariates on CL/F. A nearly proportional change in CL/F with weight was estimated corresponding to a decrease by 50% in CL/F and an increase by 67% for subjects with minimum/maximum body weight (44 and 157 kg), compared to the typical value observed with a mean body weight of 92 kg.

Age was not formally included as a covariate but was found to correlate with CL/F and explained differences in CL/F to almost the same degree as eGFR. A decreased CL/F with age was observed. However, it was not possible to distinguish the effect of eGFR and age due to high correlation between the two covariates. As eGFR exhibited a slightly greater drop in objective function value it was retained in the final model.

African American/African heritage racial group was associated with a 22% lower CL/F than other racial groups which is considered not being clinical relevant.

Based on comparison between the estimated CL/F in the phase II study GLP110125 (n= 267) and study in GLP110932 in Japanese patients (n=215) the exposure was 30 to 40% higher in Japanese patients than Caucasians.

No studies have been conducted to investigate the pharmacokinetics of albiglutide in paediatric patients.

Pharmacokinetic interaction studies

Albiglutide is a large therapeutic recombinant fusion protein of approximately 73,000 Dalton molecular weight. Therefore, no mechanistic in vitro and in vivo drug-drug interactions have been submitted.

A number of in vivo interaction studies with drugs commonly coadministered with albiglutide; oral contraceptives, simvastatin, warfarin and digoxin; have been submitted. No interactions were seen between albiglutide and these drugs except for an effect of albiglutide on simvastatin (40% decrease in AUC and 20% decrease in Cmax) and simvastatin acid (40% increase in AUC and 100% increase in Cmax).

Delayed gastric emptying is a known GLP-1 receptor agonist class effect. Therefore, the effect of 100 mg albiglutide on the gastric emptying of solid and liquid components was investigated.

There was, as expected, a statistically significant increase in the time to 50% gastric emptying of about 2-fold for both solids and liquids.

2.4.3. Pharmacodynamics

Mechanism of action

As a class, GLP-1 and its analogues are known to stimulate insulin release from the pancreatic islets (insulinotropic release), suppress glucagon secretion and delay gastric emptying.

Primary and Secondary pharmacology

The ability of albiglutide to stimulate insulin secretion is indirectly shown via elevated C-peptide levels and calculated insulin secretion rates during hyper- and euglycaemic clamp conditions in study GLP108372 (a glucose clamp a Phase II stepped glucose clamp study in subjects with T2DM). Derived insulin secretion rates following albiglutide treatment (a single dose of albiglutide (50 mg)) were significantly higher than placebo during the hyperglycaemia plateau (9 mmol/L [162 mg/dL]) and at the euglycaemic level of 5 mmol/L (90 mg/dL) and were similar to placebo at lower glucose levels.

In addition, attenuated insulin and C-peptide response after a mixed meal tolerance test was seen after 16 weeks in the albiglutide treated subjects in study GLP110932, a Phase IIb study conducted in Japanese subjects with T2DM. The ability of albiglutide to suppress glucagon secretion in the post-prandial state is also indicated by findings from data in this study.

It is clear that albiglutide, like other GLP-1 receptor agonists, delays gastric emptying both for solids and liquids and this is shown in in healthy men (study GLP107030). For solids, the gastric emptying t1/2 increased from 1.14 hrs at Day 4 to 2.23 hrs at Day 11 (p=0.0112). For liquids, gastric emptying t1/2 increased from 0.28 hrs at Day 4 to 0.69 hrs at Day 11 (p=0.0018). This effect on gastric emptying is of importance for timing of concomitant medications (as mentioned) and adverse events such as nausea, vomiting and potentially obstipation and this is reflected in the SmPC sections 4.4 special warnings and precaution for use (patients with gastroparesis) and section 4.5 other forms of interaction.

The counteracting hormone response to hypoglycaemia was evaluated in Study GLP108372. The results indicate that the counter-regulatory hormone response is preserved during provoked hypoglycaemia in the presence of albiglutide. In the hypoglycaemic range levels glucagon increased in a comparable manner for both groups. As a matter of fact, the increase in glucagon response is enhanced in the albiglutide group. Albiglutide treatment did not impair the adrenergic (epinephrine, norepinephrine), pituitary (growth hormone), or hypothalamic-pituitary-adrenal (HPA) axis (cortisol) counter-regulatory response to hypoglycaemia. No significant difference in the recovery time from hypoglycaemia between albiglutide and placebo.

In the thorough QTc study, there were no indication of a QT prolonging effect but an increase in heart rate is seen. The mean changes from baseline in heart rate (ΔHR) were similar for albiglutide 30 mg (one dose), placebo, and moxifloxacin (approx 1 bpm for all) but after repeat dosing with albiglutide 50 mg, the mean placebo-corrected ΔHR (ΔΔHR) increased with approx 6-8 bpm. This is a finding that also has been seen with other GLP-1 receptor agonists.

PK/PD

Exposure-response analyses were conducted to characterize the relationship between albiglutide concentration and improvement in glycaemic control observed in the phase III studies GLP112754, GLP112756, GLP112757 and GLP114130. PD markers of glycaemic control were fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c). Covariate evaluations were also performed to identify covariates influencing the exposure-efficacy relationship.

An effect compartment model was employed to account for the lag in achieving maximal HbA1c reductions. FPG reduction was assumed to be a more rapid process. The concentration effect relationship for both PD markers was characterized using an inhibitory Emax model and the placebo response by a modified exponential function

The final PK-HbA1c model included age as a covariate for baseline where older age was associated with lower baseline HbA1c. For FPG age and sex were identified as covariates for baseline. Older age was associated with lower baseline FPG and female subjects had approximately 5% lower baseline than male subjects.

Results from the final PK/PD model suggested that albiglutide dosing could produce a theoretically possible maximum percentage reduction (Emax) in HbA1c and FGP of 15.8% and 26%, respectively. The concentration required to reduce HbA1c and FPG by half of the Emax (EC50) was 2030 ng/mL and 1690 ng/ml, respectively. Model predicted weekly average albiglutide concentration in the phase III trials analyzed in the PPK analysis were for the 30-mg and 50-mg dose levels 2681 and 4469 ng/mL, respectively.

2.4.4. Discussion on clinical pharmacology

The reason for the observed shift in albiglutide concentration was identified and subsequently could be attributed to switching from manual to robotic pipetting in the sample handling. The Applicant have corrected the pre-shift data, where needed, and described/justified the decision to correct or not correct selected pre-shift data.

The comparability between active substance from process 1, used in the initial characterisation of albiglutide, and active substance from process 2 or 3 were based on quality and preclinical data.

Population PK (PPK) analysis

The PPK analysis of the phase III data in patients with T2DM was in general well performed and reported. The results were in accordance with earlier PPK analyses of the phase II data. The estimated assay shift factor (AS1) seems to be a reasonable approach to account for and quantify the bioanalytical shift.

In the analysis of phase III data the estimates of V/F and Ka differed from the previous studies probably due to the limited sampling during absorption and distribution. The difference may also be a result of the ignored inter-individual variability on V/F (including a correlation with CL/F) although being highly significant and a likely relationship between weight and V/F. The estimates of V/F and Ka might thereby not be completely reliable.

The goodness-of-fit plots for the final model reveal a reasonable fit with respect to the overall data. Predictive performance was illustrated by prediction corrected visual Predictive Checks which in general showed an adequate description of the data.

Special Populations

The difference in exposure in different weight groups is considered less important in clinical practice. In case of low exposure due to high clearance (in patients with a high bodyweight), there is a possibility to increase the dose to 50 mg. In case of high exposure (in light patients) safety of the 30 mg dose regimen is covered by the safety data of the 50 mg dose regimen. Furthermore, BMI does not appear to influence efficacy (see section on Clinical efficacy).

Interactions

The mechanistic reason for the observed interaction between albiglutide and simvastatin is unclear. Based on the clinical safety study data included in this application, the PK interaction with simvastatin did not result in a change in the frequency of simvastatin adverse event when coadministered with albiglutide.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of albiglutide is of a more descriptive nature since albiglutide is a recombinant fusion protein with a molecular weight of approximately 73 kDa and is to be administered via subcutaneous injection.

Different injection sites (abdomen, leg and arm) did not impact the exposure of albiglutide. Albiglutide steady state was reached after 3-4 weeks, in line with its half-life of 3.6-6.8 days (in subjects with type 2 diabetes), and accumulated 1.5-2 times after repeated dosing. A delayed gastric emptying, a known GLP-1 receptor agonist class effect, was evident also for albiglutide.

As a class, GLP-1 and its analogues are known to stimulate insulin release from the pancreatic islets (insulinotropic release), suppress glucagon secretion and delay gastric emptying. These mechanisms of action has been confirmed directly or indirectly in the performed pharmacodynamic studies which indicate that there do not seem to be any major difference between the mechanisms of albiglutide compared to other compounds in the class of GLP-1 receptor agonists. In addition, albiglutide does not seem to blunt the hypoglycaemic response. The effect on gastric emptying is of importance for timing of concomitant medications and adverse events such as nausea, vomiting and (potentially) constipation. This is adequately reflected in the SmPC.

2.5. *Clinical efficacy*

The safety and efficacy of albiglutide in humans has been evaluated in 10 clinical studies (Table 5). A total of 6043 subjects have participated in the clinical development program, of which 3358 have received albiglutide.

Three of the Phase III studies were complete (GLP114179, GLP108486, and GLP114130) at the time of the submission, and 5 were ongoing in long-term extension phases past the primary endpoints (GLP112753, GLP112754, GLP112755, GLP112756 and GLP115757). The initial

analyses for this submission were conducted when all remaining subjects in the five 156-week studies (GLP112753, GLP112754, GLP112755, GLP112756 and GLP112757) had completed at least 2 years of treatment and had been assessed for the primary efficacy endpoint. The final study reports for the ongoing studies were submitted by the Applicant during the procedure.

2.5.1. Dose response studies

Clinical Comparability of Process 2 (Phase III Material) and Process 3 (Commercial Formulation) Derived Albiglutide Product – Efficacy

During the clinical development of albiglutide (GSK716155) there have been three manufacturing processes used to produce albiglutide active substance: Process 1, (Phase I, Phase II studies) Process 2 (Phase II Japan and Phase III studies) and Process 3 (intended commercial formulation).

All the Phase III clinical studies were conducted with Process 2 drug product. Process 3 is the intended commercial formulation. The clinical comparability of Process 2 drug product (Phase III) and Process 3 drug product (commercial formulation) was investigated following repeat dosing for 12 weeks in study GLP114856 which included 308 subjects, randomised 1:1. The secondary efficacy endpoints showed no statistically significant differences between Process 2 and Process 3 and the mean changes from Baseline were consistent with the clinical profile of albiglutide: HbA1c mean change from Baseline to Week 17 was -0.75% and -0.84% for Process 2 and 3, respectively.

Further, as part of the clinical comparability assessment, Process 3 albiglutide was introduced into the extension phase of 2 Phase III clinical studies: GLP112754 (open-label insulin comparison) and GLP112756 (double-blind monotherapy study). In these studies a masked "switch" of albiglutide in all study subjects from Process 2 to Process 3 was assessed, with subjects acting as their own controls. A total of 456 patients have received Process 3 albiglutide with an average exposure of 35 weeks (range 8-65 weeks). A total of 225 patients remained on Process 2 albiglutide throughout the studies. Drop-out rates were rather low (0-10 %), however, higher in the comparator groups and the group only treated with Process 2, which could introduce bias by selecting patients more compliant and tolerant to treatment in the Process 2/3 group. Across the GLP112754 and GLP112756 studies, HbA1c remained stable in the observed cases without rescue populations in those subjects who were switched.

Dose response studies

The doses and dosing regimen for the albiglutide Phase III studies were determined based on results from nonclinical studies and PK and PD data from clinical studies in healthy volunteers and in subjects with T2DM.

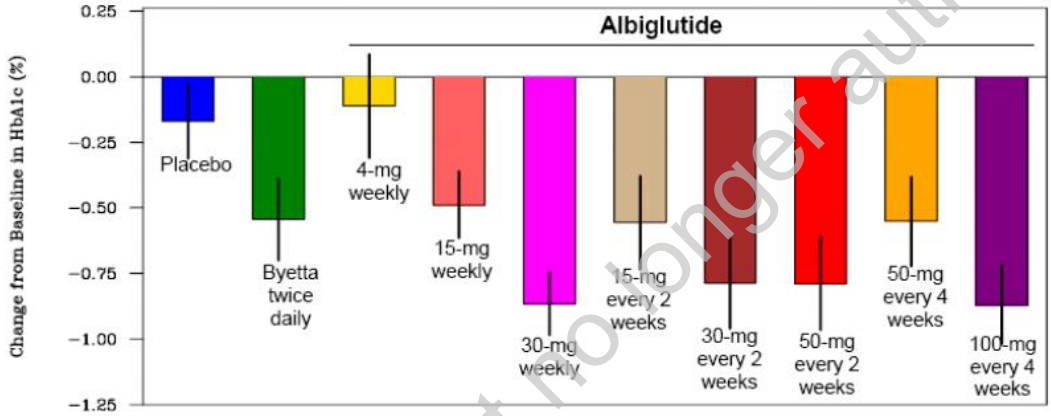
The 2 Phase IIB dose-finding studies were both conducted in subjects with T2DM (Study GLP110125 and study GLP110932).

Study GLP110125 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy, safety, and tolerability of various dose levels and regimens of albiglutide compared with placebo and with exenatide BID (Byetta) as an open-label reference arm over a 16-week treatment period in subjects with type 2 diabetes mellitus. A total of 356

subjects with T2DM who were treated with either diet and exercise or with metformin, whose HbA1c results were between 7% and 10%, inclusive, and who had a BMI of at least 20 kg/m^2 but no more than 40 kg/m^2 were randomly assigned to dosing regimens that were formed as combinations of dose level (4, 15, 30, 50, and 100 mg) and dosing interval (weekly, every other week, or every 4 weeks subcutaneous injections).

The outcome of the primary endpoint of model-adjusted change from Baseline in HbA1c at Week 16 is shown in Figure 5. The results were statistically significant versus placebo for the 30 mg weekly (p=0.0027), 30 mg and 50 mg every other week (p=0.0057 and p=0.0032), and 100 mg every 4 weeks (p=0.0022) regimens.

Figure 5 Mean (+/- SE) Change from baseline HbA1c at Week 16 (ITT – LOCF) in Study GLP110125



Study GLP110932 was a multicenter, randomized, double-blind, placebo-controlled, 4 parallel-group study evaluating the efficacy, safety, and tolerability of various dose levels and regimens of albiglutide compared with placebo over a 16-week treatment period in Japanese subjects with type 2 diabetes mellitus. A total of 215 Japanese subjects with T2DM who were treated with either diet and exercise or with a stable dose of 1 oral antidiabetic medication other than thiazolidinedione for at least 8 weeks before screening, whose HbA1c results were between 7% and 10%, inclusive, and who had a BMI of at least 18 kg/m^2 but no more than 35 kg/m^2 and fasting C-peptide of at least 0.26 nmol/L were randomly assigned in a 1:1:1:1 ratio to albiglutide 15 mg or 30 weekly, 30 mg every other week or placebo weekly.

The primary endpoints of model-adjusted change from Baseline in HbA1c at Week 16 were -0.61%, -1.27%, -0.82%, and +0.28% respectively, in the 15 mg weekly, 30 mg weekly, 30 mg every other week, and placebo weekly regimens. The results were statistically significant versus placebo for each of the active treatment regimens (p<0.0001).

Based on these data and taking the tolerability profile into account, the 30 mg weekly dose was selected for the Phase III program.

Evaluation of the 50 mg weekly dose

All Phase III studies except GLP112755 included an albiglutide treatment arm of 30 mg weekly with either optional or forced uptitration to 50 mg weekly. Although the 50 mg weekly dosing

regimen was not studied in the Phase IIB dose-ranging studies, the 50 mg and 100 mg doses were used with longer dosing intervals in study GLP110125. Since there was some increase in efficacy as the dose increased within the regimens tested, it was postulated that a subset of subjects would require and tolerate an albiglutide dose higher than 30 mg weekly to achieve appropriate HbA1c control.

In Phase III, the uptitration occurred either because of insufficient glycaemic control with albiglutide 30 mg (optional uptitration following a protocol-specific algorithm) or in study GLP112756 and study GLP114179, uptitration occurred for all subjects treated with albiglutide irrespective of the degree of glycaemia (forced uptitration) provided a study design that allowed independent efficacy assessment of the albiglutide 50-mg weekly regimen.

Benefit of Uptitration of Albiglutide to 50 mg Weekly

Study GLP112756 demonstrated that the reduction from Baseline in HbA1c, FPG, and body weight at Week 52 were numerically greater with a 50 mg once weekly dose of albiglutide compared to a 30 mg once weekly dose (HbA1c change from baseline -0.70 % for 30 mg and -0.89 % for 50 mg). This differential effect was maintained out to at least Week 130.

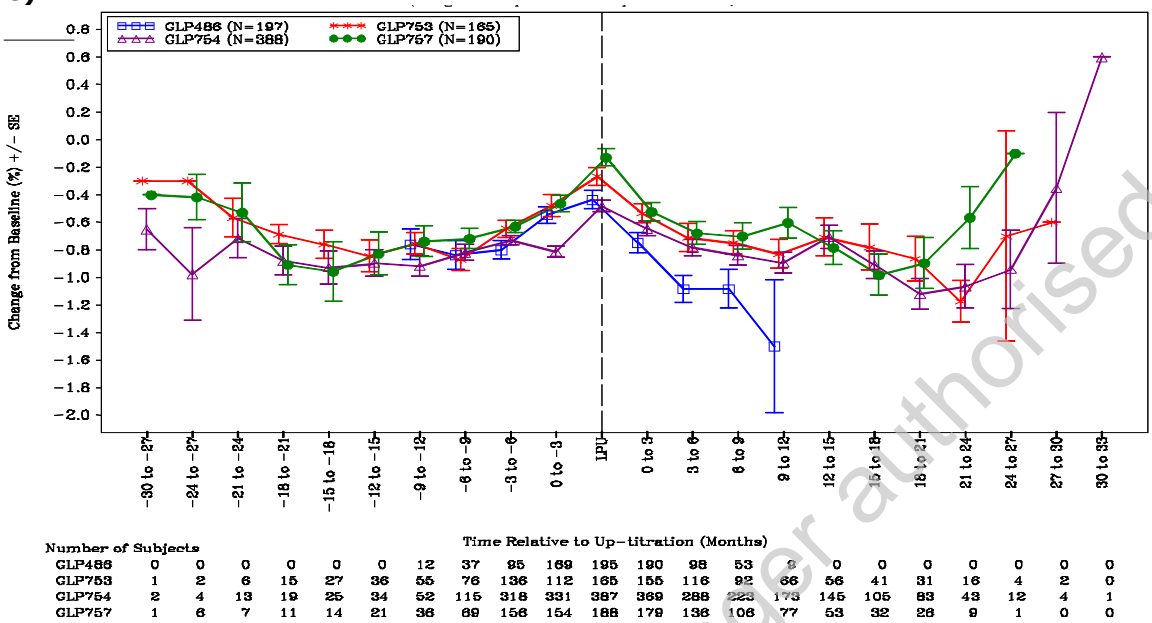
In Study GLP114179 where there was forced uptitration of albiglutide from 30 mg to 50 mg at Week 6, subjects showed a clinically significant decrease in HbA1c from Baseline at Week 32 [-0.78% (95% CI –0.87, –0.69)].

Efficacy of Optional Uptitration from Individual Studies

In Phase III studies (GLP108486, GLP112753, GLP112754, and GLP112757) the dose of albiglutide was increased to 50 mg according to clinical need. As shown in Figure 6, subjects in the 4 studies initially had a glycaemic response to albiglutide 30 mg. However, as HbA1c started to rise, dose uptitration to 50 mg resulted in further improvements in HbA1c. The improvements in glycaemic parameters after increasing to 50 mg albiglutide weekly occurred across all the concurrent background antidiabetic therapies included in the albiglutide studies. A total of 77.0% of albiglutide subjects had their dose uptitrated from 30 mg to 50 mg; with 27.4% uptitrating within the first 6 months of treatment. The mean time to uptitration was 31.2 weeks. Compared with the group that was not uptitrated, a greater proportion of subjects in the uptitrated group had a BMI ≥35 kg/m^2, HbA1c that was ≥8%, and used metformin and a sulfonylurea as baseline antihyperglycaemia oral therapy.

With this strategy, HbA1c was maintained or further decreased up to 130 weeks.

Figure 6 Mean Change From Baseline in HbA1c (%) Relative to Time of Uptitration Excluding Postrescue Values (Albiglutide Uptitrated Population – OC)



Number of Subjects

GLP486	0	0	0	0	0	0	12	37	95	169	195	190	98	53	0	0	0	0	0	0	0	0
GLP753	1	2	6	15	27	36	55	76	136	112	165	155	116	92	66	56	41	31	16	4	2	0
GLP754	2	4	13	19	25	34	52	115	318	331	387	369	288	223	173	145	105	83	43	12	4	1
GLP757	1	6	7	11	14	21	36	69	156	154	188	179	136	106	77	53	32	28	9	1	0	0

HbA1c = glycosylated haemoglobin; LPU = last dose prior to uptitration; OC = observed cases; SE = standard error.

2.5.2. Main studies

Pivotal Studies GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP114179, GLP108486 and GLP114130

The 8 studies included in the phase III program share a number of methodological features, thus these features will be discussed together. A short description of the study designs is given in the following:

GLP112753 was a double-blind, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with masked optional uptitration to 50 mg weekly) to treatment with placebo, glimepiride (2 mg daily with masked optional uptitration to 4 mg daily) and sitagliptin comparators in subjects with T2DM already treated with background metformin therapy. The primary endpoint was at Week 104 and the study continued to Week 156 (3 years).

This study investigated the use of albiglutide therapy as add-on to metformin and provides comparison to the oral therapies, sitagliptin and glimepiride.

GLP112754 was an open-label, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with open optional uptitration to 50 mg weekly) to treatment with insulin glargine (titrated as per protocol) in subjects with T2DM already treated with background metformin ± SU therapy. The primary endpoint was at Week 52 and the study continued to Week 156 (3 years).

This study investigated the use of albiglutide therapy as add-on to metformin or as add-on to metformin plus SU in subjects who are candidates for insulin.

GLP112755 was a double-blind, randomized, Phase III study which compared albiglutide treatment (30 mg weekly) to treatment with placebo in subjects with T2DM already treated with background pioglitazone ± metformin therapy. The primary endpoint was at Week 52 and the study continued to Week 156 (3 years).

This study investigated the use of albiglutide therapy as add-on to TZDs or as add-on to TZDs plus metformin.

GLP112756 was a double-blind, randomized, Phase III study which compared albiglutide treatment (both 30 mg and 50 mg weekly) to treatment with placebo in subjects with T2DM treated with no background OAD therapy. The primary endpoint was at Week 52 and the study continued to Week 156 (3 years). No optional albiglutide dose uptitration occurred and subjects in the 50-mg dose arm all underwent a forced uptitration from albiglutide 30 mg to 50 mg weekly at Week 12.

This study investigated the use of albiglutide as monotherapy added to diet and exercise therapy. The two separate albiglutide treatment arms allows for dose response assessment.

GLP112757 was a double-blind, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with masked optional uptitration to 50 mg weekly) to treatment with pioglitazone (30 mg daily with masked optional uptitration to 45 mg daily) and placebo in subjects with T2DM already treated with background metformin ± glimepiride therapy (maximum glimepiride dose of 4 mg). The primary endpoint was at Week 52 and the study continued to Week 156 (3 years).

This study investigated the use of albiglutide therapy added to metformin plus SU in a population with more advanced disease and permits direct comparison to pioglitazone.

GLP114179 was an open-label, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with forced uptitration to 50 mg weekly at Week 6) to treatment with liraglutide (titrated over a 2 week period from 0.6 mg to 1.8 mg daily as per the package insert) in subjects with T2DM who were already treated with a background regimen of metformin, SU, TZD, or any combination of these oral antidiabetic medications. The primary endpoint was at Week 32 and the treatment period also ended at Week 32.

This study investigated the use of albiglutide therapy added on to metformin, SU, TZD, or any combination of these 3 agents and permits direct comparison to another member of the GLP-1R agonist class.

GLP108486 was an open-label, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with optional uptitration to 50 mg weekly) to treatment with pre-prandial insulin lispro (titrated as per protocol) in subjects with T2DM already treated with a background regimen of insulin glargine plus oral agents. Subjects continued on their current regimen of oral antidiabetic medication, including metformin, TZDs, and alpha-glucosidase inhibitors, for the duration of the study with the exception that use of SUs, glinides, or DPP-IV

inhibitors were discontinued. The primary endpoint was at Week 26 and the study continued to Week 52.

This study investigated the use of albiglutide therapy added to insulin glargine and added on to dual oral therapy (metformin ± TZD and metformin ± alpha-glucosidase inhibitors) and permits direct comparison to prandial insulin lispro.

GLP114130 was a double-blind, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with masked optional uptitration to 50 mg weekly) to treatment with sitagliptin (25 mg, 50 mg or 100 mg; dose adjusted by GFR at randomization as per the sitagliptin package insert) in subjects with T2DM with mild, moderate, or severe renal impairment (eGFR ≥15 and <90 mL/min/1.73 m^2) already treated with a background regimen of metformin, SU, or TZD, alone or in combination. The primary endpoint was at Week 26 and the treatment period ended at Week 52. The GLP114130 study population was consistent with the albiglutide Phase III studies with the exception that subjects with moderate and severe renal impairment were also enrolled. The other Phase III albiglutide studies excluded subjects with moderate and severe renal impairment.

This study investigated the use of albiglutide therapy in patients with renal impairment.

Methods

The Phase III studies were all comprised of 4 study periods: a Pre-screening and Screening Period of 2 weeks; a Run-in/Stabilization Period of 4 weeks (4-8 weeks in GLP108486 since subjects on other types of insulin were required to switch to insulin glargine and 6-8 weeks in GLP112757 since subjects on other types of SU were required to switch and be stabilized on daily doses of 4 mg glimepiride and at least 1500 mg of metformin for at least 8 weeks before randomization); a Treatment Period evaluating efficacy and safety, and Post-treatment Follow-up Period of 8 weeks.

Study Participants

For all Phase III studies, the inclusion/exclusion criteria were reflective of the general population of adults with T2DM i.e., there was no upper restriction on age (with the exception of study GLP108486 where the upper age limit was 75 years) and subjects with a history of CV disease were permitted to participate (although subjects with clinically significant CV disease within 2 months or a cerebrovascular event within 1 month of screening [3 months in France] were excluded). The inclusion and exclusion criteria were selected to be consistent throughout the program with modifications as appropriate per the objectives of the protocols and in consideration of subject safety.

Key inclusion criteria were: male or female of 18 years or older, body mass index (BMI) ≥20 kg/m^2 and ≤45 kg/m^2, HbA_{1c} between 7% and 10% (10.5% for Study GLP108486) and creatinine clearance >60 mL/min, calculated as estimated glomerular filtration rate (eGFR) using the Cockcroft Gault criteria, with the exception of Study GLP114130, where subjects with Stages 2-4 chronic kidney disease were recruited.

Randomization of eligible subjects was stratified by prior history of myocardial infarction (MI) (yes versus no), HbA1c (<8.0% or ≥8.0%; all studies except GLP112755), age (<65 or ≥65 years of age; all studies except GLP108486) and where appropriate, by background antidiabetic

medication (studies GLP108486, GLP112754, and GLP112755 only). In the renal impairment study GLP114130, eligible subjects were also stratified by severity of renal impairment (mild, moderate, or severe).

The inclusion and exclusion criteria were generally more open than usually seen.

Treatments

Albiglutide had a starting dose of 30 mg weekly throughout the Phase III studies. Background treatments and comparators are given in Table 6.

Objectives

However, given the intent of diabetes treatment and the duration of the Phase III studies, select albiglutide studies allowed subjects who experienced persistent hyperglycaemia (after randomization) to undergo optional dose titration (with the exception of study GLP112755) and/or hyperglycaemia rescue. While the study protocol provided glycaemia rescue criteria, the decision as to when the use of diabetes medication was captured as a rescue medication and the decision of rescue medication class (specific drug) was determined by the investigator, except that addition of other GLP-1 receptor agonists was prohibited in subjects known to be in the albiglutide treatment group (e.g., open label studies). The addition of a dipeptidyl peptidase IV inhibitor (sitagliptin) was discouraged.

The preferred post-rescue add-on treatments were insulin (all studies) and metformin (study GLP112756). Subjects already receiving insulin glargine as study medication or background therapy (studies GLP112754 and GLP108486) may have required a prandial insulin to achieve glycaemic control. If the investigator used insulin, careful monitoring was advised because of the subjects' continued use of blinded medications. Other medications may have been added at the investigator's discretion.

Subjects who qualified for hyperglycaemia rescue according to the glycaemic criteria defined in the protocol continued in the study after initiation of rescue therapy, receiving active masked (if applicable) study treatment, as assigned, with albiglutide and comparators until the study was completed.

Outcomes/endpoints

The primary efficacy endpoint for the individual albiglutide Phase III studies was change in HbA_{1c} from Baseline. The timing of the primary endpoint assessment ranged from 26 weeks to 104 weeks (see Table 6).

The secondary efficacy endpoints for the individual albiglutide Phase III studies and the integrated analysis include:

- Change from Baseline in HbA_{1c} over time
- Change from Baseline in FPG at primary endpoint and over time
- Proportion of subjects who achieve an HbA_{1c} treatment goal of <6.5%, <7.0%, or <7.5% at the primary endpoint
- Time to hyperglycaemia rescue

- Change from Baseline in body weight at primary endpoint and over time

Sample size

The individual phase III studies were powered to demonstrate superiority vs. placebo or non-inferiority vs. an active comparator with a non-inferiority margin of 0.3% or 0.4% (studies GLP108486 vs. lispro insulin and GLP114130 vs. sitagliptin).

Randomisation

Randomization was stratified by prior history of myocardial infarction (MI) (yes versus no), HbA1c (<8.0% or ≥8.0%; all studies except GLP112755), age (<65 or ≥65 years of age; all studies except GLP108486) and where appropriate, by background antidiabetic medication (studies GLP108486, GLP112754, and GLP112755 only). In the renal impairment study GLP114130, eligible subjects were also stratified by severity of renal impairment (mild, moderate, or severe).

Blinding (masking)

Five of the studies were double-blind using matching placebo as comparator and/or as a mean to achieve blinding using double-dummy technique in studies with active comparators. In the three studies that had an open-label design (GLP112754, GLP108486 and GLP114179) this was justified by that subjects on active control used injectable products (glargine, lispro, liraglutide), and frequent placebo injection over the duration of the studies was not considered acceptable.

Statistical methods

The same overall analysis approach and analysis methods/tests were used for all eight phase III studies.

The primary efficacy population was the ITT Population that consisted of all randomized subjects who received at least 1 dose of study medication, had a baseline assessment and at least one post-baseline assessment (scheduled or unscheduled) for the primary endpoint of HbA1c. Analyses were performed on both last observation carried forward (LOCF), and observed case (OC) data sets with the former being primary. By using the LOCF method, subjects who qualified for hyperglycaemia rescue before the primary efficacy assessment had their HbA1c recorded at the time of rescue and carried forward for primary analyses. Follow-up assessments continued beyond rescue, and post-rescue HbA1c assessments were used in sensitivity analysis. For subjects who withdrew from the study, the last valid observation recorded on treatment (scheduled or unscheduled) was carried forward to all remaining visits.

The primary efficacy analysis was based on an analysis of covariance (ANCOVA) model with main effects for treatment group, region, history of prior myocardial infarction (MI) (yes versus no), and age category (<65 years versus ≥65 years) and with Baseline HbA1c as a continuous covariate. In study GLP 114130 the primary model also included a factor for renal impairment (mild, moderate, severe) and in studies GLP112754, GLP112755 and GLP108486 respectively also a factor for current oral anti-diabetic therapy.

Sensitivity analyses of the primary endpoint were performed based on the OC algorithm that used observed HbA1c values with no missing data imputation and, in one analysis excluded post rescue values and in another analysis included post rescue values (in some of the studies the latter analysis was post-hoc).

Additional sensitivity analyses were based on repeated measure ANCOVA models with inclusion of all observed measurements, including post-rescue measurements and also with terms for treatment-by-rescue interaction. Another sensitivity analysis was performed based on ITT using LOCF but excluding subjects with major protocol deviations (in some studies this analysis was post-hoc).

Secondary efficacy analyses of FPG and body weight were based on the same ANCOVA model as for the primary efficacy variable. In analyses of the proportion of subjects achieving HbA1c goals, extended Mantel-Haenszel tests were used with supportive analyses based on logistic regression models with effects for treatment and other main effects variables (region, history of prior MI, age category, and Baseline HbA1c category). Time to hyperglycaemia rescue was compared using log-rank tests.

Multiple comparisons adjustment strategies using sequential testing procedures were implemented among the primary and pre-specified key secondary objectives to preserve the nominal significance level of 0.05. Specifically, in studies with a non-inferiority objective, if non-inferiority was established, a superiority test was to be conducted.

Within each study a set of sub group analyses were planned and to support efficacy consistency across subgroups treatment-by-subgroup interactions were explored.

All safety summaries and analyses were to be performed for the safety population consisting of all randomised subjects who received at least one dose of study treatment with analyses according to treatment received. Post-rescue measurements of safety parameters were included in analyses without any special handling.

All blinded and unblinded statistical analyses for studies that were performed prior to study completion (that is, prior to subjects completing 3 years of treatment and the freezing of the clinical database) were performed by separate statistical teams at the CRO, otherwise not involved in the conduct of the study. All personnel involved in the conduct of a study were to remain blinded. All procedures were detailed in a separate document before executing any analysis (Charter for Work Process Flow for Maintaining Blind: Albiglutide Phase III studies).

Results

In the following, summary tables for the results across studies are provided.

Participant flow

Table 6 Disposition of All Subjects Enrolled in Albiglutide Phase III Studies (up to 2-year data)

Disposition	Clinical Study Disposition, n (%)							
	GLP112753	GLP112754	GLP112755	GLP112756	GLP112757	GLP108486	GLP114179	GLP114130
Randomized population[1]	1049	779	310	309	685	586	841	507
Safety population[1]	1012 (96.5)	754 (95.6)	301 (97.1)	301 (97.4)	663 (96.8)	566 (96.6)	812 (96.6)	495 (97.6)
Discontinued treatment[1]	335 (31.9)	237 (30.4)	91 (29.4)	107 (34.6)	254 (37.1)	81 (13.8)	128 (15.2)[1]	119 (23.5)
Adverse event	51 (4.9)	54 (6.9)	22 (7.1)	24 (7.8)	53 (7.7)	18 (3.1)	72 (8.6)	52 (10.3)
Protocol violation	17 (1.6)	13 (1.7)	7 (2.3)	N/A	11 (1.6)	2 (0.3)	3 (0.4)	5 (1.0)
Noncompliance	34 (3.2)	32 (4.1)	5 (1.6)	8 (2.6)	20 (2.9)	8 (1.4)	9 (1.1)	8 (1.6)
Severe or repeated occurrences of hypoglycaemia	1 (0.1)	1 (0.1)	N/A	N/A	N/A	N/A	0	0
Lost to follow-up	40 (3.8)	32 (4.1)	9 (2.9)	21 (6.8)	19 (2.8)	18 (3.1)	16 (1.9)	8 (1.6)
Withdrew consent	156 (14.9)	94 (12.1)	36 (11.6)	40 (12.9)	122 (17.8)	28 (4.8)	22 (2.6)	38 (7.5)
Investigator decision	16 (1.5)	7 (0.9)	4 (1.3)	4 (1.3)	5 (0.7)	2 (0.3)	2 (0.2)	8 (1.6)
Termination of site by sponsor	17 (1.6)	1 (0.1)	5 (1.6)	5 (1.6)	16 (2.3)	4 (0.7)	0	0
Other	21 (3.4)	3 (0.4)	3 (1.0)	5 (1.6)	8 (1.2)	1 (0.2)	4 (0.5)	0
Completed active treatment/continuing in study	677 (64.5)	508 (65.2)	210 (67.7)	194 (62.8)	409 (59.7)	485 (82,8)	686 (81.6)	376 (74.2)
ITT population[1]	999 (95.2)	735 (94.4)	299 (96.5)	296 (95.8)	657 (95.9)	563 (96.1)	805 (95.7)	486 (95.9)
Duration of treatment period	3 years	3 years	3 years	3 years	3 years	52 weeks	32 weeks	52 weeks

ITT = Intent-to-Treat; N/A = not available.

Note: The study treatment durations were as follows: Studies GLP112753, GLP112754, GLP112755, GLP112756 and GLP112757 are all 3-year duration (ongoing at time of submission with 2-year data reported), Study GLP108486 = 52-weeks, Study GLP114179 = 32 weeks, and Study GLP114130 = 52 weeks.

1 The study populations and discontinued subjects are totals, representing all subjects in all treatment groups.

Discontinuation rates were relatively high which should be seen in the light of the long duration of the studies. In the shorter studies, discontinuation rates were about 15 %. During the third year, the drop-out rate ranged from 4 to 7 %. When looking at the individual studies, there were no gross imbalances between the different study arms with regards to discontinuations. Differences in withdrawal rates due to AEs were small.

Recruitment

The clinical development program for albiglutide has been conducted in 19 countries: US, Spain, Germany, France, UK, Russia, South Africa, Israel, Columbia, Brazil, Mexico, Peru, Australia, Hong Kong, India, Japan Korea, Philippines, and Taiwan. Japan development and China development are progressing along separate timelines. By region, the US contributed approximately 75% of albiglutide-treated subjects, with approximately 5% from Asian regions, whereas Europe contributed the smallest percentage of subjects.

All studies were multicenter studies, each study involving between 134 to 289 centers.

Conduct of the studies

A routine GCP inspection of three sites (two investigator sites and a CRO site) were performed in connection with the evaluation of this Marketing Authorization Application. During these inspections, no critical deviations were observed.

Baseline data

Table 7 Demographics and Baseline Characteristics of Subjects Enrolled in Albiglutide Phase III Studies

	GLP112753	GLP112754	GLP112755	GLP112756	GLP112757	GLP108486	GLP114179	GLP114130	TOTAL n (%)
Mean age at randomization (years)	54.5	55.5	55.0	52.9	55.2	55.6	55.6	63.3	55.9 (10.02)
Age Category, n (%)									
<65 years	853 (84.3)	626 (84.0)	253 (84.1)	251 (83.4)	548 (82.7)	481 (85.0)	667 (82.1)	279 (56.4)	3958 (80.9)
≥65 years	159 (15.7)	119 (16.0)	48 (15.9)	50 (16.6)	115 (17.3)	85 (15.0)	145 (17.9)	216 (43.6)	937 (19.1)
Sex, n (%)									
Female	530 (52.4)	327 (43.9)	121 (40.2)	135 (44.9)	310 (46.8)	298 (52.7)	403 (49.6)	229 (46.3)	2353 (48.1)
Male	482 (47.6)	418 (56.1)	180 (59.8)	166 (55.1)	353 (53.2)	268 (47.3)	409 (50.4)	266 (53.7)	2542 (51.9)
Race[2], n (%)									
White - White/Caucasian/ European Heritage	723 (71.4)	500 (67.1)	212 (70.4)	242 (80.4)	458 (69.1)	345 (61.0)	562 (69.2)	226 (45.7)	3268 (66.8)
Mean duration of diabetes (years)	6.02	8.77	7.10	3.97	8.93	11.07	8.37	11.23	
Diabetic condition, n(%) Subjects with any conditions	61.4-70.2	75.2-79.3	72.0-80.1	52.5-63.4	77.1-81.6	84.5	80.0-83.8	90.0-94.3	
Prior MI (%)	4.1	5.0	4.3	3.0	4.2	8.7	3.9	8.7	
Mean HbA1c (%)	8.09	8.31	8.11	8.10	8.24	8.46	8.17	8.18	
Mean body weight (kg)	90.68	94.91	98.90	96.09	90.79	92.06	92.25	83.04	91.83 (20.723)
Mean body mass index (kg/m^2)	32.58	33.12	34.11	33.52	32.17	33.03	32.79	30.39	32.62
Body mass index category, n (%)									
<25 kg/m^2	52 (5.1)	34 (4.6)	11 (3.7)	11 (3.7)	51 (7.7)	44 (7.8)	56 (6.9)	71 (14.3)	330 (6.7)
≥25 to <30 kg/m^2	282 (27.9)	179 (24.0)	67 (22.3)	65 (21.6)	177 (26.7)	126 (22.3)	207 (25.5)	171 (34.5)	1274 (26.0)
≥30 to <35 kg/m^2	330 (32.6)	238 (31.9)	85 (28.3)	95 (31.6)	221 (33.3)	158 (27.9)	245 (30.2)	141 (28.5)	1513 (30.9)
≥35 kg/m^2	348 (34.4)	294 (39.5)	137 (45.7)	130 (43.2)	214 (32.3)	238 (42.0)	304 (37.4)	112 (22.6)	1777 (36.3)

The population included is considered representative for T2DM and with no large differences across the study program, with the exception of study GLP114130 (renal impairment), which included older patients who were less obese. The duration of disease was longer in study

GLP108486 (add-on to insulin) and study GLP114130. Mean HbA1c was slightly above 8 % in all studies. The majority of patients in all studies had signs of diabetes complications. CV co-morbidity represented as prior MI was present in 3-9 % of patients. Within all studies, treatment groups were well balanced with regards to baseline characteristics.

Regarding metformin background medication, the majority of subjects were on a daily dose of 1500 mg or higher, and dose distribution was balanced among treatment groups in each study. In study GLP112755 the mean dose of pioglitazon was similar (range 33.6 to 33.9 mg) in both treatment groups. Mean background glimipiride dose was 5.4 mg in both treatment arms in study GLP112754 and in the range 3.9 and 4 mg in study GLP112757. The majority of patients were Caucasian. Although most of the patients were recruited outside of Europe, it is reasonable to extrapolate the data to a European population.

Numbers analysed

Outcomes and estimation

Table 8 Summary of Efficacy for Key Endpoints in the Phase III Studies (Intent-to-Treat Population-LOCF)

	HbA_{1c} LS Mean Change from Baseline (%)	Subjects (%) Achieving HbA_{1c} <7.0%[5]	FPG LS Mean Change from Baseline (mmol/L)	FPG LS Mean Change from Baseline (mg/dL)	Weight LS Mean Change from Baseline (kg)
GLP112753 – Add on to Met[1]					
Albiglutide	-0.63	38.6	-0.98	-17.6	-1.21
Placebo	+0.27	15.5	+0.55	10.1	-1.00
Difference (95% CI)	-0.91 (-1.16, -0.65)	2.413 (1.273, 4.575)	-1.53 (-2.16, -0.90)	-27.7 (-39.0, -16.4)	-0.20 (-1.14, 0.73)
Superiority P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.6677
Sitagliptin	-0.28	31.6	-0.12	-2.1	-0.86
Difference (95% CI)	-0.35 (-0.53, -0.17)	1.307 (0.888, 1.926)	-0.86 (-1.30, -0.41)	-15.5 (-23.5, -7.5)	-0.35 (-1.01, 0.31)
NI P-value *Superiority P-value*	<0.0001 0.0001	0.1490	0.0002	0.0002	0.2991
Glimepiride	-0.36	31.4	-0.41	-7.5	+1.17
Difference (95% CI)	-0.27 (-0.45, -0.09)	1.275 (0.858, 1.896)	-0.56 (-1.01, -0.12)	-10.1 (-18.1, -2.1)	-2.37 (-3.03, -1.71)
NI P-value *Superiority P-value*	<0.0001 0.0033	0.1546	0.0133	0.0137	<0.0001
GLP112754 – Comparison to insulin glargine[2]					
Albiglutide	-0.67	31.6	-0.87	-15.7	-1.05
Insulin glargine	-0.79	32.8	-2.06	-37.1	+1.56
Difference (95% CI)	0.11 (-0.04, 0.27)	0.976 (0.675, 1.413)	1.19 (0.75, 1.63)	21.4 (13.5, 29.4)	-2.61 (-3.20, -2.02)
NI P-value *Superiority P-value*	0.0086 0.1463	0.9046	<0.0001	<0.0001	<0.0001
GLP112755 – Add on to TZD +/- Met[2]					
Albiglutide	-0.81	44.3	-1.28	-23.1	+0.28
Placebo	-0.05	14.8	+0.35	6.4	+0.45
Difference (95% CI)	0.75 (-0.95, -0.56)	4.080 (2.304, 7.226)	-1.64 (-2.19, -1.09)	-29.5 (-39.4, -19.6)	-0.18 (-1.15, 0.79)
P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.7193
GLP112756 - Monotherapy[2]					

	HbA_{1c} LS Mean Change from Baseline (%)	Subjects (%) Achieving HbA_{1c} <7.0%[5]	FPG LS Mean Change from Baseline (mmol/L)	FPG LS Mean Change from Baseline (mg/dL)	Weight LS Mean Change from Baseline (kg)
Albiglutide 30 mg	-0.70	49.0	-0.88	-16.0	-0.39
Albiglutide 50 mg	-0.89	40.2	-1.38	-24.8	-0.86
Placebo	+0.15	21.4	+1.00	18.0	-0.66
Difference 30 mg (95% CI)	-0.84 (-1.11, -0.58)	3.503 (1.737, 7.065)	-1.89 (-2.55, -1.22)	-34.0 (-45.9, -22.1)	0.27 (-0.91, 1.46)
P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.6526
Difference 50 mg (95% CI)	-1.04 (-1.31, -0.77)	3.563 (1.685, 7.535)	-2.38 (-3.05, -1.71)	-42.8 (-54.9, -30.7)	-0.20 (-1.40, 1.01)
P-value	<0.0001	0.0002	<0.0001	<0.0001	0.7485
GLP112757 – Add on to Met and SU[2]					
Albiglutide	-0.55	29.8	-0.69	-12.4	-0.42
Placebo	+0.33	8.7	+0.64	11.5	-0.40
Difference (95% CI)	-0.87 (-1.07, -0.68)	3.394 (1.740, 6.622)	-1.33 (-1.89, -0.76)	-23.9 (-34.1, -13.6)	-0.03 (-0.88, 0.82)
Superiority P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.9499
Pioglitazone	-0.80	35.1	-1.74	-31.4	+4.43
Difference (95% CI)	0.25 (0.10, 0.40)	0.638 (0.418, 0.975)	1.05 (0.61, 1.49)	19.0 (11.1, 26.9)	-4.85 (-5.51, -4.20)
NI P-value	0.2685	0.0223	<0.0001	<0.0001	<0.0001
GLP108486 – Add on to basal insulin[3]					
Albiglutide	-0.82	29.7	-0.99	-17.9	-0.73
Lispro basal insulin	-0.66	25.2	-0.71	-12.9	+0.81
Difference (95% CI)	-0.16 (-0.32, 0.00)	1.212 (0.780, 1.882)	-0.28 (-0.73, 0.18)	-4.9 (-13.2, 3.3)	-1.54 (-2.09, -1.00)
NI P-value *Superiority P-value*	<0.0001 0.0533	0.3977	0.2366	0.2390	<0.0001
GLP114179 – Comparison with liraglutide[4]					
Albiglutide	-0.78	42.2	-1.22	-22.1	-0.64
Liraglutide	-0.99	51.7	-1.68	-30.4	-2.19
Difference (95% CI)	0.21 (0.08, 0.34)	0.631 (0.456, 0.872)	0.46 (0.14, 0.78)	8.3 (2.5, 14.1)	1.55 (1.05, 2.06)
NI P-value	0.0846	0.0023	0.0048	0.0050	<0.0001
GLP114130 – Renal impairment[3]					
Albiglutide	-0.83	42.6	-1.42	-25.6	-0.79
Sitagliptin	-0.52	30.5	-0.22	-3.9	-0.19
Difference (95% CI)	-0.32 (-0.49, -0.15)	1.597 (1.076, 2.372)	-1.20 (-1.71, -0.69)	-21.7 (-30.9, -12.5)	-0.60 (-1.14, -0.06)
NI P-value *Superiority P-value*	<0.0001 0.0003	0.0077	<0.0001	<0.0001	0.0281

Abbreviations: FPG = fasting plasma glucose, H2H = head-to-head, Met = metformin, LS = least squares, NI = noninferiority; SU = sulfonylurea, TZD = thiazolidinedione.

Differences given are for albiglutide vs. Placebo or albiglutide vs. active comparator just above. P-values are for noninferiority and/or superiority as indicated.

1. Studies with primary endpoint at 104 weeks.
2. Study with primary endpoint at 52 weeks.
3. Studies with primary endpoint at 26 weeks.
4. Study with primary endpoint at 32 weeks.
5. For subjects achieving HbA_{1c} <7.0%, odds ratio is based on nonparametric Mantel-Haenszel test after adjusting for Baseline HbA_{1c} category, prior myocardial infarction history, age category, and region.

Study GLP112756 is considered as the pivotal study with regards to the monotherapy indication. In this study both the 30 mg and 50 mg weekly dose of albiglutide was compared to placebo in drug-naïve patients. Consistent and clinically relevant placebo-corrected reductions of baseline HbA1c was observed for both doses with a slightly higher placebo-corrected decrease with the higher dose (-0.84 % vs -1.04 % for the lower and higher dose, respectively). This was supported by a decrease in FPG. With regards to responders (subjects achieving HbA1c < 7.0 %), the rate of responders was higher in the low dose group (49.0 %) compared to the high dose group (40.2 %). This may be explained by differences in baseline HbA1c being 8.05% in the albiglutide 30mg group and 8.21% in the albiglutide 50 mg group. In both the two actively dosed groups, the rate of responders was significantly higher than in the placebo treated group. In the low dose treated group, weight reduction was numerically less than observed in the placebo treated group, whereas a numerically greater weight reduction compared to placebo was observed in the high dose group.

Three studies investigated the use of albiglutide as add-on to metformin (GLP112753), add-on to TZD +/- metformin (GLP112755) or add-on to metformin and SU (GLP112757). In all three studies, statistically significant and clinically relevant placebo-corrected reductions in baseline HbA1c, ranging from -0.75 to -0.91 % were observed. This was supported by reductions in FPG. Responder rates were significantly higher in all three studies compared to placebo, with differences between 21 and 30 % compared to placebo. Weight reduction did not differ from that observed with placebo treatment and in study GLP112755 (add-on to TZD) a weight increase was observed in both the albiglutide and the placebo group.

Five of the studies included one or two active comparators added to various background therapies.

In study GLP112753, albiglutide was compared to sitagliptin (100 mg/day) and glimepiride (2-4 mg/day) as add-on to metformin. Superiority could be shown for albiglutide versus both sitagliptin and glimepiride. The treatment effect on reduction of baseline HbA1c was rather low for both sitagliptin (-0.28 %) and glimepiride (-0.36 %), however, the placebo-subtracted reduction in HbA1c was -0.55%, and -0.63% for sitagliptin, and glimepiride, respectively. In the sitagliptin group, the mean duration of exposure to the 100 mg dose was 637 days (which is comparable to the exposure time in the albiglutide treated group). The mean albiglutide dose at Week 104 was 40.52 mg (manual calculation) and the mean glimepiride dose at Week 104 was 3.076 mg (manual calculation). The weight reduction was numerically less with sitagliptin than with albiglutide whereas a weight increase was observed with glimepiride as expected.

In study GLP112757, albiglutide was compared to pioglitazone as add-on to metformin and SU. Pioglitazone showed a superior effect with a treatment difference in reduction of baseline HbA1c of 0.25 % (95 % CI, 0.10, 0.40). This was supported by the rates of responders and outcome of FPG. An increase in weight was observed in the pioglitazone treated group.

Study GLP112754 compared albiglutide with insulin glargine as add-on to metformin +/- SU. Non-inferiority for albiglutide vs insulin glargine could be shown with regards to the reduction of baseline HbA1c. Responder rates were comparable between the two groups (about 32 % in both groups). Treatment with insulin glargine resulted in a significantly lower FPG compared to albiglutide treatment. As expected, albiglutide treatment resulted in a modest weight reduction of 1.05 kg whereas insulin glargine treatment resulted in a weight increase of 1.56 kg. In the

insulin glargine treatment group, the median daily dose of insulin glargine used prior to rescue increased by 3-fold from the study start to the study end. Subjects in the insulin glargine group had a starting total daily dose of insulin glargine that ranged between 2 and 40 units (median daily dose of 10 units), at Week 52 had a total daily dose of insulin glargine that ranged between 3 and 230 units (median daily dose of 30 units), and an ending total daily dose of insulin glargine that ranged from 0 to 220 units (median daily dose of 34 units). Guidance for uptitration of the insulin dose based on FPG was in place.

Study GLP108486 compared albiglutide with insulin lispro as add-on to insulin glargine + OADs. In this study, a wide variety of background treatment was allowed. These treatments were balanced between groups. The absolute HbA1c reduction was slightly higher in the albiglutide treated group (-0.82 % vs -0.66 %) and non-inferiority versus insulin lispro was shown. Comparable outcomes with regards to rate of responders and FPG supported the primary endpoint. Responder rates were somewhat lower than in the other studies, which may be explained by the fact that this study included patients with a longer diabetes duration and a higher baseline HbA1c. The lispro was started based on the subject's home blood glucose monitoring data and distributed among the subject's meal times at the investigator's discretion and based on the standard of care for multiple-dose insulin therapy at the study site. The insulin lispro dose range was wide both at baseline (1 to 90 units) and at 52 weeks (3 to 222 units). Mean doses increased from 15 units to 34 units per day.

Study GLP114179 compared albiglutide with liraglutide as add-on to metformin, SU and TZD (either alone or in combination). Liraglutide was statistically superior to albiglutide with an absolute difference in reduction of baseline HbA1c of 0.21 %. This was supported by a higher rate of responders and a significantly higher reduction of FPG. A statistically and clinically relevant larger reduction in body weight was observed with liraglutide (1.55 kg).

Hyperglycaemia Rescue.

The proportion of subjects requiring hyperglycaemia rescue was higher in the placebo comparator groups than for albiglutide, and the time to first rescue was shorter (earlier) for placebo than for albiglutide treated subjects. The median time to hyperglycaemia rescue was significantly longer in the albiglutide groups than placebo (132.00 weeks vs. 67.71 weeks, $p<0.0001$ for Study GLP112753 and 116.14 weeks vs. 49.71 weeks, $p<0.0001$ for Study GLP112756). The values were similar for albiglutide compared with insulin glargine (106.14 weeks vs. 130.57 weeks, $p=0.2165$ for Study GLP112754).

In Study GLP112753, a significantly higher proportion of subjects treated with sitagliptin (30%) required hyperglycaemia rescue at Week 104 compared to albiglutide (21.2%) treated subjects. Similar results were obtained in renally impaired subjects in Study GLP114130 (sitagliptin 28.3%; albiglutide 17.9%). On the other hand, a higher proportion of subjects treated with albiglutide (36.8%) required hyperglycaemia rescue compared to those treated with pioglitazone (29.3%) in Study GLP112757 and a higher proportion of subjects treated with albiglutide (15.2%) required hyperglycaemia rescue compared to those treated with liraglutide (8.4%) in Study GLP114179. No difference in the proportion of subjects requiring hyperglycaemia rescue was observed between albiglutide, glimepiride and insulin treated subjects.

Ancillary analyses

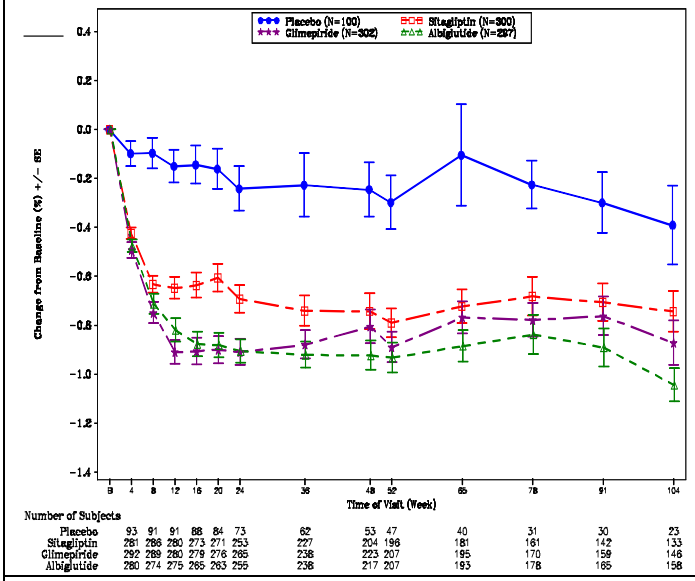
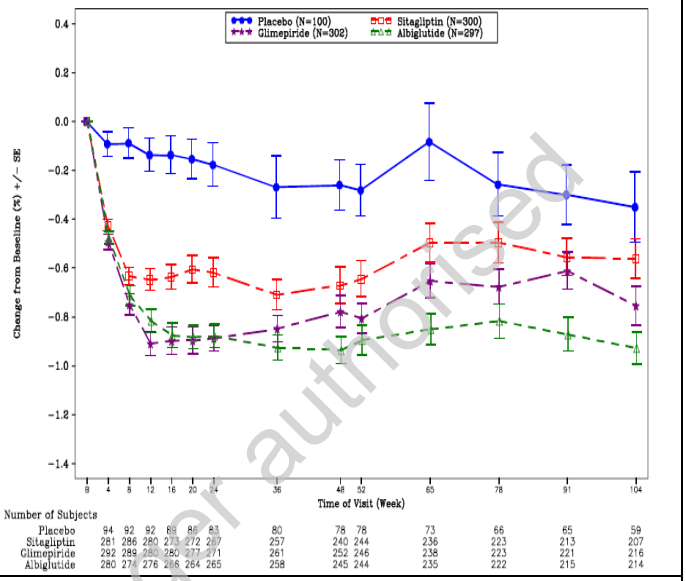
HbA1c over time

Study GLP112753 assessed the primary efficacy endpoint at Week 104 and evaluated the efficacy and safety of albiglutide compared with sitagliptin, glimepiride and placebo in T2DM subjects failing metformin. The study incorporated optional albiglutide uptitration from 30 mg to 50 mg based on protocol-specified glycaemic parameters. In the glimepiride group within that study, uptitration from 2 mg to 4 mg was recommended based on the same protocol-specified glycaemic parameters as were used for albiglutide uptitration. Note that there was no actual uptitration in the placebo and sitagliptin groups even though subjects went through the masked uptitration process. Uptitration occurred most commonly in the placebo group (69.3%) followed by the groups treated with sitagliptin (60.9%) and glimepiride (56.0%). Uptitration occurred in 54.6% of subjects randomly assigned to receive albiglutide. Albiglutide demonstrated durable efficacy, as demonstrated by change from Baseline in HbA1c at Week 104, compared to all the treatment groups - sitagliptin, glimepiride and placebo. There was an early loss of efficacy in the glimepiride and sitagliptin groups occurring within the first 24 to 52 weeks, whereas HbA1c remained stable in the albiglutide group for the full 2-year duration.

Four of the albiglutide Phase III studies (GLP112754, GLP112755, GLP112756, and GLP112757) assessed glycaemic efficacy at a primary endpoint of Week 52 and a secondary efficacy endpoint at Week 104. In each study, albiglutide demonstrated durable glycaemic control out to Week 104 and this persistence of efficacy occurs regardless of whether albiglutide was administered to treatment-naïve subjects or whether albiglutide was added to subjects who were already receiving a range of background medications including metformin alone or metformin plus a sulfonylurea, a thiazolidinedione, insulin, and/or an α-glucosidase inhibitor.

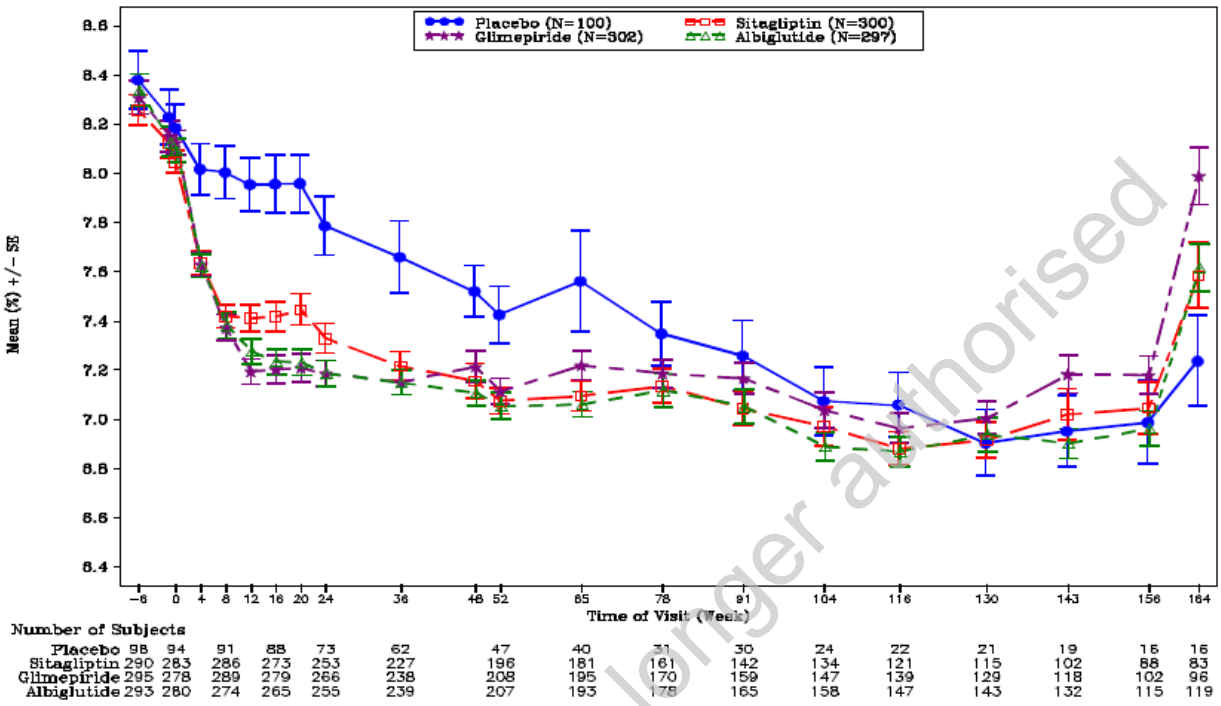
Overall, the inclusion of hyperglycaemia rescue provided appropriate glycaemic control throughout the long duration of randomized studies, particularly for subjects treated with placebo. In general, even with all post-rescue HbA_{1c} values included, subjects randomly assigned to albiglutide treatment had changes in HbA_{1c} that were consistent with the results from the analysis that excluded post-rescue values (exemplified in Figure 7).

Figure 7 Study GLP112753 - Mean Change from Baseline in HbA1c Over Time, Postrescue Values Excluded (Left Panel) and Included (Right Panel) (Intent-to-Treat Population – OC)

Postrescue Values Excluded	Postrescue Values Included
	
B = Baseline; SE = standard error. Note: The albiglutide group is the green dashed line.	B = Baseline; SE = standard error. Note: The albiglutide group is the green dashed line.

Five of the albiglutide Phase III studies (GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757) had an overall study duration of three years. Data show that the effect on HbA1c reduction was maintained over the study period as exemplified in Figure 8.

Figure 8 Line Graph of Mean (+/- SE) HbA1c (%) Over Time, Excluding Postrescue Values (Intent-to-Treat Population – OC)



Source Data: Figure Y3-14.2-1.1.
HbA_{1c} = glycosylated hemoglobin; OC = observed case; SE = standard error.

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 9 Summary of Efficacy for Trial GLP114179

Title: A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Liraglutide in Subjects With Type 2 Diabetes Mellitus		
Study identifier	GLP114179	
Design	This was a randomized, open-label, 2-parallel group, multicenter, 46-week study evaluating the efficacy and safety of weekly subcutaneous albiglutide compared with daily subcutaneous liraglutide in subjects with T2DM whose glycemia was inadequately controlled on their current regimen of metformin, TZD, SU, or any combination of OAD medications. Enrolled subjects continued on their current regimen of OAD medication for the duration of their participation in the study, with the exception that use of SU may have been modified.	
	Duration of prescreening and screening:	2 weeks
	Duration of run-in/stabilization:	4 weeks
	Duration of treatment:	32 weeks
	Duration of posttreatment follow-up:	8 weeks
Hypothesis	Noninferiority to active control	

Treatments groups	Albiglutide	A total of 422 subjects on a current regimen of OAD medication were randomly assigned to receive a weekly subcutaneous injection of 30 mg albiglutide (with forced uptitration to 50 mg weekly at Week 6).	
	Liraglutide	A total of 419 subjects on a current regimen of OAD medication were randomly assigned to receive 0.6 mg liraglutide daily for the first week followed by an increase in dose to 1.2 mg at Week 1 and to 1.8 mg at Week 2.	
Endpoints and definitions	Primary Endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 32.
	Secondary Endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 32.
	Secondary Endpoint	Rescue n (%)	Proportion of subjects with hyperglycemia rescue at Week 32.
	Secondary Endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal of <7.0% at Week 32.
	Secondary Endpoint	Body weight (kg)	Change from Baseline in body weight at Week 32.
Database lock	28Oct2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 32. (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Liraglutide
	Number of subjects[a]	398	402
	Baseline – Mean (SD)	8.18 (0.892)	8.15 (0.841)
	Week 32 – Mean (SD)	7.39 (1.114)	7.18 (1.079)
	LS mean change from Baseline (SE)	-0.78 (0.047)	-0.99 (0.046)
	(95% CI)	(-0.87, -0.69)	(-1.08, -0.90)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Albiglutide vs Liraglutide
		Difference of LS means[b]	0.21
		95% CI	(0.08, 0.34)
		Noninferiority P-value	0.0846
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model.		
Analysis description	**Key Secondary Analyses**		
Analysis population and time point description	Model-adjusted change from Baseline[b] in FPG (mmol/L) at Week 32 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Liraglutide
	Number of subjects[a]	400	402
	Baseline – Mean (SD)	9.39 (2.912)	9.27 (2.697)
	Week 32 – Mean (SD)	8.12 (2.722)	7.63 (2.580)
	LS mean change from Baseline (SE)	–1.22 (0.115)	–1.68 (0.115)
	95% CI	(–1.45, –1.00)	(–1.91, –1.46)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Liraglutide
		Difference of LS means[b]	0.46
		95% CI	(0.14, 0.78)
		P-value[c]	0.0048

Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model. c The p-value is from a 1-sided t test to test whether the difference in LS means was less than or equal to the prespecified noninferiority margin of 0.3%.		
Analysis population and time point description	Proportion of subjects with hyperglycemia rescue at Week 32 (ITT population)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Lispro insulin
	Number of subjects with hyperglycemia rescue, n (%)	61 (15.2)	34 (8.4)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Lispro insulin
		Nonparametric Mantel-Haenszel odds ratio	2.000
		95% CI	(1.230, 3.252)
		P-value	0.0004
		Logistic regression odds ratio	2.202
		95% CI	(1.380, 3.513)
		P-value	0.0009
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 32 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Liraglutide
	Number of subjects	398	402
	N (%)	168 (42.2)	208 (51.7)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Liraglutide
		Nonparametric Mantel-Haenszel odds ratio	0.631
		95% CI	(0.456, 0.872)
		P-value	0.0023
		Logistic regression odds ratio	0.598
		95% CI	(0.438, 0.816)
		P-value	0.0012
Analysis population and time point description	Model-adjusted change from Baseline [b] in body weight (kg) at Week 32 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Liraglutide
	Number of subjects[a]	400	402
	Baseline – Mean (SD)	91.54 (21.274)	92.94 (22.202)
	Week 32 – Mean (SD)	90.92 (21.254)	90.73 (22.086)
	LS mean change from Baseline (SE)	–0.64 (0.182)	–2.19 (0.182)
	95% CI	(–1.00, –0.28)	(–2.55, –1.83)
Effect estimate per comparison	Secondary Endpoint	Comparison groups	Albiglutide vs Liraglutide
		Difference of LS means[b]	1.55
		95% CI	(1.05, 2.06)
		P-value[c]	<0.0001

Notes	a Number of subjects with a value at Baseline and at the specified visit. b Difference of least squares means was from the ANCOVA model. c The p value was from a 2-sided t test for the difference in means.

Table 10 Summary of Efficacy for Trial GLP108486

Title: A Randomized, Open-Label, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Albiglutide Administered in Combination With Insulin Glargine as Compared With the Combination of Insulin Glargine and Preprandial Lispro Insulin in Subjects With Type 2 Diabetes Mellitus			
Study identifier	GLP108486		
Design	This was a Phase III randomized, active-controlled, parallel-group multicenter study to evaluate the efficacy and safety of weekly subcutaneously injected albiglutide combined with insulin glargine as compared with the combination of insulin glargine and lispro in subjects with T2DM. Enrolled subjects taking other intermediate- or long-acting insulins were switched to insulin glargine for the duration of this study.		
	Duration of prescreening and screening:	2 weeks	
	Duration of run-in/stabilization:	4 to 8 weeks	
	Duration of treatment	52 weeks (including 26 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 26 weeks of treatment for additional evaluation of efficacy and safety).	
	Duration of posttreatment follow-up:	8 weeks	
Hypothesis	Noninferiority to lispro insulin, and if established then superiority to lispro insulin was tested.		
Treatment groups	Albiglutide plus insulin glargine	A total of 292 subjects taking a current regimen of OAD medication (except SU, glinides, or DPP-IV inhibitors), were randomly assigned to receive a weekly subcutaneous injection of 30 mg albiglutide, (with uptitration to 50 mg weekly, if required, plus daily insulin glargine (with uptitration if required) at an initial dose level as prescribed by their physician	
	Lispro insulin plus insulin glargine	A total of 294 subjects taking a current regimen of OAD medication (except SU, glinides, or DPP-IV inhibitors), were randomly assigned to receive once daily sc preprandial lispro insulin with uptitration if required, plus daily insulin glargine with uptitration if required, both at initial dose levels as prescribed by their physician.	
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 26.
	Secondary endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 26.
	Secondary endpoint	Rescue n (%)	Proportion of subjects with hyperglycemia rescue at Week 26
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal of <7.0% at Week 26.
	Secondary endpoint	Body weight (kg)	Change from Baseline in body weight at Week 26.
Database lock	23Nov2011		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 26 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Lispro insulin
	Number of subjects[a]	279	278
	Baseline – Mean (SD)	8.47 (0.924)	8.43 (0.858)
	Week 26 – Mean (SD)	7.65 (1.113)	7.78 (1.120)
	LS mean change from Baseline (SE)	-0.82 (0.058)	-0.66 (0.058)
	95% CI	(-0.93, -0.70)	(-0.77, -0.54)
Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide vs Lispro insulin
		Difference of LS means[b]	-0.16
		95% CI	(-0.32, 0.00)
		Noninferiority p-value[c]	<0.0001
		Superiority p-value[d]	0.0533
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model. c The p-value is from a 1-sided *t* test to test whether the difference in LS means was equal to the prespecified noninferiority margin of 0.4%. d The p-value is from a 2-sided *t* test to test whether the difference in LS means equals zero.		
Analysis Description	**Key Secondary Analyses**		
Analysis population and time point description	Model-adjusted change from Baseline in FPG (mmol/L) at Week 26 (ITT – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Lispro insulin
	Number of subjects	282	279
	Baseline – Mean (SD)	8.46 (3.033)	8.50 (3.107)
	Week 26 – Mean (SD)	7.48 (2.893)	7.78 (2.949)
	LS mean change from Baseline (SE)	-0.99 (0.164)	-0.71 (0.164)
	95% CI	(-1.31, -0.67)	(-1.04, -0.39)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Lispro insulin
		Difference of LS means	-0.28
		95% CI	(-0.73, -0.18)
		P-value	0.2366
Analysis population and time point description	Proportion of subjects with hyperglycemia rescue at Week 26 (ITT population)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Lispro insulin
	Subjects with hyperglycemia rescue n (%)	77 (26.4)	76 (25.9)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Lispro insulin
		Nonparametric Mantel-Haenszel odds ratio	0.998
		95% CI	(0.607, 1.640)
		P-value	0.9099
		Logistic regression odds ratio	0.889
		95% CI	(0.577, 1.370)
		P-value	0.5937
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 26 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Lispro insulin
	Number of subjects	279	278
	n (%)	83 (29.7)	70 (25.2)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Lispro insulin
		Nonparametric Mantel-Haenszel odds ratio	1.212
		95% CI	(0.780, 1.882)
		p-value	0.3977
		Logistic regression odds ratio	1.223
		95% CI	(0.821, 1.823)
		P-value	0.3229
Analysis population and time point description	Model-adjusted LS mean change from Baseline in body weight (kg) at Week 26 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Lispro insulin
	Number of subjects	282	280
	Baseline – Mean (SD)	92.54 (21.472)	91.59 (20.991)
	Week 26 – Mean (SD)	91.82 (21.463)	92.39 (20.954)
	LS mean change from Baseline in body weight (SE)	-0.73 (0.194)	0.81 (0.195)
	95% CI	(-1.11, -0.35)	(0.43, 1.19)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Lispro insulin
		Difference of LS means	-1.54
		95% CI	(-2.09, -1.00)
		P-value	<0.0001

Table 11 Summary of Efficacy for Trial GLP112753

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination With Metformin Compared With Metformin Plus Sitagliptin, Metformin Plus Glimepiride, and Metformin Plus Placebo in Subjects With Type 2 Diabetes Mellitus.		
Study identifier		GLP112753
Design	This was a Phase III, randomized, double-blind, placebo and active controlled, parallel group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin as compared with metformin plus sitagliptin, metformin plus glimepiride and metformin plus placebo in subjects with T2DM whose glycemia was not adequately controlled on their current regimen of metformin.	
	Duration of pre-screening and screening	2 weeks
	Duration of run-in/ stabilization	4 weeks
	Duration of treatment	156 weeks (including 104 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 52

		weeks of treatment for additional evaluation of efficacy and safety).	
	Duration of posttreatment follow-up	8 weeks	
Hypothesis	Superiority over placebo; Noninferiority to active controls, and if established then superiority to active controls		
Treatment groups	Albiglutide	A total of 315 subjects on a current regimen of at least 1500 mg metformin daily (unless documented MTD <1500 mg), were randomly assigned to receive a weekly sc injection of 30 mg albiglutide (with treatment-masked up-titration to 50 mg weekly, if required) , daily matched placebo sitagliptin tablets and daily matched placebo glimepiride capsules.	
	Sitagliptin	A total of 313 subjects on a current regimen of at least 1500 mg metformin daily (unless documented MTD <1500 mg), were randomly assigned to receive a daily oral 100 mg tablet (Januvia), overcoated to achieve blinding, , weekly sc injection of albiglutide placebo and daily matched placebo glimepiride capsules.	
	Glimepiride	A total of 317 subjects taking at least 1500 mg metformin daily (unless documented MTD <1500 mg), were randomly assigned to receive a daily oral 2 mg tablet (Amaryl), overencapsulated to achieve blinding (with treatment-masked up-titration to 4 mg daily, if required), weekly sc injection of albiglutide placebo and daily placebo sitagliptin tablets.	
	Placebo	A total of 104 subjects taking at least 1500 mg metformin daily (unless documented MTD <1500 mg), were randomly assigned to receive a weekly sc injection of placebo albiglutide, daily placebo sitagliptin tablets and daily placebo glimepiride capsules.	
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 104.
	Secondary endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 104.
	Secondary endpoint	Rescue time (weeks)	Time to hyperglycemia rescue.
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects at an HbA_{1c} treatment goal of <7.0% at Week 104.
	Secondary endpoint	Body weight (kg)	Change from Baseline in body weight at Week 104.
Database lock	27Feb2012		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 104 (ITT population - LOCF)		

Descriptive statistics and estimate variability	Treatment group	Placebo	Sitagliptin	Glimepiride	Albiglutide
	Number of subjects[a]	97	297	299	293
	Baseline - Mean (SD)	8.12 (0.887)	8.06 (0.797)	8.12 (0.843)	8.09 (0.803)
	Week 104 – Mean (SD)	8.38 (1.352)	7.79 (1.317)	7.75 (1.252)	7.46 (1.140)
	LS mean	0.27 (0.113)	-0.28 (0.065)	-0.36 (0.064)	-0.63 (0.065)

	change from Baseline (SE)				
	95% CI	(0.05, 0.50)	(-0.41, -0.15)	(-0.49, -0.24)	(-0.76, -0.51)

Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide vs placebo
		Difference of LS means[b]	-0.91
		95% CI	(-1.16, -0.65)
		P-value	<0.0001[c]
	Secondary endpoint	Comparison groups	Albiglutide vs sitagliptin
		Difference of LS means[b]	-0.35
		95% CI	(-0.53, -0.17)
		P-value	<0.0001[d], 0.0001[e]
	Secondary endpoint	Comparison groups	Albiglutide vs glimepiride
		Difference of LS means[b]	-0.27
		95% CI	(-0.45, -0.09)
		P-value	<0.0001[d], 0.0033[e]

Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of LS means was from an ANCOVA model. c This p-value was from a 2-sided t-test to test for superiorityvs placebo at the 0.05 level. d This p-value was from a 1-sided t-test testing for noninferiority vs active comparators at the 0.0125 level. e This p-value was from a 2-sided t-test testing for superiority vs active comparators at the 0.025 level.
Analysis description	**Key Secondary Analyses**
Analysis population and time point description	Model-adjusted change from Baseline in FPG (mmol/L) at Week 104 (ITT population - LOCF)

Descriptive statistics and estimate variability	Treatment group	Placebo	Sitagliptin	Glimepiride	Albiglutide
	Number of subjects[a]	100	299	302	296
	Baseline - Mean (SD)	9.01 (2.341)	9.16 (2.593)	9.30 (2.547)	9.14 (2.767)
	Week 104 – Mean (SD)	9.67 (3.217)	9.05 (3.402)	8.83 (3.011)	8.17 (2.578)
	LS mean change from Baseline – Mean (SE)	0.55 (0.277)	-0.12 (0.160)	-0.41 (0.159)	-0.98 (0.161)
	95% CI	(0.01, 1.10)	(-0.43, 0.20)	(-0.73, -0.10)	(-1.29, -0.66)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs placebo
		Difference of LS means[b]	-1.53
		95% CI	(-2.16, -0.90)
		P-value	<0.0001[c]
	Secondary endpoint	Comparison groups	Albiglutide vs sitagliptin
		Difference of LS means[b]	-0.86
		95% CI	(-1.30, -0.41)
		P-value	0.0002[d]
	Secondary endpoint	Comparison groups	Albiglutide vs glimepiride
		Difference of LS means[b]	-0.56
		95% CI	(-1.01, -0.12)
		P-value	0.0133[d]
Notes	a Number of subjects with a value at Baseline and at the specified visit.		

	b Difference of least squares means is from the ANCOVA model. c This p-value was from a 2-sided t-test to test for superiority vs placebo at the 0.05 level. d This p-value was from a 2-sided t-test to test for superiority vs active comparators at the 0.025 level.				
Analysis population and time point description	Time of first hyperglycemia rescue (ITT population)				
Descriptive statistics and estimate variability	Treatment Group	Placebo	Sitagliptin	Glimepiride	Albiglutide
	Number of subjects	100	300	302	297
	Median time to rescue (weeks)[a]	67.71	130.43	130.43	132.00
	95% CI	(52.86, 122.14)	(118.71, NA)	(130.43, NA)	(130.86, 137.86)
Effect estimate per comparison	Secondary endpoint	Comparison groups			Albiglutide vs placebo
		Log-rank test p-value (pairwise comparison)			<0.0001
	Secondary endpoint	Comparison groups			Albiglutide vs sitagliptin
		Log-rank test p-value (pairwise comparison)			0.0131
	Secondary endpoint	Comparison groups			Albiglutide vs glimepiride
		Log-rank test p-value (pairwise comparison)			0.2177
Notes	a Based on Kaplan-Meier estimates				
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 104 (ITT population - LOCF)				
Descriptive statistics and estimate variability	Treatment group	Placebo	Sitagliptin	Glimepiride	Albiglutide
	Number of subjects	97	297	299	293
	Subjects n (%)	15 (15.5)	94 (31.6)	94 (31.4)	113 (38.6)
Effect estimate per comparison	Secondary endpoint	Comparison groups			Albiglutide vs placebo
		Nonparametric Mantel-Haenszel odds ratio			2.413
		95% CI			(1.273, 4.575
		P-value			<0.0001
		Logistic regression odds ratio			3.779
		95% CI			(2.023, 7.059)
		P-value			<0.0001
	Secondary endpoint	Comparison groups			Albiglutide vs sitagliptin
		Nonparametric Mantel-Haenszel odds ratio			1.307
		95% CI			(0.888, 1.926)
		P-value			0.1490
		Logistic regression odds ratio			1.384
		95% CI			(0.963, 1.989)
		P-value			0.0791
	Secondary endpoint	Comparison groups			Albiglutide vs glimepiride
		Nonparametric Mantel-Haenszel odds ratio			1.275
		95% CI			(0.858, 1.896)
		P-value			0.1546
		Logistic regression odds ratio			1.285
		95% CI			(0.894, 1.847)
		P-value			0.1761

Analysis population and time point description	Model-adjusted change from baseline in body weight (kg) at Week 104 (ITT population - LOCF)				
Descriptive statistics and estimate variability	Treatment group	Placebo	Sitagliptin	Glimepiride	Albiglutide
	Number of subjects[a]	100	300	302	296
	Baseline – Mean (SD)	91.73 (19.385)	90.40 (19.046)	91.88 (20.512)	89.61 (18.384)
	Week 104 – mean (SD)	90.71 (18.843)	89.54 (18.811)	93.03 (20.774)	88.43 (18.473)
	LS mean change from baseline (SE)	-1.00 (0.411)	-0.86 (0.237)	1.17 (0.237)	-1.21 (0.239)
	95% CI	(-1.81, -0.20)	(-1.32, -0.39)	(0.70, 1.63)	(-1.68, -0.74)
Effect estimate per comparison	Secondary endpoint	Comparison groups			Albiglutide vs placebo
		Difference of LS means[b]			-0.20
		95% CI			(-1.14, 0.73)
		P-value			0.6677
	Secondary endpoint	Comparison groups			Albiglutide vs sitagliptin
		Difference of LS means[b]			-0.35
		95% CI			(-1.01, 0.31)
		P-value			0.2991
	Secondary endpoint	Comparison groups			Albiglutide vs glimepiride
		Difference of LS means[b]			-2.37
		95% CI			(-3.03, -1.71)
		P-value			<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b Difference of least squares means is from the ANCOVA model. The p-value is from a 2-sided *t* test for the difference in LS means.				

Table 12 Summary of Efficacy for Trial GLP112754

Title: A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus.		
Study identifier		GLP112754
Design	This was a Phase III, randomized, open label, active control, 2-parallel group, multicenter study of 3 years duration, to evaluate the efficacy and safety of a weekly subcutaneously injected dose of 30 mg (with uptitration to 50 mg, if required) of albiglutide as compared with insulin glargine administered daily in subjects with T2DM whose glycemia was not adequately controlled on their current regimen of metformin (±SU). Enrolled subjects continued on their current dose(s) of metformin, with or without SU for the duration of the study.	
	Duration of pre-screening and screening:	2 weeks
	Duration of run-in/ stabilization:	4 weeks
	Duration of treatment:	156 weeks (including 52 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 104 weeks of treatment for additional evaluation of efficacy and safety).
	Duration of posttreatment follow-up:	8 weeks
Hypothesis	Non-inferiority to insulin glargine, and if established then superiority to insulin glargine was tested.	
Treatment groups	Albiglutide	A total of 516 subjects on a current regimen of daily metformin with or without SU, were randomly assigned to receive a weekly subcutaneous injection of 30 mg albiglutide (with up-titration to 50 mg weekly, if required).

	Insulin glargine	A total of 263 subjects on a current regimen of daily metformin with or without SU, were randomly assigned to receive daily insulin glargine at a dose level as prescribed by their physician (with uptitration if required).	
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} at Week 52.
	Secondary endpoint	FPG (mmol/L)	Change from baseline in FPG at Week 52.
	Secondary endpoint	Rescue time (weeks)	Time to hyperglycemia rescue.
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal of <7.0% at Week 52.
	Secondary endpoint	Body weight (kg)	Change from baseline at Week 52.
Database lock	01Mar2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Insulin glargine
	Number of subjects[a]	493	238
	Baseline – Mean (SD)	8.28 (0.900)	8.36 (0.954)
	Week 52 – Mean (SD)	7.62 (1.122)	7.55 (1.040)
	LS mean change from Baseline (SE)	-0.67 (0.044)	-0.79 (0.064)
	95% CI	(-0.76, -0.58)	(-0.91, -0.66)
Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide vs Insulin glargine
		Difference of LS means[b]	0.11
		95% CI	(-0.04, 0.27)
		Noninferiority p-value[c]	0.0086
		Superiority p-value[d]	0.1463
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model. c This p-value was from a 1-sided *t* test to test whether the difference of LS means was equal to the prespecified noninferiority margin of 0.3%. d This p-value was from a 2-sided *t* test to test whether the difference of LS means was equal to zero.		

Analysis description	**Key Secondary Analyses**		
Analysis population and time point description	Model-adjusted change from Baseline in FPG (mmol/L) at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Insulin glargine
	Number of subjects[a]	494	238
	Baseline – Mean (SD)	9.40 (2.826)	9.72 (2.967)
	Week 52 – Mean (SD)	8.59 (2.999)	7.53 (2.958)
	LS mean change from Baseline (SE)	-0.87 (0.127)	-2.06 (0.184)
	95% CI	(-1.12, -0.62)	(-2.42, -1.70)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs insulin glargine
		Difference of LS means[b]	1.19
		95% CI	(0.75, 1.63)
		P-value[c]	<0.0001
Notes	a. Number of subjects with a value at Baseline and at the specified visit. b. Difference of least squares means is from the ANCOVA model.		

	c. The p-value is from a 2-sided *t* test for the difference in means.		
Analysis population and time point description	Time of first hyperglycemia rescue (ITT population)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Insulin glargine
	Number of subjects	496	239
	Median time to hyperglycemia rescue (weeks)[a]	106.14	130.57
	95% CI	(96.43, 121.14)	(95.14, NA)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Insulin glargine
		Log-rank test p-value (pairwise comparison)	0.2165
Notes	a Based on Kaplan-Meier estimates		
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Insulin glargine
	Number of subjects	493	238
	n (%)	156 (31.6)	78 (32.8)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Insulin glargine
		Logistic regression odds ratio	0.918
		95% CI	(0.645, 1.306)
		P-value	0.6339
Analysis population and time point description	Model-adjusted change from Baseline in body weight (kg) at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Insulin glargine
	Number of subjects[a]	495	238
	Baseline – Mean (SD)	95.23 (19.571)	94.64 (19.091)
	Week 52 – Mean (SD)	94.18 (19.288)	96.21 (19.711)
	LS mean change from Baseline (SE)	-1.05 (0.171)	1.56 (0.247)
	95% CI	(-1.39, -0.72)	(1.07, 2.04)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs insulin glargine
		Difference of LS means[b]	-2.61
		95% CI	(-3.20, -2.02)
		P-value	<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b Difference of least squares means is from the ANCOVA model. The p-value is from a 2-sided *t* test for the difference in means.		

Table 13 Summary of Efficacy for Trial GLP112755

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination with Pioglitazone With or Without Metformin in Subjects With Type 2 Diabetes Mellitus		
Study identifier		GLP112755
Design	This was a Phase III, randomized, double-blind, placebo controlled,2-parallel group, multicenter study of 3 years duration to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with in combination with pioglitazone (with or without metformin) as compared with pioglitazone (with or without metformin) in subjects with T2DM. Enrolled subjects continued to receive their current dose regimen of pioglitazone with or without metformin.	
	Duration of pre-screening and screening	2 weeks

	Duration of run-in/ stabilization	4 weeks	
	Duration of treatment	156 weeks (including 52 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 104 weeks of treatment for additional evaluation of efficacy and safety).	
	Duration of posttreatment follow-up	8 weeks	
Hypothesis	Superiority to placebo.		
Treatment groups	Albiglutide	A total of 155 subjects on a current regimen of daily pioglitazone with or without metformin were randomly assigned to receive a weekly sc injection of 30 mg albiglutide.	
	Placebo	A total of 155 subjects on a current regimen of daily pioglitazone with or without metformin were randomly assigned to receive a weekly sc injection of placebo albiglutide.	
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 52.
	Secondary endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 52.
	Secondary endpoint	Rescue time (weeks)	Time to initial hyperglycemia rescue.
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal of <7.0% at Week 52.
	Secondary endpoint	Body weight (kg)	Change from Baseline in body weight at Week 52.
Database lock	20Dec2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Model-adjusted LS mean change from baseline in HbA_{1c} (%) at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide
	Number of subjects[a]	149	149
	Baseline – mean (SD)	8.13 (0.851)	8.10 (0.955)
	Week 52 – mean (SD)	8.08 (0.994)	7.29 (1.085)
	LS mean change from Baseline (SE)	-0.05 (0.071)	-0.81 (0.071)
	95% CI	(-0.19, 0.08)	(-0.95, -0.67)
Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide vs placebo
		Difference of LS means[b]	-0.75
		95% CI	(-0.95, -0.56)
		P-value[c]	<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model. c The p-value is from a 2-sided *t* test for the difference in means.		

Analysis description	**Key Secondary Analyses**		
Analysis population and time point description	Model-adjusted change from Baseline in FPG (mmol/L) at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide
	Number of subjects	149	149
	Baseline – mean (SD)	9.27 (2.65)	9.18 (2.51)
	Week 52 – mean (SD)	9.61 (2.96)	7.92 (2.40)
	LS mean change from Baseline (SE)	0.35 (0.197)	-1.28 (0.197)

	95% CI	(-0.03, 0.74)	(-1.67, -0.89)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs placebo
		Difference of LS means	-1.64
		95% CI	(-2.19, -1.09)
		p-value	<0.0001
Analysis population and time point description	Time to first hyperglycemia rescue (ITT population)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide
	Number of subjects	149	150
	Median time to hyperglycemia rescue (weeks)	48.14	130.14
	95% CI	(36.43, 52.29)	(103.57, NA)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo
		Log-rank test p-value (pairwise comparison)	<0.0001
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide
	Number of subjects	149	149
	n (%)	22 (14.8)	66 (44.3)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo
		Nonparametric (Cochran Mantel-Haenszel) odds ratio	4.080
		95% CI	(2.304, 7.226)
		p-value	<0.0001
		Logistic regression odds ratio	4.702
		95% CI	(2.668, 8.288)
		p-value	<0.0001
Analysis population and time point description	Model-adjusted change from Baseline in body weight (kg) at Week 52 (ITT population - LOCF)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide
	Number of subjects	149	149
	Baseline – Mean (SD)	100.20 (23.253)	97.59 (22.079)
	Week 52 – Mean (SD)	100.68 (23.814)	97.85 (21.839)
	LS mean change from Baseline (SE)	0.45 (0.348)	0.28 (0.348)
	95% CI	(-0.23, 1.14)	(-0.41, 0.96)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo
		Difference of LS means	-0.18
		95% CI	(-1.15, 0.79)
		P-value	0.7193

Table 14 Summary of Efficacy for Trial GLP112756

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Two Dose Levels of Albiglutide Compared With Placebo in Subjects With Type 2 Diabetes Mellitus	
Study identifier	GLP112756
Design	This was a Phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of 2 dose levels of weekly subcutaneously injected albiglutide compared with placebo in subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise and who had received less than 7 contiguous days of treatment with any antidiabetic therapy within the 3 months before Screening.

	Duration of prescreening and screening:		2 weeks	
	Duration of run-in/ stabilization:		4 weeks	
	Duration of treatment:		156 weeks (including 52 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 104 weeks of treatment for additional evaluation of efficacy and safety).	
	Duration of posttreatment follow-up:		8 weeks	
Hypothesis	Superiority to placebo			
Treatment groups	Albiglutide 30 mg weekly	A total of 102 subjects taking a current regimen of diet and exercise were randomized to receive a weekly sc injection of 30 mg albiglutide.		
	Albiglutide 50 mg weekly	A total of 102 subjects taking a current regimen of diet and exercise were randomized to receive a weekly sc injection of 30 mg albiglutide with forced uptitration to 50 mg weekly at Week 12.		
	Placebo	A total of 105 subjects taking a current regimen of diet and exercise were randomized to receive a weekly sc injection of placebo albiglutide.		
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 52.	
	Secondary endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 52.	
	Secondary endpoint	Rescue time (weeks)	Time to hyperglycemia rescue.	
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal of <7.0% at Week 52.	
	Secondary endpoint	Body weight (kg)	Change from Baseline in body weight at Week 52.	
Database lock	07Mar2012			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 52 (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide 30 mg Weekly	Albiglutide 50 mg Weekly

	Number of subjects[a]	98	100	97
	Baseline – Mean (SD)	8.02 (0.908)	8.05 (0.867)	8.21 (0.942)
	Week 52 – Mean (SD)	8.20 (1.458)	7.35 (1.150)	7.29 (1.104)
	LS mean change from Baseline (SE)	0.15 (0.097)	-0.70 (0.096)	-0.89 (0.097)
	95% CI	(-0.04, 0.34)	(-0.89, -0.51)	(-1.08, -0.70)
Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide 30 mg weekly vs. placebo	Albiglutide 50 mg weekly vs. placebo
		Difference of LS means[b]	-0.84	-1.04
		95% CI	-1.11, -0.58	-1.31, -0.77
		Superiority p-value[c]	<0.0001	<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model. c The p-value is from a 2-sided *t* test for (difference in means equals zero).			
Analysis description	**Key Secondary Analyses**			
Analysis population and time point description	Model-adjusted change from Baseline[b] in FPG (mmol/L) at Week 52 (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide 30 mg Weekly	Albiglutide 50 mg Weekly
	Number of subjects[a]	99	100	97
	Baseline – Mean (SD)	9.07 (2.372)	9.09 (2.309)	9.51 (2.400)
	Week 52 – Mean (SD)	10.12 (3.414)	8.21 (2.503)	8.07 (2.762)
	LS mean change from Baseline (SE)	1.00 (0.239)	-0.88 (0.237)	-1.38 (0.241)
	95% CI	(0.53, 1.47)	(-1.35, -0.42)	(-1.85, -0.90)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide 30 mg weekly vs. placebo	Albiglutide 50 mg weekly vs. placebo
		Difference of LS means	-1.89	-2.38
		95% CI	-2.55, -1.22	-3.05, -1.71
		Superiority p-value	<0.0001	<0.0001
Notes	a. Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model.			
Analysis population and time point description	Time to hyperglycemia rescue (ITT population)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide 30 mg Weekly	Albiglutide 50 mg Weekly
	Number of subjects	99	100	97
	Median time to rescue (weeks)[a]	49.71	116.14	NA
	95% CI	(32.14, 67.29)	(79.43, NA)	(NA, NA)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide 30 mg Weekly vs Placebo	Albiglutide 50 mg Weekly vs Placebo
		P-value[b]	<0.0001	<0.0001

Notes	a Based on Kaplan-Meier estimates b Log-rank test P-value (pairwise comparison)			
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 52 (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide 30 mg Weekly	Albiglutide 50 mg Weekly
	Number of subjects	98	100	97
	n (%)	21 (21.4)	49 (49.0)	39 (40.2)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide 30 mg weekly vs. placebo	Albiglutide 50 mg weekly vs. placebo
		Nonparametric Mantel-Haenszel odds ratio	3.503	3.563
		95% CI	1.737, 7.065	1.685, 7.535
		P-value	<0.0001	0.0002
		Logistic regression odds ratio	4.684	3.722
		95% CI	2.340, 9.377	1.830, 7.569
		P-value	<0.0001	0.0003
Analysis population and time point description	Model-adjusted change from Baseline in body weight (kg) at Week 52 (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Albiglutide 30 mg Weekly	Albiglutide 50 mg Weekly
	Number of subjects[a]	99	100	97
	Baseline – Mean (SD)	95.54 (20.068)	95.82 (19.642)	96.81 (17.884)
	Week 52 – Mean (SD)	94.93 (20.086)	95.36 (19.862)	95.97 (18.136)
	LS mean change from Baseline (SE)	-0.66 (0.428)	-0.39 (0.424)	-0.86 (0.432)
	95% CI	-1.50, 0.18	-1.22, 0.45	-1.71, -0.01
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide 30 mg weekly vs. placebo	Albiglutide 50 mg weekly vs. placebo
		Difference of LS means[b]	0.27	-0.20
		95% CI	-0.91, 1.46	-1.40, 1.01
		P-value	0.6526	0.7485
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of least squares means was from the ANCOVA model.			

Table 15 Summary of Efficacy for Trial GLP112757

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide Administered in Combination With Metformin and Glimepiride Compared With Metformin Plus Glimepiride and Placebo and With Metformin Plus Glimepiride and Pioglitazone in Subjects With Type 2 Diabetes Mellitus	
Study identifier	GLP112757

Design	This was a Phase III, randomized, double-blind, placebo- and active controlled, 3 parallel-group, multicenter study evaluating the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin and glimepiride compared with metformin plus glimepiride and placebo and with metformin plus glimepiride and pioglitazone in subjects with T2DM whose glycemia was not adequately controlled on their current regimen of metformin plus a sulfonylurea. Enrolled subjects had their current regimen switched to 4 mg daily glimepiride.			
	Duration of prescreening and screening:	2 weeks		
	Duration of run-in /stabilization:	6 to 8 weeks		
	Duration of treatment:	156 weeks (including 52 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 104 weeks of treatment for additional evaluation of efficacy and safety).		
	Duration of posttreatment follow-up:	8 weeks		
Hypothesis	Superiority over placebo; Noninferiority to pioglitazone, and if established, then superiority to pioglitazone was tested			
Treatments groups	Albiglutide	A total of 281 subjects were randomized to receive metformin plus open-label glimepiride (4 mg daily) plus albiglutide (30 mg weekly SC injection; treatment-masked uptitration if needed to 50 mg weekly) plus matching pioglitazone placebo		
	Pioglitazone	A total of 288 subjects were randomized to receive metformin plus open-label glimepiride (4 mg daily) plus pioglitazone (30 mg daily; with treatment-masked uptitration if needed to 45 mg daily) plus matching albiglutide placebo		
	Placebo	A total of 116 subjects were randomized to receivemetformin plus open-label glimepiride (4 mg daily) plus matching pioglitazone placebo plus matching albiglutide placebo		
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 52.	
	Secondary endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 52.	
	Secondary endpoint	Rescue time (weeks)	Time to hyperglycemia rescue.	
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal of <7.0% at Week 52.	
	Secondary endpoint	Body weight (kg)	Change from Baseline in body weight at Week 52.	
Database lock	22Feb2012			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 52. (ITT population; LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Pioglitazone	Albiglutide
	Number of subjects[a]	115	268	265
	Baseline - Mean (SD)	8.26 (0.978)	8.28 (0.879)	8.18 (0.908)
	Week 52 - Mean (SD)	8.57 (1.169)	7.47 (1.015)	7.66 (1.093)
	LS mean change from Baseline (SE)	0.33 (0.083)	-0.80 (0.055)	-0.55 (0.055)
	95% (CI)	(0.16, 0.49)	(-0.90, -0.69)	(-0.65, -0.44)

Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide vs Placebo	Albiglutide vs Pioglitazone
		Difference of LS means[b]	-0.87	0.25
		95% CI	(-1.07, -0.68)	(0.10, 0.40)
		P-value	0.0012	
		Noninferiority p-value[c]		0.2685
Notes	a Number of subjects with a value at Baseline and at the specified visit. b Difference of least squares means is from the ANCOVA model. c The p-value is from a 1-sided *t* test testing at the 0.025 level of significance for (difference of least squares means less than or equal to the prespecified noninferiority margin of 0.3%). Noninferiority was not established.			
Analysis description	**Key Secondary Analyses**			
Analysis population and time point description	Model-adjusted change from Baseline[b] in FPG (mmol/L) at Week 52 (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Pioglitazone	Albiglutide
	Number of subjects[a]	115	272	268
	Baseline - Mean (SD)	9.65 (2.731)	9.84 (3.114)	9.48 (2.896)
	Week 52 - Mean (SD)	10.29 (3.123)	8.02 (2.666)	8.87 (3.124)
	LS mean change from Baseline (SE)	0.64 (0.243)	-1.74 (0.158)	-0.69 (0.159)
	95% CI	(0.16, 1.11)	(-2.05, -1.43)	(-1.00, -0.38)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo	Albiglutide vs Pioglitazone
		Difference of LS means[b]	-1.33	1.05
		95% CI	(-1.89, -0.76)	(0.61, 1.49)
		P-value[c]	<0.0001	<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b Difference of least squares means is from the ANCOVA model. c The p-value is from a 2-sided *t* test for the difference in means.			
Analysis population and time point description	Time to first hyperglycemia rescue (ITT population)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Pioglitazone	Albiglutide
	Number of subjects	115	273	269
	Median time to rescue (weeks)[a]	49.57	136.29	120.43
	95% CI[a]	(38.86, 55.14)	(117.57, N/A)	(93.71, N/A)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo	Albiglutide vs Pioglitazone
		P-value[b]	<0.0001	0.1045
Notes	a Based on Kaplan-Meier estimates b Log-rank test P-value (pairwise comparison)			
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 52. (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Pioglitazone	Albiglutide
	Number of subjects[a]	115	268	265
	n (%)	10 (8.7%)	94 (35.1%)	79 (29.8%)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo	Albiglutide vs Pioglitazone
		Nonparametric Mantel-Haenszel odds ratio	3.394	0.638
		95% CI	(1.740, 6.622)	(0.418, 0.975)
		P-value	<0.0001	0.0223
		Logistic regression odds ratio	5.305	0.668
		95% CI	(2.530, 11.124)	(0.448, 0.996)
		P-value	<0.0001	0.0475
Analysis population and time point description	Model-adjusted change from Baseline in body weight (kg) at Week 52 (ITT population – LOCF)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Pioglitazone	Albiglutide
	Number of subjects[a]	115	272	268
	Baseline - Mean (SD)	89.90 (18.820)	91.03 (21.238)	91.10 (20.174)
	Week 52 - Mean (SD)	89.48 (18.542)	95.48 (22.505)	90.67 (20.139)
	LS mean change from Baseline (SE)	-0.40 (0.362)	4.43 (0.235)	-0.42 (0.237)
	95% CI	(-1.11, 0.31)	(3.97, 4.89)	(-0.89, 0.04)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Placebo	Albiglutide vs Pioglitazone
		Difference of LS means[b]	-0.03	-4.85
		95% CI	(-0.88, 0.82)	(-5.51, -4.20)
		P-value[c]	0.9499	<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b Difference of least squares means is from the ANCOVA model. c The p-value is from a 2-sided *t* test for the difference in means.			

Table 16 Summary of Efficacy for Trial GLP114130

Title: A Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Sitagliptin in Subjects With Type 2 Diabetes Mellitus With Renal Impairment		
Study identifier	GLP114130	
Design	This was a Phase III, randomized, double-blind, active-controlled, 2 parallel group, multicenter, 52-week study evaluating the efficacy and safety of a weekly subcutaneously injected 30-mg dose of albiglutide (with treatment-masked uptitration, if needed, to 50 mg weekly) as compared with sitagliptin in renally impaired subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise or their OAD medication regimen of metformin, TZD, SU, or any combination of these OAD medications. Enrolled subjects continued on their current regimen of OAD medication for the duration of the study, with the exception of those subjects who were on a regimen of metformin and/or an SU.	
	Duration of prescreening and screening:	2 weeks
	Duration of run-in/ stabilization:	4 weeks
	Duration of treatment:	52 weeks (including 26 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 26 weeks of treatment for additional evaluation of efficacy and safety)

	Duration of posttreatment follow-up:		8 weeks
Hypothesis	Noninferiority to sitagliptin, and if established then superiority to sitagliptin was tested.		
Treatments groups	Albiglutide		A total of 254 subjects on a current regimen of OAD medication were randomly assigned to receive a weekly subcutaneous injection of albiglutide 30 mg (with optional treatment-masked uptitration to 50 mg if needed) plus matching sitagliptin placebo.
	Sitagliptin		A total of 253 subjects on a current regimen of OAD medication were randomly assigned to receive a daily oral tablet of sitagliptin 25, 50, or 100 mg (based on subject's severity of renal impairment as per prescribing information) plus matching albiglutide placebo.
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from Baseline in HbA_{1c} at Week 26
	Secondary endpoint	FPG (mmol/L)	Change from Baseline in FPG at Week 26
	Secondary endpoint	Rescue n (%)	Proportion of subjects with hyperglycemia rescue at Week 26
	Secondary endpoint	HbA_{1c} (%)	Proportion of subjects achieving an HbA_{1c} treatment goal <7.0% at Week 26
	Secondary endpoint	Body weight (kg)	Change from Baseline in body weight at Week 26
Database lock	15-Jun-2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Model-adjusted change from Baseline in HbA_{1c} (%) at Week 26 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Sitagliptin
	Number of subjects[a]	242	236
	Baseline – Mean (SD)	8.08 (0.858)	8.22 (0.908)
	Week 26 – Mean (SD)	7.27 (1.017)	7.68 (1.246)
	LS mean change from Baseline (SE)	–0.83 (0.062)	–0.52 (0.063)
	95% CI	(–0.96, –0.71)	(–0.64, –0.39)
Effect estimate per comparison	Primary endpoint	Comparison groups	Albiglutide vs Sitagliptin
		Difference of LS means[b]	–0.32
		95% CI	(–0.49, –0.15)
		Noninferiority p-value[c]	<0.0001
		Superiority p-value[d]	0.0003
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of LS means was from the ANCOVA model. c The p-value was from a 1-sided *t* test to test whether the difference of LS means was less than or equal to the prespecified noninferiority margin of 0.4%. d The p-value was from a 2-sided *t* test to test whether the difference in the LS means was equal to zero.		
Analysis Description	**Key Secondary Analyses**		
Analysis population and time point description	Model-adjusted change from Baseline in FPG (mmol/L) at Week 26 (ITT population – OC)		

Descriptive statistics and estimate variability	Treatment group	Albiglutide	Sitagliptin
	Number of subjects	244	240
	Baseline – Mean (SD)	9.18 (3.231)	9.16 (2.873)
	Week 26 – Mean (SD)	7.75 (3.104)	8.95 (3.456)
	LS mean change from Baseline (SE)	–1.42 (0.183)	–0.22 (0.184)
	95% CI	(–1.78, –1.06)	(–0.58, 0.14)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Sitagliptin[a]
		Difference of LS means	–1.20
		95% CI	(–1.71, –0.69)
		P-value	<0.0001
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of LS means was from the ANCOVA model. d The p-value was from a 2-sided *t* test to test for the difference in means.		
Analysis population and time point description	Proportion of subjects with hyperglycemia rescue by Week 26 (ITT population)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Sitagliptin
	Subjects with hyperglycemia rescue n (%)	15 (6.1)	29 (12.1)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Sitagliptin
		Logistic regression odds ratio	0.458
		95% CI	(0.235, 0.894)
		P-value	0.0221
Analysis population and time point description	Proportion of subjects who achieved HbA_{1c} of <7.0% at Week 26 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Sitagliptin
	Number of subjects	242	236
	n (%)	103 (42.6)	72 (30.5)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Sitagliptin
		Nonparametric Mantel-Haenszel odds ratio	1.597
		95% CI	(1.076, 2.372)
		P-value	0.0077
		Logistic regression odds ratio	1.704
		95% CI	(1.162, 2.499)
		P-value	0.0064
Analysis population and time point description	Model-adjusted LS mean change from Baseline in body weight at Week 26 (ITT population – LOCF)		
Descriptive statistics and estimate variability	Treatment group	Albiglutide	Sitagliptin
	Number of subjects	244	240
	Baseline – Mean (SD)	83.69 (19.846)	82.73 (20.633)
	Week 26 – Mean (SD)	82.88 (19.753)	82.55 (20.695)

	LS mean change from Baseline in body weight (SE)	–0.79 (0.192)	–0.19 (0.194)
	95% CI	(–1.17, –0.41)	(–0.57, 0.19)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Albiglutide vs Sitagliptin
		Difference of LS means	–0.60
		95% CI	(–1.14, –0.06)
		P-value	0.0281
Notes	a Number of subjects with a value at Baseline and at the specified visit. b The difference of LS means was from the ANCOVA model. d The p-value was from a 2-sided *t* test to test for the difference in means.		

Clinical studies in special populations

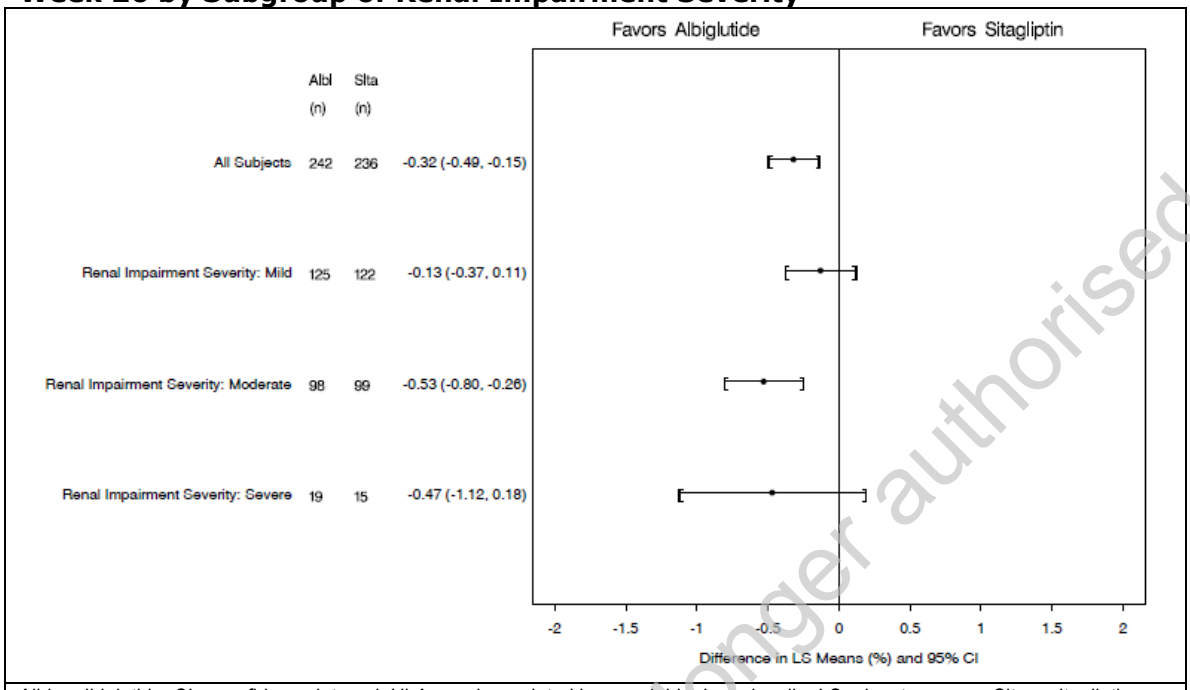
GLP114130 was a double-blind, randomized, Phase III study which compared albiglutide treatment (30 mg weekly with masked optional uptitration to 50 mg weekly) to treatment with sitagliptin (25 mg, 50 mg or 100 mg; dose adjusted by GFR at randomization as per the sitagliptin package insert) in subjects with T2DM with mild, moderate, or severe renal impairment (eGFR ≥15 and <90 mL/min/1.73 m^2) already treated with a background regimen of metformin, SU, or TZD, alone or in combination. The primary endpoint was at Week 26 and the treatment period ended at Week 52. The GLP114130 study population was consistent with the albiglutide Phase III studies with the exception that subjects with moderate and severe renal impairment were also enrolled.

The results of this study showed that albiglutide was statistically superior to sitagliptin for the change from Baseline in HbA1c at the primary endpoint of Week 26 (-0.83% for albiglutide versus -0.52% for sitagliptin, p=0.0003) in this special population.

The model-adjusted mean change from Baseline HbA1c was similar in the mild (n=125) and moderate (n=98) renal impairment subgroups treated with albiglutide (-0.80% and -0.83% respectively) and slightly greater in the albiglutide treated severe (n=19) renal impairment group (-1.08%). The treatment difference at Week 26 (albiglutide - sitagliptin) was -0.13% (95% CI: -0.37, 0.11), -0.53% (95% CI: -0.80, -0.26), and -0.47% (95% CI: -1.12, 0.18) for subjects with mild, moderate, or severe renal impairment, respectively. The analysis results should be interpreted with caution due to the small number of subjects in the severe renal impairment subgroup (n=19 in the albiglutide arm and n=15 in the sitagliptin arm).

The HbA1c values for subjects in the albiglutide group were generally lower after treatment than for subjects in the sitagliptin group at each time point through Week 26, irrespective of the severity of baseline renal impairment. Furthermore, subgroup analyses for the primary efficacy endpoint by baseline renal impairment severity (forest plot, Figure 9) showed a uniform treatment effect across the 3 subgroups consistent with that for the primary efficacy endpoint, with 95% CI overlapping across the 3 renal impairment severity subgroups.

Figure 9 Study GLP114130, Difference of LS Mean Model-adjusted Change From Baseline in HbA1c (%) and 95% CI for Albiglutide Versus Sitagliptin at Week 26 by Subgroup of Renal Impairment Severity



Albi = albiglutide; CI = confidence interval; HbA_{1c} = glycosylated haemoglobin; Ins = insulin; LS = least squares; Sita = sitagliptin.
Note: Week 52 data are presented as the primary endpoint for all studies in Group A.

The treatment effect seen at Week 26 for the overall albiglutide group was well maintained through Week 52 (the end-of-treatment visit). Fewer subjects in the albiglutide group were rescued or withdrew from study treatment compared with the sitagliptin group, which means that there were less data for the sitagliptin subjects than for the albiglutide subjects.

Efficacy in Renally Impaired Subjects From Pooled Phase III Studies

Subjects were excluded from the 7 Phase III studies that contribute to the pooled efficacy analyses if their creatinine clearance at screening was <60 mL/min using the Cockcroft-Gault method of determining creatinine clearance. For purposes of analyzing the renal status data in these study groups, normal renal function was defined as eGFR ≥90 mL/min/1.73 m^2 and renal impairment was defined as <90 mL/min/1.73 m^2 using the MDRD Study Group formula.

The magnitude of the HbA1c reduction for albiglutide versus placebo was consistent in subjects with normal renal function and in those with renal impairment. Compared to OADs or insulin, albiglutide achieved a similar treatment effect in subjects with normal renal function and those with renal impairment.

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

An integrated/pooled analysis was performed across 7 Phase III studies (excluding the Phase III GLP114130 study, comparing albiglutide to sitagliptin in renally impaired subjects). The efficacy data in renally impaired subjects are summarized in the previous section (studies in special populations).

For the pooled analysis, efficacy results from subjects randomly assigned to albiglutide were compared with efficacy results from subjects randomly assigned to corresponding treatment comparators (placebo, OADs, insulin, and liraglutide) both overall and within each subgroup. In the following only the overall subgroup analysis data are presented.

Change From Baseline in HbA1c in Specific Demographic Subgroups

Age

The treatment effect on HbA1c for albiglutide versus placebo was seen across all 3 age categories (<65 years, ≥65 to <75 years, and ≥75 years). There were no treatment differences between albiglutide and OAD or insulin within each of the 3 age categories. In comparing albiglutide to liraglutide in the subgroup of subjects aged ≥65 years, there was no difference in the treatment effect, although in younger subjects liraglutide achieved a slightly greater reduction in HbA1c compared to albiglutide (difference in LS means 0.24% [95% CI: 0.10, 0.39]), similar to the result for overall difference.

Gender

The treatment effect on HbA1c for albiglutide versus placebo was seen across both genders. There were no treatment differences between albiglutide and OAD or insulin within each gender. Comparing albiglutide to liraglutide, in the subgroup of male subjects, there was no difference in the treatment effect, although in women liraglutide achieved a greater reduction in HbA1c compared to albiglutide (difference in LS means 0.4% [95% CI: 0.22, 0.58]).

Race/Ethnicity

Large numbers of subjects of non-white race/ethnicity were recruited into the Phase III studies (716 [14.6%] of African-American/African heritage, 305 (6.2%) American Indian or Alaskan native, 174 (3.6%) Asian - Central/South Asian Heritage, 173 (3.5%) Asian - East Asian Heritage, 12 (0.2%) Asian - Japanese Heritage, 202 (4.1%) Asian - South East Asian Heritage, 21 (0.4%) Native Hawaiian or Other Pacific Islander and 1276 (26.1%) Hispanic/Latino. The treatment effect on HbA1c for albiglutide versus placebo was consistent across all race/ethnicity subgroups, and the magnitude of the HbA1c reduction for albiglutide versus placebo in African-American, Hispanic, and Asian subjects was similar to that for non-Hispanic white subjects.

Compared to OADs in the integrated analyses, albiglutide achieved a similar treatment effect in non-Hispanic white, Hispanic, and Asian subjects. There appeared to be a positive HbA1c treatment difference in favour of albiglutide versus OAD therapies in African-American subjects (difference in LS means -0.40%, 95% CI: -0.69, -0.10).

Compared to insulin, albiglutide achieved a similar treatment effect in African American, non-Hispanic white, and Hispanic subjects. There appeared to be a positive HbA1c treatment difference in favour of albiglutide versus insulin in Asian subjects (difference in LS means -0.52%, 95% CI: -0.83, -0.22).

Comparing albiglutide to liraglutide, a treatment difference in favour of liraglutide was observed in black and white subjects and those subjects who were not Hispanic or Latino. The difference in treatment effect was of similar magnitude across these subgroups (difference in LS means ranged between 0.20% and 0.43%). However, albiglutide achieved a similar treatment effect to liraglutide in Hispanic/Latino subjects (difference in LS means -0.02%, 95% CI: -0.25, 0.22).

Region

The treatment effect on HbA1c of albiglutide versus placebo was seen across all regions, and the magnitude of the HbA1c reduction for albiglutide versus placebo was also consistent across all regions and also within different areas of the US.

Compared to OAD therapy in the integrated analyses, albiglutide achieved a similar treatment effect in all regions although in the Rest of the World region a treatment effect in favour of albiglutide versus OAD was noted (difference in LS means -0.38%, 95% CI: -0.61, -0.15). Within the US, the treatment effect for albiglutide versus OAD was consistent in all areas.

Compared to insulin, albiglutide achieved a similar treatment effect in all regions although in the Asia region a treatment effect in favour of albiglutide versus insulin was noted (difference in LS means -0.55%, 95% CI: -0.94, -0.15). Within the US, the treatment effect for albiglutide versus OAD was consistent in all areas.

Comparing albiglutide to liraglutide, the treatment effect of albiglutide versus liraglutide was consistent across areas within the US as well as the ex-US region as was in favour of liraglutide.

Duration of T2DM

The treatment effect on HbA1c for albiglutide versus placebo was seen across all 3 categories of diabetes duration, and the magnitude of the HbA1c reduction for albiglutide versus placebo was also consistent within each category.

Compared to OADs, albiglutide achieved a greater HbA1c treatment effect in subjects with diabetes duration <5 years (difference in LS means -0.20%, 95% CI: -0.36, -0.04) although the treatment effect was similar in patients with longer duration of diabetes.

Compared to insulin, albiglutide achieved a similar treatment effect in all 3 categories of diabetes duration.

Comparing albiglutide to liraglutide, the treatment effect of albiglutide versus liraglutide was consistent across all categories of diabetes duration, favouring liraglutide.

Baseline HbA1c

No summary presentation of subgroup analyses by baseline HbA1c has been provided, however, the data is present in the file. As known form other antidiabetic medications, the treatment effect was larger with higher baseline HbA1c.

BMI

No summary presentation of subgroup analyses by BMI has been provided, however, the data is present in the file. No apparent difference in treatment effect by BMI was observed.

Effect of Anti-albiglutide Antibodies on Efficacy

Immunogenicity data from the 7 integrated Phase III studies were analyzed for any effects of anti-albiglutide antibodies on the change from baseline in HbA1c or FPG. The analysis involved data from 2098 albiglutide-treated subjects, 116 of which (5.5%) tested positive for anti-albiglutide antibodies at 1 or more time points post-baseline. None of the antibodies were neutralizing, except for 1 follow-up sample from a baseline-positive subject who tested weakly

positive for albiglutide neutralizing antibodies. The change from baseline in HbA1c at the primary endpoint (defined for each individual study) was similar for antibody-positive and antibody-negative subjects (-0.72% vs -0.71%, respectively). The presence of neutralizing antibodies in the individual baseline-positive subject did not appear to impact the glycaemic response to albiglutide, because the change in HbA1c at the primary endpoint was -2.90%. There was no trend seen of greater or lesser HbA1c lowering when maximum titer values per subject were plotted against change from baseline in HbA1c or against FPG levels at the primary endpoint. Furthermore, there was no correlation between maximum antibody titer and FPG levels at the time of maximum antibody titer.

In Study GLP114130, anti-albiglutide antibodies developed in 3.0% (6/231) of evaluated albiglutide-treated subjects. Antibody titers were very low (<500) and antibody incidence and characteristics were similar to those reported for subjects from other Phase III studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The safety and efficacy of albiglutide in humans has been evaluated in 10 clinical studies. A total of 6043 subjects have participated in the clinical development program, of which 3358 have received albiglutide. Three of the Phase III studies were complete (GLP114179, GLP108486, and GLP114130) at submission, and 5 were ongoing in long-term extension phases past the primary endpoints (GLP112753, GLP112754, GLP112755, GLP112756 and GLP115757). The initial analyses for this submission were conducted when all remaining subjects in the five 156-week studies had completed at least 2 years of treatment and had been assessed for the primary efficacy endpoint. The final study reports for the extension were submitted with the Day 121 responses. Two dose-finding studies were performed. The phase III programme covers the different aspects of the development of medicinal products for the treatment of diabetes as outlined in the EMA Guideline (CHMP/EWP/1080/00 Rev. 1). The study program is further in line with given scientific advice.

During the clinical development of albiglutide there was a change in the manufacturing processes used to produce albiglutide active substance. All the Phase III clinical studies were conducted with Process 2 drug product. Process 3 is the intended commercial formulation. Data in support of a clinical comparability in terms of efficacy and safety between Process 2 and Process 3 have been provided from the bioequivalence study GLP114856. In addition, patients in studies GLP112754 and GLP112756 were switched to the Process 3 drug product after 2 years to provide further clinical data. The strategy to switch patients in the ongoing phase III studies was subject of a Scientific Advice provided in December 2010. In total 456 patients have been switched from Process 2 to Process 3 in studies GLP112754 and GLP112756 with an average exposure of 35 weeks (range 8-65 weeks). However, there is no indication of any substantial and clinically relevant difference in the efficacy of Process 2 and Process 3 albiglutide, which was therefore found to be satisfactory by CHMP.

Two dose-finding studies were performed. Data provided with study GLP110125, which included eight different dose regimens and exenatide (Byetta) as an external control, support the choice of the 30 mg weekly dose. Higher doses (50 mg and 100 mg) were tested with wider dosing

intervals resulting in a comparable or lower effect than the 30 mg weekly dose. Study GLP110932 investigated somewhat different dosing regimens that study GLP110125; however, the 30 mg weekly dose was included. The effect on HbA1c was comparable to that observed in study GLP110125.

The 50 mg weekly dose was not included in the dose finding studies but was investigated within the phase III studies. Both the 30 mg and 50 mg weekly doses were evaluated in studies GLP112756 (one study arm 30 mg and one study arm 50 mg) and GLP114179 (forced uptitration) although not formally compared. Slightly larger reductions in HbA1c and FPG were observed with the higher dose.

In studies GLP108486, GLP112753, GLP112754, and GLP112757, the dose was uptitrated based on clinical need, i.e. increasing HbA1c. With this strategy, HbA1c was maintained or further decreased up to 130 weeks. It is noted that in studies GLP108486, GLP112753, GLP112757, and GLP112754 (optional uptitration of albiglutide from 30 mg weekly to 50 mg weekly if the subject met the protocol-defined uptitration criteria), a total of 77.0% of albiglutide subjects had their dose uptitrated from 30 mg to 50 mg indicating that the 30 mg dose may not be sufficient in the majority of the patients. It has been adequately shown that uptitration of the dose from 30 mg to 50 mg adds to the glycaemic control and the data support the current recommendations on dosing given in section 4.2 of the SmPC.

The Phase III study program included studies adequately designed to investigate the use of albiglutide both in monotherapy and as add-on to metformin, metformin plus SU, TZDs and basal insulin. Further to this, sitagliptin, glimepiride, insulin glargine, insulin lispro and liraglutide were included as active comparators in the program. A separate study investigated the use of albiglutide therapy in patients with renal impairment. The inclusion and exclusion criteria were generally more open than usually seen. No upper age limit was applied apart from study GLP108486. Patients with a history of CV disease were allowed to participate.

All studies allowed rescue medication and some of the studies allowed uptitration of albiglutide. Recommendations regarding rescue medication were given; however, the final decision was left to the discretion of the investigator. Allowing rescue medication made it possible to keep patients within the study until follow-up was complete also when placebo was used as comparator.

The primary and secondary endpoints were adequate and in line with current guidelines. In the follow-up advice given in March 2011, the CHMP expressed that time to hyperglycaemia rescue was considered of special interest, considering that patients were to continue in the studies also after rescue.

The randomisation and the stratification in each study was considered appropriate as well as blinding procedures. The justification for the open-label studies is acceptable.

The sample size calculations seemed appropriate. A non-inferiority margin larger than 0.3% is generally not accepted, however, whether non-inferiority will be accepted or not ultimately depends on the assessment of the data. The randomisation and the stratification in each study seem appropriate as well as blinding procedures. The justification for the open-label studies is acceptable.

The same overall statistical analysis approach was used for all the phase III studies and statistical methods were in general appropriate. Missing data, specifically post rescue data that in

the primary analysis were ignored and hence treated as missing was handled as last observation carried forward (LOCF) as primary approach. Subjects who qualified for hyperglycaemia rescue before the primary efficacy assessment had their HbA1c recorded at the time of rescue and carried forward for primary analyses. Since the initiation of rescue medication should be seen as evidence of lack of efficacy, LOCF in subjects qualifying for rescue is then considered acceptable if the value carried forward implied treatment failure. In all other cases the acceptance of LOCF rests on if there were differences between treatment arms in the proportion and timing of withdrawals, and the reason for the withdrawals.

In summary across studies where albiglutide were compared to placebo, both the proportion of subjects rescued as well as the proportion of values carried forward was higher in the placebo groups than in the albiglutide treatment arms.

While the proportion of values carried forward in the placebo arms ranged from 58% (week 52, study GLP112755) to 76% (week 104, study GLP112753) the corresponding proportions for albiglutide arms ranged from 32% (week 52, study GLP112755) to 46% (week 104, study GLP112753). The proportion of subjects rescued was approx. 40-50% in the placebo groups and approx. 22-25% in the albiglutide 30 mg weekly treatment groups.

Comparing albiglutide vs. the different active comparators the proportion of subjects rescued and the proportion of values carried forward were approximately similar. Regarding the proportion of values carried forward and looking across the active treatment groups including albiglutide there were some differences but foremost between studies depending on the time point for primary assessment. In summary the proportion of values carried forward in the analyses were 16-30% week 26/32, 35-40% for analyses week 52 and 45-55% for week 104 (GLP112753).

The main reason for using LOCF seems to have been subjects qualifying for rescue treatment. Overall, looking at the active treatment arms including albiglutide, the proportion of subjects rescued relative to the proportion of values carried forward were approx. 50-70% in analyses week 52/104 with, however, bigger differences between the short term studies, from 38% (liraglutide study 114179) through 94% (both albiglutide and lispro insulin in study GLP108486). In the placebo arms this ratio was, not surprisingly considering the higher proportions of subjects qualifying for rescue, in general somewhat higher 60%-80% (week 52/104).

For subjects who qualified for hyperglycaemia rescue, follow-up assessments continued beyond rescue, and a number of sensitivity analyses for the primary endpoint were provided including analyses using data after initiation of rescue therapy. Sensitivity analyses were mainly based on ITT using observed cases only (i.e. an OC algorithm) with analyses both excluding and, including post rescue values respectively. While an OC approach excluding post rescue data may be considered a "best case" scenario foremost for subjects in active arms under the assumption that the active treatment (i.e. albiglutide) is effective, analyses including post rescue may be considered a "best case" scenario foremost/also among subjects receiving placebo*.*

It is evident from the sensitivity analyses based on comparisons of albiglutide vs. placebo, that including post rescue data had an impact on the outcome. While a high proportion of values carried forward in the placebo groups due to high proportions of subjects in need of rescue seems to have had an impact on the difference seen between albiglutide and placebo this can be considered as additional proof for the efficacy of albiglutide. In the analysis including post rescue data (ITT-OC), the difference between albiglutide and placebo was, although smaller, however

still highly statistically significant in favour of albiglutide in all studies except for albiglutide 30 mg weekly in study GLP112756. Here, there was still a statistically significant difference for albiglutide 50 mg weekly vs. placebo. The loss of superiority, 30 mg vs. placebo, may be due to the relatively small number of subjects per arm and that 50% of subjects in the placebo group qualified for rescue.

In the studies with comparisons of albiglutide vs. an active comparator, sensitivity analyses supported the primary outcome with in general small differences in point estimates and corresponding 95% CI.

Using the same analysis approach in all studies implied that there were no differences in how analysis populations were defined. What is not supported is that irrespective of if the objective was to show superiority or non-inferiority the primary analysis was to be based on an ITT population. Although in some studies post-hoc, sensitivity analyses were however also performed based on ITT but excluding subjects with major protocol deviations. In two of the studies (GLP112754 vs. insulin glargine and GLP108486 vs. lispro insulin) non-inferiority was showed but not superiority. The conclusion of non-inferiority was however further supported by a sensitivity analyses based on ITT (LOCF) excluding subjects with major protocol deviations.

Overall, the studies appear to have been well conducted. In every study, 1-3 sites were closed because of repeated noncompliance with GCP/ICH guidelines, however, these issues appear to have been adequately handled. Other sites were closed for reasons such as inactivity. All these issues as well as protocol deviations have been transparently accounted for in the study protocols. Additional analyses were also performed, excluding patients from those sites showing that the impact were negligible due to the small number of subjects concerned.

In order not to jeopardize the five studies still ongoing at the time of data cut and analyses for submission, a work process flow was defined and documented separately. While not easy to penetrate what impact, if any, this none the less might have had on the studies still ongoing, the procedures seem appropriately planned. Of importance is that all primary endpoint assessments were already performed at the time for data cut.

In summary from a methodological aspect, data are considered robust in that the totality of evidence presented seems to support the efficacy of albiglutide. No serious issues regarding the methodology have been identified. Although not fully clear whether the values carried forward in case of rescue truly implied treatment failure or when in time LOCF were applied in other cases this is not thought to have an impact sufficient to alter overall conclusions regarding efficacy.

Efficacy data and additional analyses

All studies have reported the primary endpoint and extensions have been finalised. Data up to three years were presented. Discontinuation rates were relatively high (30-37 %) which should be seen in the light of the long duration of the studies. An additional 4-7 % of patients dropped out during the third study year. In the shorter studies, discontinuation rates were about 15 %. When looking at the individual studies, there were no gross imbalances between the different study arms with regards to discontinuations. Differences in withdrawal due to AEs were small.

The population included is considered representative for T2DM and with no large differences across the study program, with the exception of study GLP114130 (renal impairment), which

included older patients who were less obese. The duration of disease was longer in study GLP108486 (add-on to insulin) and study GLP114130. Mean HbA1c was slightly above 8 % in all studies. The majority of patients in all studies had signs of diabetes complications. CV co-morbidity represented as prior MI was present in 3-9 % of patients. In all studies treatment groups were well balanced with regards to baseline characteristics.

The baseline medication in studies investigating albiglutide as add-on treatment was adequate in all relevant studies.

The majority of patients were Caucasian. Less than 5 % of subjects were recruited in Europe, whereas the vast majority were recruited in the US.

Study GLP112756 is considered as the pivotal study with regards to the monotherapy indication as this study compared both the 30 mg and 50 mg weekly dose of albiglutide to placebo in drug-naïve patients. Consistent and clinically relevant placebo-corrected reductions of baseline HbA1c was observed for both doses with a slightly higher placebo-corrected decrease with the higher dose (-0.84 % vs -1.04 % for the lower and higher dose, respectively). This was supported by a decrease in FPG. The rate of responders (subjects achieving HbA1c < 7.0 %) was higher in the low dose group (49.0 %) compared to the high dose group (40.2 %) whereas the responder rate in the placebo group was 21.4 %. This may be explained by the difference observed in baseline HbA1c. In the low dose treated group, weight reduction was numerically less (-0.39 kg) than observed in the placebo treated group (-0.66 kg), whereas a numerically greater weight reduction compared to placebo was observed in the high dose group (-0.86). Thus, this study shows a significant and clinically relevant effect of albiglutide versus placebo on HbA1c whereas no significant effect on weight was observed.

Three studies investigated the use of albiglutide as add-on to metformin (GLP112753), add-on to TZD +/- metformin (GLP112755) or add-on to metformin and SU (GLP112757). In all three studies, statistically significant and clinically relevant placebo-corrected reductions in baseline HbA1c, ranging from -0.75 to -0.91 % were observed. This was supported by reductions in FPG. Responder rates were significantly higher in all three studies compared to placebo, with differences to placebo ranging from 21 - 30 %. Weight reduction (-0.42 to -1.21 kg) did not differ from that observed with placebo treatment (-0.40 to -1.0 kg) and in study GLP112755 (add-on to TZD) a weight increase was observed in both groups (+0.28 kg for albiglutide and +0.45 kg for placebo). A clinically relevant effect of albiglutide when used as add-on was shown, however, there are remaining uncertainties with regards to the background treatment that need to be resolved before a definite conclusion can be drawn. The findings with regards to weight reduction were consistent with those observed in the monotherapy study.

Five studies included one or two active comparators added to various background therapies. In study GLP112753, albiglutide was compared to sitagliptin (100 mg/day) and glimepiride (2-4 mg/day) as add-on to metformin. Superiority could be shown for albiglutide versus both sitagliptin and glimepiride. The treatment effect on reduction of baseline HbA1c was low for both sitagliptin (-0.28 %) and glimepiride (-0.36 %), however, the placebo-corrected outcome for sitagliptin and glimepiride in study GLP112753 were -0.55% and -0.63% respectively, which is in line with published data (taking into account that the primary endpoint was measured at 104 weeks). In the sitagliptin group, the mean duration of exposure to the 100 mg dose was 637 days (which is comparable to the exposure time in the albiglutide treated group). The mean

albiglutide dose at Week 104 was 40.52 mg (manual calculation) and the mean glimepiride dose at Week 104 was 3.076 mg (manual calculation). It thus appears that the patients on active comparators were adequately dosed. The weight reduction was numerically less with sitagliptin than with albiglutide whereas a weight increase was observed with glimepiride as expected.

In study GLP112757, albiglutide was compared to pioglitazone as add-on to metformin and SU. Pioglitazone was shown to be superior to albiglutide with a treatment difference in reduction of baseline HbA1c of 0.25 % (95 % CI, 0.10, 0.40). This was supported by the rates of responders and outcome of FPG. An increase in weight was observed in the pioglitazone treated group whereas a slight weight reduction was observed in the albiglutide treated group comparable to that observed in the placebo treated group included in the study.

Study GLP112754 compared albiglutide with insulin glargine as add-on to metformin +/- SU. Non-inferiority for albiglutide vs insulin glargine could be shown with regards to the reduction of baseline HbA1c (-0.11 %; 95 % CI; -0.04, 0.27, thus the upper limit of the 95 % CI below the 0.3 % non-inferiority margin). Responder rates were comparable between the two groups (about 32 % in both groups). Treatment with insulin glargine resulted in a significantly lower FPG compared to albiglutide treatment. As expected, albiglutide treatment resulted in a modest weight reduction of 1.05 kg whereas insulin glargine treatment resulted in a weight increase of 1.56 kg. In the insulin glargine treatment group, the median daily dose of insulin glargine used prior to rescue increased by 3-fold from the study start to the study end. Subjects in the insulin glargine group had a starting total daily dose of insulin glargine that ranged between 2 and 40 units (median daily dose of 10 units), at Week 52 had a total daily dose of insulin glargine that ranged between 3 and 230 units (median daily dose of 30 units), and an ending total daily dose of insulin glargine that ranged from 0 to 220 units (median daily dose of 34 units). Guidance for uptitration of the insulin dose based on FPG were in place, and the patients in the insulin glargine treated group appears to have been adequately dosed. Thus the data showing non-inferiority appear robust.

Study GLP108486 compared albiglutide with insulin lispro as add-on to insulin glargine + OADs. In this study, a wide variety of background treatment was allowed. These treatments were balanced between groups. The absolute HbA1c reduction was slightly higher in the albiglutide treated group (-0.82 % vs -0.66 %) and non-inferiority versus insulin lispro was shown. Comparable outcomes with regards to rate of responders and FPG supported the primary endpoint. Responder rates were somewhat lower than in the other studies, which may be explained by the fact that this study included patients with a longer diabetes duration and a higher baseline HbA1c. The lispro was started based on the subject's home blood glucose monitoring data and distributed among the subject's meal times at the investigator's discretion and based on the standard of care for multiple-dose insulin therapy at the study site. Mean doses increased from 15 units to 34 units per day. Thus it appears that insulin lispro was adequately adjusted during the study. Thus the data showing non-inferiority appear robust.

Study GLP114179 compared albiglutide with liraglutide as add-on to metformin, SU and TZD (either alone or in combination). Liraglutide was statistically superior to albiglutide with an absolute difference in reduction of baseline HbA1c of 0.21 %. This was supported by a higher rate of responders and a significantly higher reduction of FPG. A statistically significant, larger reduction in body weight was observed with liraglutide (difference between treatments 1.55 kg).

Across the study program only a modest weight reduction was observed with albiglutide treatment. The Applicant puts forward two potential explanations for the difference in weight reducing potential between albiglutide and liraglutide. Firstly, the incidence of nausea and vomiting was more common with liraglutide which may contribute to the weight reduction. Secondly, liraglutide has been shown to act directly on areas in the brain controlling the sense of hunger. Albiglutide, being a larger protein, is less likely to diffuse into the brain and will thus only exert its effects indirectly via the afferent gastrointestinal nervous system. This was acknowledged by CHMP.

As hyperglycaemia was allowed in all studies, time to hyperglycaemia rescue was included as a secondary efficacy endpoint. Albiglutide treatment resulted in a significant longer time to hyperglycaemia rescue when compared to placebo, whereas no difference was observed between albiglutide and insulin glargine.

A durability of effect up to 104 weeks could be demonstrated. This was observed both in the study were no uptitration was allowed (GLP112755) and in studies with optional or forced uptitration. When post-titration data are included, the difference between albiglutide and comparators is attenuated but remain. Efficacy data up to three years of treatment has been provided with the long-term extensions of studies GLP112757, GLP112753, GLP112754 GLP112755 and GLP112756. Efficacy was maintained over the entire study duration, with a lower proportion needing rescue in the albiglutide treated groups compared to placebo. Comparable rescue rates were observed for albiglutide and active comparators. Body weight continued to slowly decrease or was maintained across all studies.

Study GLP114130 was focused on the effect of albiglutide in patients with renal impairment. The other Phase III albiglutide studies excluded subjects with moderate and severe renal impairment. In this study, albiglutide again was shown to be superior to sitagliptin treatment (HbA1c reduction -0.83 % vs -0.52 % for albiglutide and sitagliptin, respectively) and in this study the treatment effect with sitagliptin was as expected (-0.52 %). For both treatments there was an increased effect with decreasing renal function. The effect was maintained over the 52 week treatment period. More patients in the sitagliptin group needed rescue or withdrew from the study. Due to the low number of subjects with severe renal impairment, the data has to be interpreted with caution. The limited data is reflected in the SmPC. The outcome of FPG and responder rates supported the primary outcome. The body weight reduction was modest in both groups and higher in the albiglutide treated group.

Further to this, a subgroup analysis of patients with impaired renal function defined as eGFR 60 – 90 mL/min/1.73 m^2 included in the 7 phase III studies give no indication of a difference in treatment effect due to renal function. No subgroup analysis for renal function was conducted to compare albiglutide with liraglutide.

In the integrated analysis of the 7 Phase III studies (excluding study GLP114130), 5.5 % of subjects treated with albiglutide were found to have anti-albiglutide antibodies and only one patient had neutralizing antibodies. There was no difference in the change from baseline in HbA1c between antibody positive and antibody negative subjects. Anti-albiglutide antibodies, regardless of their titer, did not appear to impact the efficacy of albiglutide treatment.

Subgroup analyses performed across the 7 phase III studies showed that the effect of albiglutide does not appear to be affected by age, however, the number of patients in the age group > 75 is

low and the data has to be interpreted with caution. The subgroup analysis reveals no difference in effect due to gender. In the placebo controlled pool, no difference in the treatment effect due to race/ethnicity was observed, whereas the effect appears larger in the Asian population when albiglutide was compared to insulin. However, overall there appears to be no influence of race/ethnicity on the effect of albiglutide.

The subgroup analysis revealed no difference in effect due to duration of disease. No summary presentation of subgroup analyses by baseline HbA1c or BMI has been provided, however, the data is present in the file. As known from other antidiabetic medications, the treatment effect was larger with higher baseline HbA1c. No apparent difference in treatment effect by BMI was observed.

The subgroup analyses revealed no difference in treatment effect by region, race/ethnicity or BMI. In spite of the low recruitment of European patients, the subgroups analyses support the extrapolation of the results from the study program to a European population.

2.5.4. Conclusions on the clinical efficacy

The efficacy of albiglutide as monotherapy and as add-on to metformin, metformin + SU and TZDs was investigated in a well-designed and conducted study program. A clinically relevant and statistically significant effect on HbA1c was observed when albiglutide was used as monotherapy and as add-on to different background therapies. The effect size with regard to the primary outcome parameters was a placebo-corrected reduction of the HbA1c by -0.8% - 1.0% in most studies. Data indicate that albiglutide was superior to sitagliptin and glimepiride, and non-inferior to insulin glargine and insulin lispro. Pioglitazone and liraglutide were found to be superior to albiglutide. Data showing a maintained effect up to three years of treatment has been provided. Across the study program a small weight reduction was observed with albiglutide treatment, not differing from that observed with placebo. Thus based on these data albiglutide is considered to be weight neutral.

2.6. Clinical safety

The overall exposure in the entire albiglutide clinical development program (all phases/all treatments) was 6258 subjects, 3122 T2DM subjects treated with albiglutide, 2689 T2DM subjects treated with placebo or active comparators, 252 healthy volunteers treated with albiglutide and 49 subjects with CHF treated with albiglutide, in an additional ongoing Phase II study (Study GHF112670).

Patient exposure

Overall exposure in the 7 studies included in the Phase III integrated safety population was 2284 subjects for all comparators (3628.46 person-years) and 2116 subjects for albiglutide (3369.65 person-years). In addition, in the Phase III renal impairment study GLP114130, 249 (253.84 person-years) subjects were exposed to albiglutide and 246 subjects (238.36 person-years) to sitagliptin. Disposition of subjects by treatment group (albiglutide vs. all comparators, placebo and active comparators, respectively) is summarized in the Table 17 below. The number and proportion of subjects with >52 weeks exposure was similar for all comparators 1366 (59.8%)

and albiglutide 1182 (55.8%) subjects. Overall, there were 2116 subjects with a total of exposure of 1720 person-years to 30 mg albiglutide and 1416 subjects with a total of exposure of 1650 person-years exposed to 50 mg albiglutide (2280 person-years exposure to a maximum dose of 50 mg albiglutide).

The comparative assessment of the clinical safety of albiglutide is primarily based on the the Phase III integrated safety population. Trials not included in the integrated database included 13 clinical pharmacology studies, 2 Phase IIb studies and 1 ongoing Ph II study in non-diabetic subjects (congestive heart failure).

Table 17 Subject disposition by treatment group comparison (Phase III Integrated Safety Population)

	Albiglutide vs. All Comparators[1]		Albiglutide vs. Placebo[2]		Albiglutide vs. Active Comparators[3]	
	All Comparators	Albiglutide	Placebo	Albiglutide	Active Comparators	Albiglutide
	N=2284 (%)	N=2116 (%)	N=468 (%)	N=923 (%)	N=1816 (%)	N=1766 (%)
Safety population	2284 (100.0)	2116 (100.0)	468 (100.0)	923 (100.0)	1816 (100.0)	1766 (100.0)
Completed active treatment	582 (25.5)	589 (27.8)	0	0	582 (32.0)	589 (33.4)
Discontinued active treatment	659 (28.9)	572 (27.0)	191 (40.8)	301 (32.6)	468 (25.8)	471 (26.7)
Continuing study participation	1043 (45.7)	955 (45.1)	277 (59.2)	622 (67.4)	766 (42.2)	706 (40.0)
Number of subjects rescued	781 (34.2)	704 (33.3)	262 (56.0)	305 (33.0)	519 (28.6)	578 (32.7)

Adverse events

The summary of adverse events reported by at least 5% in albiglutide-treated subjects or in the all comparators group in the Phase III Integrated Safety Population is shown in Table 18 below.

Table 18 On-therapy adverse events overall, all comparators versus albiglutide, in more than 5% of subjects in either treatment group (Phase III Integrated Safety Population)

	All Comparators (N=2284)		Albiglutide (N=2116)	
Preferred Term	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Upper respiratory tract infection	256 (11.2)	337 / 9.29	274 (12.9)	345 / 10.24
Diarrhoea	209 (9.2)	273 / 7.52	272 (12.9)	374 / 11.10
Nausea	242 (10.6)	283 / 7.80	243 (11.5)	351 / 10.42
Nasopharyngitis	209 (9.2)	273 / 7.52	190 (9.0)	248 / 7.36
Injection site reaction	45 (2.0)	142 / 3.91	187 (8.8)	1171 / 34.75
Urinary tract infection	187 (8.2)	254 / 7.00	156 (7.4)	196 / 5.82
Headache	181 (7.9)	228 / 6.28	156 (7.4)	190 / 5.64
Hypertension	165 (7.2)	180 / 4.96	156 (7.4)	166 / 4.93
Sinusitis	111 (4.9)	145 / 4.00	130 (6.1)	157 / 4.66
Back pain	140 (6.1)	160 / 4.41	125 (5.9)	133 / 3.95
Bronchitis	147 (6.4)	173 / 4.77	123 (5.8)	144 / 4.27
Arthralgia	135 (5.9)	161 / 4.44	122 (5.8)	154 / 4.57
Cough	134 (5.9)	162 / 4.46	115 (5.4)	132 / 3.92
Oedema peripheral	136 (6.0)	146 / 4.02	79 (3.7)	84 / 2.49

Source Data: IAS Table SP3-7.1.1.

AE = adverse event.

Note: On-therapy AEs are those that had a start date on or after the first day of study medication and within 56 days after the end of study medication. This summary presents on-therapy AEs that occurred in >5% of the subjects in either treatment group. For each level of summarization, a subject was counted once if the subject reported 1 or more AEs. Percentages are based on the number of subjects in each treatment group. Hypoglycemic events are excluded from this table and are reported separately. The preferred terms are presented by decreasing proportions of subjects with AEs for the albiglutide treatment group.

1. Number of AEs = the total number of AEs at each level of summarization. Density per 100 person-years = 100 * (number of

The most common adverse events (>10%) associated with albiglutide are diarrhoea (13%) and nausea (12%). This is not unexpected since gastrointestinal adverse events are common among GLP-1 receptor agonists. The prevalence of nausea is somewhat lower than previously reported for other GLP-1 receptor agonists (exenatide 40-50 %, liraglutide 10-20% and lixisenatide 20-25%). In addition, the adverse events occurring with a frequency ≥5% and at a higher number of AEs/density for albiglutide were injection site reactions (8.8% vs. 2.0%). In study GLP114179 in which albiglutide was compared open-label to liraglutide injection site reactions occurred in 6.9% vs. 1.2% of patients, respectively.

The summary of adverse events reported more frequently in the albiglutide group at any time point in the Phase III Integrated Safety Population is shown in Table 19 below.

Table 19 On-therapy adverse events occurring more frequently in the albiglutide group at any time point. albiglutide versus all comparators (Phase III Integrated Safety Population)

	Week 26			Week 52			Overall (104+ Weeks)		
AE Preferred Term	All Comparators (N=2284) n (%)	Albiglutide (N=2116) n (%)	RR and 95% CI[1]	All Comparators (N=2284) n (%)	Albiglutide (N=2116) n (%)	RR and 95% CI[1]	All Comparators (N=2284) n (%)	Albiglutide (N=2116) n (%)	RR and 95% CI[1]
Diarrhoea	152 (6.7)	212 (10.0)	1.53 (1.25, 1.88)	177 (7.7)	236 (11.2)	1.46 (1.21, 1.76)	209 (9.2)	272 (12.9)	1.43 (1.20, 1.71)
Injection site reaction	32 (1.4)	135 (6.4)	4.18 (2.87, 6.08)	36 (1.6)	167 (7.9)	4.74 (3.31, 6.79)	45 (2.0)	187 (8.8)	4.35 (3.13, 6.04)
Constipation	57 (2.5)	64 (3.0)	1.29 (0.89, 1.85)	73 (3.2)	80 (3.8)	1.25 (0.90, 1.74)	87 (3.8)	100 (4.7)	1.30 (0.96, 1.75)
Dyspepsia	47 (2.1)	54 (2.6)	1.21 (0.82, 1.79)	51 (2.2)	67 (3.2)	1.39 (0.97, 1.98)	58 (2.5)	80 (3.8)	1.37 (0.99, 1.92)
Fatigue	36 (1.6)	44 (2.1)	1.28 (0.81, 2.04)	46 (2.0)	56 (2.6)	1.27 (0.85, 1.91)	61 (2.7)	74 (3.5)	1.26 (0.88, 1.80)
Gastrooesophageal reflux disease	34 (1.5)	40 (1.9)	1.29 (0.81, 2.07)	41 (1.8)	50 (2.4)	1.29 (0.84, 1.97)	47 (2.1)	64 (3.0)	1.49 (1.01, 2.20)

Source Data: IAS Table SP3-8.1.1, IAS Table SP3-8.2.1, IAS Table SP3-8.3.1,

1. The RR and 95% CI for the albiglutide group compared with the placebo group were calculated using the Cochran-Mantel-Haenszel estimate of RR stratified by study.

Diarrhoea, injection site reactions, constipation, dyspepsia, fatigue and gastroesophageal reflux disease (GERD) were the adverse events that were reported more frequently in albiglutide-treated subjects. In addition, the reported incidence of pneumonia was significantly higher [RR 2.28, 95%CI (1.25 to 4.19)] among albiglutide treated subjects (1.75%) vs. all comparators (0.79%). This imbalance in reporting of pneumonia between albiglutide and all comparators was noted at all-time points and across all of the individual studies. A potential mechanism for pneumonia associated to albiglutide has been discussed by the Applicant; however no mechanism has been identified. Pneumonia is included in 4.8 of the SmPC and, furthermore, pneumonia is also included as an identified risk in the RMP. There was also a slightly higher reported incidence of atrial fibrillation/flutter in the albiglutide group when compared to the all comparators group across the 8 Phase III trials. The proportion of subjects having atrial fibrillation or flutter, which is also included as an identified risk in the RMP, was 1.18% in the albiglutide group (25/2116, approximately 7.4 events/1000 patient years) and 0.48% in the all comparators group (11/2284, approximately 3.0 events/1000 patient years).

In study GLP112756 safety of 2 dose levels albiglutide (30 vs. 50 mg weekly) were compared with placebo. The incidence of on-therapy AEs considered related to study medication was higher in the albiglutide groups (34.7% in the 30-mg group and 36.4% in the 50-mg group) compared with the placebo group (20.8%). The overall AE rate in the 2 albiglutide groups (120.31 AEs/100

person-years in the albiglutide 30-mg group and 94.06 AEs/100 person-years in the albiglutide 50-mg group) was higher than that seen in the placebo group (60.30 AEs/100 person-years). This finding was mainly driven by a higher incidence of injection site reaction (ISRs) events in the albiglutide groups and ISRs were more common on the highest dose. Analysis of the integrated database comparing safety profiles between the two dose levels (30 vs. 50 mg weekly) of albiglutide, showed that the event density (i.e. the number of AEs divided by person-years x 100) for AEs overall and across all SOCs was higher in the albiglutide 30 mg group compared to the 50 mg group. This was also the case for a majority of individual AEs, including e.g. diarrhoea (event density 14.07 and 8.00 for 30mg and 50 mg respectively), nausea (13.78 and 6.91 respectively) and upper respiratory tract infection (11.40 and 9.03 respectively) in the albiglutide groups vs. all comparator comparison group. A plausible explanation for the overall lower event densities for AEs for 50 mg compared to 30 mg albiglutide could be as related to a tolerate treatment with albiglutide 30 mg before uptitration to 50 mg, wherefore many adverse event rates could be expected to be lower with use of albiglutide 50 mg as compared to 30 mg.

Clinical Comparability of Process 2 (Phase III Material) and Process 3 (Commercial Formulation) Derived Albiglutide Product – Safety

During the clinical development of albiglutide (GSK716155) there have been three manufacturing processes used to produce albiglutide active substance: Process 1, (Phase I, Phase II studies) Process 2 (Phase II Japan and Phase III studies) and Process 3 (intended commercial formulation).

In total, 598 subjects have been exposed to Process 3 albiglutide for a mean duration of 215 days.

Adverse events

The overall rate of AEs (number/PYs) was generally lower in the switched group compared to the group only treated with Process 2 albiglutide. A slight increase in serious adverse event rate was observed after switch to Process 3: 9.31/100 person years before switch vs. 12.84/100 person years after switch, although the event rate was lower than patients remaining on Process 2 (22.05/100 patient years). Only 4 patients had AEs leading to withdrawal of treatment. Hypoglycaemia incidence rate decreased after switch to process 3, likely due to deterioration of blood glucose control over time in type 2 diabetes. No increase in injection side reactions was observed (49.29/100 patient years events before switch vs. 11.42 after). No events of pancreatitis were seen after switch although one post-therapy event of benign pancreatic neoplasm was reported. Other AEs of special interest occurred infrequently before and after switch, making it difficult to compare their incidence.

Serious adverse event/deaths/other significant events

In the Phase III integrated safety population, the overall incidence of on-therapy SAEs was similar for the all comparators compared with albiglutide (10.9%, 9.40/100 person-years vs. 11.2%, 9.85/100 person-years respectively; and placebo (11.1% vs. 13.7%), and active comparators groups (11.3% vs. 10.2%). The reporting of SAEs was comparable between the treatment groups. On-therapy SAEs that occurred in >4 subjects in the albiglutide group with a proportion of subjects more than 2-fold higher than the all comparators group were pneumonia, atrial fibrillation, transient ischemic attack, myocardial infarction and cerebrovascular accident as

shown in Table 20 below. The event density for SAEs overall was similar in the albiglutide 50 mg group compared to the 30 mg group vs. all comparators and placebo respectively. Infection and infestation SAEs were more frequently reported and with a higher event density with 50 mg albiglutide compared to 30 mg albiglutide and compared to the all comparator group vs. the placebo group. Cardiac disorders SAEs were reported more frequently with 30 mg albiglutide compared to 50 mg albiglutide and compared to the all comparator group; although not compared to the placebo group in which serious cardiac events were more frequently reported compared to both doses of albiglutide respectively. However, the number of cardiac SAEs was limited, and the higher incidence in the placebo group is reassuring.

Table 20 On-therapy serious adverse events – albiglutide versus all comparators, occurring in at least 0.2% of subjects in either treatment group (Phase III Integrated Safety Population)

System Organ Class SAE Preferred Term	All Comparators (N=2284)		Albiglutide (N=2116)	
	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Any SAE	249 (10.9)	341 / 9.40	236 (11.2)	332 / 9.85
Infections and infestations	40 (1.8)	46 / 1.27	56 (2.6)	66 / 1.96
Pneumonia	2 (0.1)	2 / 0.06	9 (0.4)	9 / 0.27
Gastroenteritis	3 (0.1)	4 / 0.11	5 (0.2)	5 / 0.15
Appendicitis	0	0	4 (0.2)	4 / 0.12
Cellulitis	11 (0.5)	11 / 0.30	4 (0.2)	9 / 0.27
Cardiac disorders	52 (2.3)	66 / 1.82	54 (2.6)	63 / 1.87
Coronary artery disease	17 (0.7)	19 / 0.52	10 (0.5)	11 / 0.33
Atrial fibrillation	2 (0.1)	3 / 0.08	9 (0.4)	9 / 0.27
Angina unstable	7 (0.3)	7 / 0.19	7 (0.3)	7 / 0.21
Acute myocardial infarction	9 (0.4)	9 / 0.25	6 (0.3)	6 / 0.18
Myocardial infarction	3 (0.1)	3 / 0.08	6 (0.3)	6 / 0.18
Cardiac failure congestive	9 (0.4)	9 / 0.25	4 (0.2)	4 / 0.12
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	37 (1.6)	38 / 1.05	23 (1.1)	23 / 0.68
Breast cancer	5 (0.2)	5 / 0.14	2 (0.1)	2 / 0.06
Nervous system disorders	22 (1.0)	26 / 0.72	23 (1.1)	26 / 0.77
Transient ischaemic attack	3 (0.1)	3 / 0.08	7 (0.3)	7 / 0.21
Cerebrovascular accident	3 (0.1)	3 / 0.08	6 (0.3)	6 / 0.18
General disorders and administration site conditions	26 (1.1)	28 / 0.77	21 (1.0)	22 / 0.65
Chest pain	17 (0.7)	18 / 0.50	12 (0.6)	12 / 0.36
Non-cardiac chest pain	4 (0.2)	4 / 0.11	5 (0.2)	5 / 0.15
Musculoskeletal and connective tissue disorders	26 (1.1)	27 / 0.74	18 (0.9)	21 / 0.62
Osteoarthritis	8 (0.4)	8 / 0.22	5 (0.2)	5 / 0.15
Back pain	5 (0.2)	5 / 0.14	0	0
Renal and urinary disorders	9 (0.4)	10 / 0.28	11 (0.5)	12 / 0.36
Nephrolithiasis	4 (0.2)	4 / 0.11	3 (0.1)	3 / 0.09
Respiratory, thoracic, and mediastinal disorders	11 (0.5)	11 / 0.30	10 (0.5)	12 / 0.36
Asthma	1 (0.0)	1 / 0.03	4 (0.2)	5 / 0.15
Hepatobiliary disorders	7 (0.3)	7 / 0.19	4 (0.2)	4 / 0.12
Cholecystitis acute	5 (0.2)	5 / 0.14	0	0
Metabolism and nutrition disorders	6 (0.3)	6 / 0.17	3 (0.1)	3 / 0.09
Hypoglycaemia	4 (0.2)	4 / 0.11	0	0

Source Data: IAS Table SP3-14.1.1.

AE = adverse event; SAE = serious adverse event; SOC = system organ class.

Note: On-therapy AEs are those that had a start date on or after the first day of study medication and within 56 days after the end of study medication. For each level of summarization, a subject was counted once if the subject reported 1 or more AEs. Percentages are based on the number of subjects in each treatment group. The SOC and preferred term within the SOC are presented by decreasing proportions of subjects with AEs for the albiglutide group.

1. Number of AEs = the total number of AEs at each level of summarization. Density per 100 person-years = 100 * (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

In the Phase III integrated safety the number of deaths reported were similar between the all comparators and albiglutide group (18 [0.8%] versus 16 [0.8%]).The most common cause of death was cardiovascular. Of the 34 fatal SAEs 21 fatal SAEs occurred within the first 26 weeks of treatment (9 subjects in the albiglutide group). A total of 4 fatal SAEs (deaths) were reported in the post-therapy period (3 subjects in the albiglutide group; verbatim=unknown death, metastases to liver, and bone neoplasm malignant).

Significant adverse events

Gastrointestinal events

The most common adverse events (>10%) associated with albiglutide are diarrhoea (13%) and nausea (12%) but in the two studies where albiglutide was compared to other GLP-1R agonists (exenatide and liraglutide), the proportion of subjects having nausea was lower in the albiglutide group as shown in Table 21 below.

Table 21 Summary of on-therapy adverse events in the gastrointestinal disorders SOC occurring in at least 5% of subjects in the placebo, Byetta or Albiglutide 30 mg-weekly Treatment Group (GLP110125 Safety Population)

System Organ Class Preferred Term (n, %)	Placebo (N=51)	Byetta twice-daily (N=35)	Albiglutide 30-mg weekly (N=31)
Gastrointestinal disorders	12 (23.5)	19 (54.3)	12 (38.7)
Abdominal pain	1 (2.0)	2 (5.7)	0
Constipation	0	2 (5.7)	1 (3.2)
Diarrhea	2 (3.9)	8 (22.9)	5 (16.1)
Dyspepsia	2 (3.9)	0	2 (6.5)
Gastro-esophageal reflux disease	1 (2.0)	0	2 (6.5)
Nausea	6 (11.8)	14 (40.0)	8 (25.8)
Vomiting	1 (2.0)	6 (17.1)	4 (12.9)

Data Source: Study GLP110125 Table 14.3.1-1.2

Note: Hypoglycaemic events have been excluded from this table and are being reported separately.

Events of hyperglycaemic rescue that prompted early termination of study drug were captured on the AE page of the eCRF. However, because these events were a study endpoint (lack of efficacy), they should not have been captured as AEs and should not have been included in this table.

Table 22 On-Therapy Adverse Events Occurring in More Than 2% of Subjects, study GLP114179 (Safety Population)

System Organ Class Preferred Term	Albiglutide (N=404)		Liraglutide (N=408)	
	n (%)	No. of AEs / Rate[1]	n (%)	No. of AEs / Rate[1]
Any Event	305 (75.5)	1258	317 (77.7)	1269
Gastrointestinal disorders				
Diarrhoea	60 (14.9)	80 / 28.19	55 (13.5)	79 / 27.89
Nausea	40 (9.9)	51 / 17.97	119 (29.2)	139 / 49.07
Vomiting	20 (5.0)	22 / 7.75	38 (9.3)	46 / 16.24
Constipation	17 (4.2)	19 / 6.70	25 (6.1)	27 / 9.53
Dyspepsia	17 (4.2)	21 / 7.40	25 (6.1)	28 / 9.88
Abdominal distension	11 (2.7)	11 / 3.88	8 (2.0)	8 / 2.82
Abdominal pain upper	11 (2.7)	13 / 4.58	10 (2.5)	10 / 3.53
Abdominal pain	10 (2.5)	11 / 3.88	11 (2.7)	11 / 3.88
Flatulence	10 (2.5)	10 / 3.52	9 (2.2)	9 / 3.18
Gastroesophageal reflux disease	9 (2.2)	11 / 3.88	14 (3.4)	15 / 5.29
Injection site reaction	28 (6.9)	123 / 43.34	5 (1.2)	6 / 2.12

Vomiting and constipation was also less frequent in albiglutide-treated subjects. In general, GLP-1R agonists have shown increased rates of nausea and vomiting in the first months after initiation. A similar pattern, although non-significant, was seen for albiglutide and most of the GI events occurred within the first 26 weeks (RR 1.03; 95% CI 0.95-1.11). The incidence of nausea and/or vomiting was shown to be related to plasma concentration level of albiglutide in the Phase IIb study (GLP110125) but no evidence of a dose response relationship was found in the Phase III integrated safety population. Intestinal obstruction is associated with the GLP-1 receptor agonists liraglutide and exenatide and was observed at a slightly higher frequency for albiglutide (0.3 %) vs all comparators (0.2 %; no cases with placebo), wherefore it is proposed that information on intestinal obstruction should be included in section 4.8 of the SmPC.

Hypoglycaemia

The AE density documented symptomatic of hypoglycaemia is overall relatively low when used as monotherapy prior to rescue, albiglutide 30 mg (2.10 events per 100 person-years), 50 mg arm (0 events per 100 person-years) compared with placebo (2.83 events per 100 person years), or as add on to metformin; albiglutide arm (2.62 events per 100 person-years) vs. placebo (3.59 per 100 person-years). When albiglutide treatment is combined with SU or basal insulin, the incidence of documented symptomatic of hypoglycaemia increases to between 50.25 and 93.37 events per 100 person-years comparable to the active comparators insulin and liraglutide. The overall number of severe hypoglycaemic events in the Phase III Integrated Safety Population and GLP114130 was small as shown in Table 23 below.

Table 23 Derived severity of on-therapy hypoglycaemic events before hyperglycaemia rescue using associated glucose levels and American Diabetes Association Definitions Through the Time of the Primary Endpoint by Study (Phase III Integrated Safety Population and GLP114130)

Study Number	Treatment	N / Total Exposure (years)	Severe		Documented Symptomatic		Asymptomatic	
			n (%)	Number of Events / Density[1]	n (%)	Number of Events / Density[1]	n (%)	Number of Events / Density[1]
GLP108486	Albiglutide	285 / 143.52	0	0	45 (15.8)	134 / 93.37	19 (6.7)	31 / 21.60
	Prepranclial lispro insulin	281 / 139.35	2 (0.7)	2 / 1.44	84 (29.9)	325 / 233.22	22 (7.8)	43 / 30.86
GLP112753	Albiglutide	302 / 457.16	0	0	9 (3.0)	12 / 2.62	4 (1.3)	6 / 1.31
	Sitagliptin	302 / 432.13	0	0	5 (1.7)	12 / 2.78	4 (1.3)	6 / 1.39
	Glimepiride	307 / 456.67	0	0	55 (17.9)	277 / 60.66	3 (1.0)	3 / 0.66
	Placebo	101 / 111.49	0	0	4 (4.0)	4 / 3.59	1 (1.0)	2 / 1.79
GLP112754	Albiglutide	504 / 461.22	2 (0.4)	2 / 0.43	86 (17.1)	277 / 60.06	32 (6.3)	51 / 11.06
	With sulfonylurea	413 / 380.82	2 (0.5)	2 / 0.53	85 (20.6)	272 / 71.43	31 (7.5)	50 / 13.13
	Without sulfonylurea	91 / 80.40	0	0	1 (1.1)	5 / 6.22	1 (1.1)	1 / 1.24
	Insulin glargine	241 / 225.03	1 (0.4)	2 / 0.89	64 (26.6)	256 / 113.76	25 (10.4)	42 / 18.66
	With sulfonylurea	196 / 182.43	1 (0.5)	2 / 1.10	56 (28.6)	242 / 132.65	23 (11.7)	39 / 21.38
	Without sulfonylurea	45 / 42.60	0	0	8 (17.8)	14 / 32.86	2 (4.4)	3 / 7.04
GLP112755	Albiglutide 30 mg	150 / 139.70	2 (1.3)	2 / 1.43	5 (3.3)	6 / 4.29	0	0
	Placebo	151 / 111.19	0	0	2 (1.3)	5 / 4.50	0	0
GLP112756	Albiglutide 30 mg	101 / 95.12	0	0	2 (2.0)	2 / 2.10	0	0
	Albiglutide 50 mg	99 / 89.17	0	0	0	0	2 (2.0)	2 / 2.24
	Placebo	101 / 70.77	0	0	2 (2.0)	2 / 2.83	0	0
GLP112757	Albiglutide	271 / 252.75	1 (0.4)	2 / 0.79	36 (13.3)	127 / 50.25	9 (3.3)	10 / 3.96
	Pioglitazone	277 / 259.43	3 (1.1)	3 / 1.16	68 (24.5)	236 / 90.97	12 (4.3)	29 / 11.18
	Placebo	115 / 84.26	0	0	8 (7.0)	29 / 34.42	0	0
GLP114179	Albiglutide	404 / 260.66	0	0	42 (10.4)	142 / 54.48	15 (3.7)	24 / 9.21
	With sulfonylurea	241 / 157.11	0	0	40 (16.6)	139 / 88.47	15 (6.2)	24 / 15.28
	Without sulfonylurea	163 / 103.55	0	0	2 (1.2)	3 / 2.90	0	0
	Liraglutide	408 / 270.97	0	0	54 (13.2)	125 / 46.13	21 (5.1)	44 / 16.24
	With sulfonylurea	232 / 153.11	0	0	47 (20.3)	112 / 73.15	18 (7.8)	40 / 26.13
	Without sulfonylurea	176 / 117.86	0	0	7 (4.0)	13 / 11.03	3 (1.7)	4 / 3.39
GLP114130	Albiglutide	249 / 136.73	0	0	26 (10.4)	48 / 35.10	20 (8.0)	32 / 23.40
	With sulfonylurea	167 / 91.72	0	0	25 (15.0)	46 / 50.15	19 (11.4)	31 / 33.80
	Without sulfonylurea	82 / 45.01	0	0	1 (1.2)	2 / 4.44	1 (1.2)	1 / 2.22
	Sitagliptin	246 / 128.56	2 (0.8)	2 / 1.56	14 (5.7)	30 / 23.34	13 (5.3)	24 / 18.67
	With sulfonylurea	173 / 90.26	2 (1.2)	2 / 2.22	14 (8.1)	30 / 33.24	13 (7.5)	24 / 26.59
	Without sulfonylurea	73 / 38.29	0	0	0	0	0	0

Source Data: IAS Table SP3-26.21.1, IAS Table SP3-26.21.2, and Study GLP114130 Table 14.3.1-2.1.17 and Table 14.3.1-2.1.18.

Note: the primary endpoint was assessed at Week 26 in Study GLP108486 and GLP114130, Week 32 in Study GLP114179, Week 52 in Studies GLP112754, GLP112755, GLP112756, and GLP112757, and Week 104 in Study GLP112753. Ontherapy events were those that had a start date on or after the first day of study medication and within 56 days after the end of study medication. Ontherapy adverse events (AEs) occurring prior to hyperglycemia rescue that were flagged by the investigator as hypoglycemic events and met the American Diabetes Association guidelines for categorization are presented in this summary. Subjects with more than one hypoglycemic event were counted in all severity categories reported. Percentages are based on the number of subjects in each treatment group for the study being summarized.

1. The hypoglycemic AE density per 100 person-years = 100 * (number of hypoglycemic AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.
2. Severity was derived using the American Diabetes Association guidelines for categorization of hypoglycemic events as follows: Severe = required assistance of another person; Documented symptomatic = typical symptoms accompanied by a plasma glucose concentration (PGC) of ≤3.9 mmol/L; and Asymptomatic = no symptoms but PGC ≤3.9 mmol/L.

In the integrated 7 Phase III studies, 7 subjects (0.3%) in the albiglutide group had 8 events of severe hypoglycaemia in the on-therapy pre-rescue period. None of these events led to hospitalization and none led to withdrawal of active treatment. All but 2 of the subjects were taking background insulin or SU. When used in combination with an SU, albiglutide was more likely to cause documented symptomatic hypoglycaemia in both the albiglutide (AE density: 50.15 events per 100 person-years) and sitagliptin (AE density: 33.24 events per 100 person-years) treatment groups than when used without an SU (4.44 and 0 events per 100 person-years, respectively). There is no data available on albiglutide in triple combination with both insulin and SU; the available data is limited experience of using SU as background medication to albiglutide.

Cardiovascular events

There was a slightly higher reported incidence of atrial fibrillation/flutter in the albiglutide group (1.3%) when compared to the all comparators group (0.5%) across the 8 Phase III trials. Clinical

review of individual cases did not provide an explanation for the observed imbalance in atrial fibrillation. In healthy volunteers (study GLP105229 and GLP107085) there were no indications of QTc prolongation but increases in heart rate (HR) were observed and a clear dose and concentration relationship was shown. In the healthy volunteers first time in human study, GLP105229, increased HR was seen at the two highest albiglutide cohorts and increases of HR of 7-13 bpm were observed. In the thorough QTC study (GLP107085) the mean changes from baseline in heart rate (ΔHR) were similar for albiglutide 30 mg (one dose), placebo, and moxifloxacin (approx 1 bpm for all) but after repeat dosing with albiglutide 50 mg, the mean placebo-corrected ΔHR (ΔΔHR) increased with approx 6-8 bpm. In the Phase III integrated analysis the mean heart rate was numerically higher (approx 1-2 bpm), at each integrated analysis visit over time for the albiglutide group compared with the all comparators group. 2.4% of albiglutide-treated subjects had heart rate increases of >30 bpm compared with 2.0% of subjects in the all comparators group. A dose relationship is further indicated since heart rate data from ECGs in the GLP112756 study show that albiglutide uptitration from 30 mg/week to 50 mg/week resulted in a transient 2 bpm heart rate increase after uptitration (change from baseline in the albiglutide 30 mg and 50 mg of 2.1 to 5.1 bpm). In the Phase III integrated analysis no consistent effect on blood pressure was found in any of the groups and the variation between baseline and end of treatment was small (within 1 mmHg of the baseline value).

A full report for a meta-analysis of cardiovascular (CV) event safety including three year data from the completed 8 Phase III studies and the Japan Phase IIb Study (GLP110932) has been provided. The incidence for the first Major Adverse Cardiovascular Event (MACE+) was similar between the treatment groups (1.2 and 1.1/100 subject-years in the albiglutide and all comparators groups, respectively). The HR was 1.00, and the upper bound of the 2-sided CI was less than 1.8 (97.55% CI: 0.68, 1.49; non-inferiority p=0.0019), thus, there is no indication that albiglutide treatment is associated with an unacceptable increase in CV risk. Regarding the patient population, it is acknowledged that a vast number of the patients included had one or more CV risk factors. Although it should be noted that in the age group ≥65 years of age, 428 (19.7%) and 448 (19.1%) patients were included in the albiglutide and all comparators groups respectively, overall only approx 5% of subjects in both treatment groups had experienced a prior myocardial infarction. Furthermore, relatively few patients had moderate and none had severe renal dysfunction. Thus, the included patient population may not represent a CV high risk population. In addition, in the ongoing Ph II study 112670 albiglutide is evaluated in non-diabetic subjects with NYHA Class II/III congestive heart failure. Moreover, the applicant plans to undertake a cardiovascular outcome study.

TIA/ Cerebrovascular accident

TIAs (0.6% vs. 0.2%) occurred in a larger proportion of patients receiving albiglutide compared with all comparators. CVA occurred in 7 (0.33%) albiglutide subjects versus 4 (0.18%) all comparator subjects in the integrated safety population. Atrial fibrillation is a strong risk factor for TIA/CVA; however atrial fibrillation occurred prior to a TIA/CVA event in only 2 out of 20 patients with a TIA/CVA event. The observed imbalance in atrial fibrillation is reflected in the SmPC and included in the RMP as an identified risk.

Review of patients with an event of TIA (n=13) revealed that all patients had a medical history at screening that included TIA, stroke, atrial fibrillation or irregular heart beat (n=5) or other cardiovascular past medical history (including hypertension (n=5), myocardial infarction or PVCs

(n=3). Events of TIA/stroke will be monitored in pharmacovigilance activities for the identified risk of atrial fibrillation and the potential risk of cardiovascular safety of antidiabetic therapy.

Neoplasms

There were 2 cases of pancreatic cancer in the Phase III integrated analysis. One subject, randomized to albiglutide, was reported a fatal SAE of pancreatic carcinoma metastatic on Day 694. The other subject, randomized to pioglitazone, reported an SAE of pancreatic adenocarcinoma. Both events were fatal. In addition, 1 subject randomized to albiglutide had a benign neuroendocrine tumor located in the pancreas. None of the events had evidence of previous pancreatitis. No pancreatic cancers were noted in the Phase III renal study (Study GLP114130).

Five subjects with confirmed thyroid cancer were diagnosed during the on-therapy or post-therapy period; and all but one of these cases had evidence of preexisting condition at baseline (1 sitagliptin-treated subject diagnosed with papillary thyroid carcinoma). Three cases of papillary thyroid carcinoma (1 subject in the albiglutide group and 2 subjects in the sitagliptin group), two cases of medullary thyroid cancer (MTC) (1 subject in the albiglutide group with a baseline calcitonin value of 140.16 pmol/L [480 pg/mL] also diagnosed with MEN 2 and pheochromocytoma and one subject in the placebo group with a baseline calcitonin value of 63.66 pmol/L [218 pg/mL] and whose pathology results showed concurrent papillary thyroid cancer.

Pancreatic and thyroid malignancies been previously identified as a potential safety issues for the GLP-1 receptor agonist class and there are currently ongoing pharmacovigilance activities e.g. retrospective database, observational, pharmacoepidemiological studies and CV outcome studies, to further evaluate this issue. Monitoring of serum calcitonin as a marker of thyroid C-cell neoplasms has been used as screening tool but the value of such laboratory screening in the context of GLP-1 receptor agonist therapy is questionable. The risk for developing malignancies cannot be fully explored from data included in the clinical program and therefore to monitor malignancies e.g. within the planned CV outcome study and/or in database studies are foreseen. Pancreatic and medullary thyroid cancer, respectively, are included as potential risks in the RMP for albiglutide. To include pancreatic cancer as a potential risk in the RMP is in accordance with the review of GLP-1-based therapies and pancreatic safety concerns under the Article 5(3) and concluded in July 2013.

Pancreatitis

Pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class. The criteria for assessing the probability of pancreatitis in the Phase III studies without routine lipase and amylase screening are presented in Table 24 below.

Table 24 Criteria for assessing the probability of pancreatitis

Probability of Pancreatitis	Abdominal Pain	Lipase >3×ULN (or 300), and/or Amylase >5×ULN (or 1000)	Imaging: Positive CT or MRI or Ultrasound (Peripancreatic fluid/ pseudocyst/ necrosis)
Definite	+	+	+
Probable	+	-	+
	+	+	-
	-	+	+
Possible (Must meet laboratory or imaging or imaging criteria)	-	+	-
	-	-	+
Not Diagnostic	Not specific	No laboratory data or data do not satisfy criteria	No laboratory data or data do not satisfy criteria
Not Likely	+/-	-	-

CT = computed tomography; MRI = magnetic resonance imaging.

Based on adjudication results of AE/SAEs suspicious for pancreatitis and abnormal amylase/lipase values from the 7 Phase III studies without routine, on-therapy amylase and/or lipase assessments, the incidence rate for all cases adjudicated by the Pancreatitis Adjudication committee (PAC) as definite or probable pancreatitis (regardless of adjudicated relationship to study treatment) was 2.1 cases per 1000 patient years) as shown in Table 25 below.

Table 25 Incidence rate of pancreatitis based on adjudication results in studies without routine lipase and amylase screening (GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP108486, GLP114130)

Study Drug	Number of Subjects	Patient Years	Incidence Rate[1]/ 1000 Patient-Years
Albiglutide - all probable/definite pancreatitis cases	7	3340	2.1
Albiglutide – probable/definite pancreatitis cases with at least possible relationship to IP	5	3340	1.5
Other comparators - all probable/definite pancreatitis cases	0	3584	0
Never randomized[2]	1	NA	NA

Source Data: see Pancreatitis Adjudication Report in m5.3.5.3
NA = not applicable.
1. Hand calculated.
2. Event in subject never randomized not included in incidence rates.

This is an identified risk class-effect and covered in section 4.4 and 4.8 of the SmPC. Acute pancreatitis is included as an important identified risk in the RMP.

Laboratory findings

There were no relevant changes from baseline to last visit noted in hematology parameters, chemistry or urinary analysis. No relevant mean changes were observed for liver tests or renal function values over time compared to baseline values in during the entire treatment period in the Phase III Integrated Safety Population (albiglutide treated subjects vs. all comparators).

Overall, there were small decreases from baseline in mean total cholesterol, LDL-cholesterol, triglycerides, and free fatty acids and small increases in HDL cholesterol in both the albiglutide and placebo groups as shown in Table 26, the changes were somewhat greater in the albiglutide than the placebo group but these differences were not clinically relevant. Lipid data was presented by statin versus non-statin usage at baseline and at week 52 and 104 respectively;

however the changes in lipid parameters between statin users and non-statin users were small and not clinically relevant.

Table 26 Change from baseline in lipid chemistry (si units) by analysis visit – albiglutide versus placebo groups (Phase III Integrated Safety Population)

	Albiglutide vs Placebo			
	Placebo (N=468)		Albiglutide (N=923)	
	Result	Change	Result	Change
Total Cholesterol (mmol/L)				
Baseline				
n	468		923	
Mean (Standard Deviation)	4.679 (1.0844)		4.737 (1.0813)	
Week 104				
n	288	288	637	637
Mean (Standard Deviation)	4.641 (1.1070)	-0.054 (0.9470)	4.633 (1.0211)	-0.100 (0.8323)
LDL Cholesterol (mmol/L)				
Baseline				
n	454		897	
Mean (Standard Deviation)	2.470 (0.8415)		2.548 (0.8991)	
Week 104				
n	270	264	616	608
Mean (Standard Deviation)	2.475 (0.9036)	-0.015 (0.7217)	2.487 (0.8629)	-0.068 (0.7156)
HDL Cholesterol (mmol/L)				
Baseline				
n	468		923	
Mean (Standard Deviation)	1.193 (0.2861)		1.191 (0.3037)	
Week 104				
n	288	288	637	637
Mean (Standard Deviation)	1.215 (0.3017)	0.027 (0.1822)	1.231 (0.3068)	0.035 (0.1852)
Triglycerides (mmol/L)				
Baseline				
n	468		923	
Mean (Standard Deviation)	2.250 (1.7409)		2.246 (1.5117)	
Week 104				
n	288	288	637	637
Mean (Standard Deviation)	2.164 (1.3758)	-0.106 (1.2708)	2.066 (1.2722)	-0.158 (1.2838)

Calcitonin results of potential clinical concern are shown in Table 27 below. A calcitonin value of >29.2 pmol/L (100 pg/mL) was predefined as value of potential clinical concern and relevance.

Table 27 Calcitonin results (si units) of clinical concern by analysis visit – albiglutide versus all comparators (Phase III Integrated Safety Population)

Calcitonin (pmol/L)	All Comparators N=2284 (%)	Albiglutide N=2116 (%)
Baseline		
n	1997	1886
≥ ULN	90 (4.5)	87 (4.6)
≥ 2 × ULN	24 (1.2)	22 (1.2)
≥ 5 × ULN	4 (0.2)	6 (0.3)
≥ 10 × ULN	3 (0.2)	5 (0.3)
≥ 14.6 pmol/L	4 (0.2)	5 (0.3)
> 29.2 pmol/L	3 (0.2)	4 (0.2)
Any On-therapy Visit		
n	2015	1868
≥ ULN	118 (5.9)	129 (6.9)
≥ 2 × ULN	34 (1.6)	29 (1.5)
≥ 5 × ULN	10 (0.5)	6 (0.3)
≥ 10 × ULN	5 (0.2)	4 (0.2)
≥ 14.6 pmol/L	9 (0.4)	6 (0.3)
> 29.2 pmol/L	4 (0.2)	3 (0.2)

Source Data: IA5 Table SP3-34.6.1a Phase III Integrated Safety Database (Studies GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, and GLP114179)
Note: Baseline is defined as the last available assessment on or prior to the first dose of study medication. ULN=upper limit of normal reference range.

In the albiglutide versus all comparators group, there were 7 subjects with any on- or post-therapy calcitonin value above this level. Four of these subjects (2 in the albiglutide group and 2 in the all comparators group) had an abnormal calcitonin value already at baseline; 2 of these 4 subjects (1 in each treatment group) were subsequently diagnosed with medullary thyroid cancer (MTC) (both cases are included in the neoplasm section above). Two subjects (both in the all comparators group) had a normal calcitonin value at baseline; other than an AE of blood calcitonin increased in 1 of these subjects, no other thyroid-related AEs were reported for these subjects. One subject (in the albiglutide group) was missing a baseline calcitonin value; no thyroid-related AEs were reported for this subject.

With respect to calcitonin shifts from baseline, there were 9 subjects (1 subject in the albiglutide group and 8 subjects in the all comparators group) in the integrated Phase III studies with a normal baseline calcitonin measurement and a subsequent post-baseline shift to an abnormal value >2×ULN (normal range: 6.42 pmol/L [21.99 pg/mL] for women and 3.49 pmol/L [11.97 pg/mL] for men). Of these 9 subjects, 2 subjects experienced an on-therapy thyroid-related event (Subject 3617754986 in the albiglutide group had an event of hypothyroidism and Subject 3784753990 in the all comparators group had an event of blood calcitonin increased).

Safety in special populations

The overall safety findings of albiglutide were consistent across all age, gender and racial groups, although the numbers of subjects with events aged ≥75 years and the proportion of Asian subjects was small as shown in Table 28.

Table 28 Overall On-therapy Adverse Events by Drug Demographic Factors – Albiglutide Versus All Comparators (Phase 3 Integrated Safety Population)

	All Comparators		Albiglutide	
	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Any event (n/N [%])	1840/2284 (80.6)	10076/277.69	1766/2116 (83.5)	11042/327.69
Any event Gender Category				
Female	895/1087 (82.3)	5289/313.42	882/1037 (85.1)	6234/387.30
Male	945/1197 (78.9)	4787/246.63	884/1079 (81.9)	4808/273.18
Any event Age Category (n/N [%])				
<65 years old	1513/1899 (79.7)	8127/269.84	1476/1780 (82.9)	9286/328.53
≥65 to <75 years old	296/351 (84.3)	1734/309.37	265/305 (86.9)	1560/315.27
≥75 years old	31/34 (91.2)	215/382.60	25/31 (80.6)	196/405.88
Race/Ethnicity (n/N [%])				
Non-Hispanic African American	224/274 (81.8)	1104/247.46	274/322 (85.1)	1336/248.49
Non-Hispanic White	928/1085 (85.5)	5765/330.36	892/1018 (87.6)	6544/392.74
Hispanic	493/660 (74.7)	2404/233.16	419/544 (77.0)	2294/276.05
Asian	156/220 (70.9)	622/187.23	133/180 (73.9)	605/248.73
Other	39/45 (86.7)	181/244.62	48/52 (92.3)	263/287.34

Overall, a larger proportion of female subjects experienced nausea and urinary tract infection both the albiglutide and all comparators groups, suggesting that there was no albiglutide – specific treatment difference. A gender difference for injection site reaction was only seen in the albiglutide group (12.0% of females and 5.8% of males) and not in the all comparators group (1.7% of females and 2.3% of males). The reason for this is unknown.

There was a trend for more adverse events for albiglutide with increasing age for serious AEs, AEs leading to withdrawals, cardiac disorders and vascular disorders respectively. Although there was also a trend in the comparator group suggesting an age-related increase; the increased events in elderly (≥75) in the SOC Cardiac disorders and Vascular disorders respectively were slightly more pronounced for albiglutide compared to the comparator group. When stratifying by age and dose, the most marked age trend was with 50 mg albiglutide in the SOC Cardiac disorders and Vascular disorders compared to albiglutide 30 mg and the comparator group. However, there were few events in the highest age strata ≥75 limiting the precision of these estimates. Information regarding the limited experience in patients ≥75 has been included in section 4.2 of the SmPC and, furthermore, included as missing information in the RMP for albiglutide.

Renal function

There were 173 patients with moderate renal impairment exposed to albiglutide in phase III studies. The proportion of subjects experiencing any on-therapy AE increased as the baseline renal function decreased and this trend was similar across both the albiglutide and all comparator groups. Among the common on-therapy AEs, the proportion of subjects who experienced nausea increased as renal function decreased in both groups (albiglutide – 9.8% of subjects with normal renal function, 11.9% for those with mild impairment, and 16.2% for those with moderate impairment; all comparators – 9.1% of subjects with normal renal function, 11.1% for those with mild impairment, and 14.9% for those with moderate impairment). Vomiting occurred in a

similar proportion of subjects in the albiglutide and all comparators groups, respectively, with small differences across renal function categories.

In the study of patients with renal impairment (GLP 114130) albiglutide was compared to sitagliptin. In this study 102 patients with moderate and 19 patients with severe renal impairment were exposed to albiglutide. In the albiglutide group, the percentages of subjects with any AE during the pre-therapy, on-therapy, and post-therapy periods was similar for subjects with mild (81.3%), moderate (86.3%), and severe (84.2%) renal impairment severity.

There is a very limited experience in patients with severe renal impairment and albiglutide is not recommended in patients with severe renal impairment and a wording regarding that is included in section 4.2 of the SmPC. Furthermore a warning regarding gastrointestinal events in this population has been included in section 4.4 of the SmPC. Use in patients with severe renal impairment is included as missing information in the RMP. Gastrointestinal events occurred more frequently in patients with moderate to severe renal impairment than in those with mild renal impairment or normal renal function, this information is included in section 4.8 of the SmPC.

Immunological events

Use of injectable protein pharmaceuticals can potentially cause immunogenic reactions associated with development of antibodies with the risk of influencing the efficacy and safety profile of the pharmaceutical.

In the integrated Phase III studies, investigator-identified systemic allergic reactions were reported in 1.4% of albiglutide-treated and 0.8% of all comparator-treated subjects. No case of anaphylactic reaction related to albiglutide was reported in the any of the studies.

Injection site reactions (ISRs) occurred very commonly (18%) in patients treated with albiglutide when compared to the placebo-group. Albiglutide-treated subjects also reported more injection site reactions compared with subjects treated with active injected therapies (albiglutide (12.9%) versus liraglutide (5.4%), albiglutide (9.5%) versus lispro insulin (5.3%) and albiglutide (16.7%) versus insulin glargine (10.0%), respectively). ISRs were reported more frequently for antibody positive than antibody negative subjects (40.5% vs. 14.2%). In most cases, the maximum intensity of ISRs was mild (72.8% subjects in the albiglutide and 94.3% subjects in the placebo group), and severe ISRs were only reported for 3 subjects (1.9%) in the albiglutide group and no subjects in the placebo group. Among the subjects who had ISRs, most only had 1 or 2 events (61.7% [100/162] in the albiglutide group and 80.0% [28/35] in the placebo group). However, a higher proportion of subjects in the albiglutide group than the placebo group experienced >11 events (14.2% [23/162] vs. 8.6% [3/35]) and some subjects reported >20 events each (6.8% [11/162] vs. 8.6% [3/35])., respectively The median duration of these ISRs was longer in the albiglutide group than in the placebo group (7.0 days and 2.0 days, respectively); many events had a duration of ≤7 days (48.0% and 82.6%, respectively). The majority of ISRs resolved during the study (92.9% vs. 79.8%, respectively), few ISRs led to the withdrawal of investigational product (1.9% vs. 0.6%, respectively), and few subjects required treatment (6.3% vs. 0.9%, respectively). In study GLP 114179, it should be noted that the incidence of injection rate reactions was higher for albiglutide compared to liraglutide. The severity of injection site reactions with albiglutide was generally mild and moderate in nature and none were considered an SAE. Information regarding injection site reactions is included in section 4.8 of the

SmPC, which was considered sufficient by the CHMP. Furthermore, injection site reactions are included as an identified risk in the RMP.

4.4% (128/2,934) of patients developed antibodies to albiglutide on-treatment. None of the on-therapy antibodies were shown to neutralize the activity of albiglutide and showed no cross-reactivity with glucagon.

Antibodies reactive with albumin (anti-HSA) were detected in a small number of subjects on treatment (n=19) but the clinical relevance is unclear. Antibodies reactive with albumin are of particular interest since albiglutide is the first albumin-modified GLP-1 receptor agonist.

Clinical Comparability of Process 2 (Phase III Material) and Process 3 (Commercial Formulation) Derived Albiglutide Product - Immunogenicity assessment

In Study GLP114856, the bioequivalence and 12-week comparability study, the anti-albiglutide antibodies incidence was 0.7% (1 of 141 subjects) for Process 2 and 4.2% (6 of 142 subjects for Process 3).

In Studies GLP112754 and GLP112756, only 1 of the 456 subjects who were switched to Process 3 albiglutide became anti-drug antibody (ADA) positive after the switch having previously tested negative for ADAs. Thirty-six (7.9%) subjects tested positive for anti-drug antibodies (ADA) at least once during the study; 35 of these 36 subjects tested positive during the first 2 years of treatment when receiving Process 2. Of the 35 subjects, who tested positive for antibodies prior to the switch to Process 3 albiglutide, 31 were ADA positive earlier in the study and had reverted back to an antibody negative state prior to the switch. These 31 subjects remained ADA negative after switching to Process 3.

Four of the 35 subjects tested positive both prior and after the switch. The antibodies in these subjects were non-neutralizing and the titers did not increase after switching to Process 3. Reactivity to albumin was observed in 2 of the 4 subjects and in both cases the albumin reactivity was already observed before the switch when subjects received Process 2 material only. Thus in this limited population there appears to be no increase in anti-albumin antibodies with Process 3 material. This is of importance since a significant increase in methionine oxidation of the albumin moiety has been observed when changing from Process 2 to Process 3 and there were concerns initially that this could affect immunogenicity.

Safety related to drug-drug interactions and other interactions

The most commonly used non-diabetic concomitant drugs were angiotensin-converting enzyme inhibitors, antithrombotic agents, and statins and statin combinations. No apparent trends in adverse events were observed. Albiglutide delays gastric emptying, and has the potential to impact the absorption of concomitantly administered oral medicinal products, which is addressed in the SmPC.

Discontinuation due to adverse events

In the Phase III integrated safety population, the rate of treatment discontinuation in the albiglutide group was 10.3 % compared with 12.2 % in the all comparators group (placebo + active) due to withdrawal of consent and 7.8% vs. 5.7% due to an adverse event. Overall, the treatment discontinuation rate in the albiglutide group was similar to the all comparators group.

The main AE which led to treatment discontinuation in the albiglutide group (and that occurred at a higher rate compared to placebo) were injection site reactions (18%) and led to discontinuation in 2% of all patients treated with albiglutide.

Discontinuation due to AE was not considered a concern. However, information on the difference in withdrawals between albiglutide and the all comparator group has been included in section 4.8 of the SmPC.

2.6.1. Discussion on clinical safety

Short term risk

In the integrated safety analysis, 2116 patients with type 2 diabetes have been exposed to albiglutide 30 or 50 µg once weekly out of which 885 have been exposed to albiglutide for at least 104 weeks.

The majority of the patients in the 8 phase III clinical studies were exposed to albiglutide on a background therapy of metformin, SU+metformin, pioglitazone with and without metformin, and basal insulin, respectively. An adequate number of patients are exposed for at least 104 weeks and the database is in general considered sufficient.

The most common adverse events associated with albiglutide are gastrointestinal side effects such as diarrhoea (13%) and nausea (13%). Vomiting was also reported more commonly and frequently in the in the albiglutide treated groups in all individual studies where another GLP-1-R agonist was not the comparator. Gastroesophageal Reflux Disease (GERD) and dyspepsia generally occurred more frequently in the albiglutide treated patients at each time point but did not occur in >2% of subjects (GERD) until the 52 week time point. In all individual studies constipation was less common than the other gastrointestinal adverse events but even so more frequent in the albiglutide arm compared to all comparators at all time points. Intestinal obstruction is now included in section 4.8 of the SmPC, following a request by CHMP during the procedure and in line with the GLP-1 receptor agonists exenatide and liraglutide. The proportion and event rate for pneumonia was also higher for albiglutide treated subjects in all comparisons but in a lower proportion (<2%) of patients. This was true also for serious events of lower respiratory tract infections.

A higher incidence of hypersensitivity reactions were seen in the albiglutide treated group in the integrated phase III studies. Investigator-identified systemic allergic reactions were reported in 1.4% of albiglutide-treated compared to 0.8% in the all comparator-treated patients and immunogenicity is included in the RMP as an identified risk. A single case of an anaphylactic reaction was identified in an albiglutide-treated subject who tested negative for anti-albiglutide antibodies. The event occurred after more than 2 years in the study, was of moderate intensity, and was attributed to lisinopril.

Injection site reactions related to albiglutide treatment were present in 8.8% of patients which is a slightly higher proportion than in other GLP-1-R agonist, however the severity of injection site reactions with albiglutide was generally mild and moderate in nature and none were considered an SAE. 4.4% of patients developed antibodies to albiglutide after the start of treatment but no neutralising anti-bodies were detected. Patients' positive for anti-albiglutide antibodies is at higher risk for developing injection site reactions compared to those without antibodies. Similar

effects have been observed for other GLP-1 receptor agonists. Antibodies reactive with albumin are of particular interest since albiglutide is the first albumin-modified GLP-1 receptor agonist. Injection site reactions are included in the product information and the RMP as an identified risk.

An increase in hypoglycaemic events is mainly seen when albiglutide treatment is combined with SU or insulin. The product information therefore states that when albiglutide is added to SU therapy or basal insulin a reduction of dose of the SU or the basal insulin may be considered to reduce the risk of hypoglycaemia. Hypoglycaemia [when used with a sulfonylurea (SU) or with basal insulin] is included in the RMP as important identified risk. No clinical experience of add-on to a combination of insulin and a SU is available.

Acute pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class based on cases of acute pancreatitis reported with the use of marketed GLP-1 receptor agonists. Potential events of clinically diagnosed acute pancreatitis occurred in 7/3,340 patient-years in albiglutide treated patients. Importantly, there were no adjudicated cases meeting the same criteria for active comparators or placebo. Acute pancreatitis is therefore included in the RMP as important identified risk.

There have been rare, spontaneously reported events of reduced renal function with other GLP-1 receptor agonists. No safety signal regarding renal function has been identified but the number of patients with severe renal impairment treated with albiglutide is limited and which is reflected in the product information.

During the procedure, safety data in a larger cohort of 456 patients has been presented with exposure to Process 3 albiglutide for up to one year. Overall, CHMP acknowledged that the additional data provided do not indicate a substantial and clinically relevant difference in the safety profile of Process 2 and Process 3 albiglutide. Especially, no difference in immunogenicity has been observed, neither with regards to anti-albiglutide antibodies nor antibodies cross-reacting with albumin, which is reassuring.

Potential long term risks

There is no preclinical or mechanistic rationale to suspect that albiglutide and other GLP-1 receptor agonists would increase the risk of cardiovascular events. Atrial fibrillation/flutter occurred in a larger proportion of patients receiving albiglutide than in the all comparators group (1.3% vs. 0.5%). Minor but consistent increases in heart rate were seen in both albiglutide-treated healthy volunteers in the thorough QTc study (Study GLP107085) and patients with type 2-diabetes (Phase III Integrated Safety Population). However, data from the 3 year CV safety meta-analysis suggest that albiglutide is not associated with an unacceptable increase in CV risk which is assuring; however CV safety will be further evaluated within a future CV outcome study. Interestingly, SAEs for congestive heart failure was slightly less common in the albiglutide group. The observed imbalance in atrial fibrillation is reflected in the SmPC and included in the RMP as an identified risk.

TIAs occurred in a larger proportion of patients receiving albiglutide compared with all comparators. Atrial fibrillation is a strong risk factor for TIA/CVA; however atrial fibrillation occurred prior to a TIA/CVA event in only 2 out of 20 patients with a TIA/CVA event. Events of TIA/stroke will be monitored in pharmacovigilance activities for the identified risk of atrial fibrillation and the potential risk of cardiovascular safety of antidiabetic therapy.

GLP-1 receptor agonists in general seem to be associated with thyroid C-cells proliferative/hyperplasia effects in non-clinical carcinogenicity studies. In the clinical development program there is no indication of any numeric increase in thyroid neoplasms (benign and malignant) in the albiglutide group in comparison to placebo or the all comparators group. Monitoring of serum calcitonin as a marker of thyroid C-cell neoplasms was implemented in all albiglutide Phase III studies. Mean and median calcitonin levels remained stable over time and other laboratory assessments did not reveal a clinical safety signal for treatment with albiglutide regarding thyroid tumours.

There were 2 cases of pancreatic cancer in the phase III integrated safety population, one case treated with albiglutide and one case treated with pioglitazone. Thus, with such a small number no trends could be observed. The risk for developing malignancies cannot be fully explored from data included in the clinical program and any possibility to monitor malignancies e.g. within database studies should be done. In line with all GLP-1 based therapies and in accordance with the finalised review of GLP-1-based therapies under the Article 5(3), pancreatic cancer has been included as a potential risk in the RMP.

Subpopulations

The clinical experience in patients > 75 years is very limited and is reflected in the SmPC and as missing information in the RMP.

The number of patients with severe renal impairment included in the renal study is limited (19) and is reflected in the SmPC and use in patients with severe renal impairment is not recommended. Use in patients with severe renal impairment is included as missing information in the RMP.

Results from the DDI study with albiglutide and simvastatin indicate that albiglutide affects the PK of simvastatin which is commonly used in this population. Lipid data was presented by statin versus non-statin usage at baseline and at week 52 and 104 respectively; however the changes in lipid parameters between statin users and non-statin users were small and not clinically relevant.

Use in pregnant women, in lactating women and in children/adolescents < 18 years is included as missing information in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile for albiglutide is in general similar to other approved GLP-1 receptor agonists. However, for albiglutide, nausea seems to be less pronounced but on the other hand injection site reactions were reported in a relatively high proportion compared to other GLP-1 antagonists. Effects on blood pressure and body weight are less pronounced compared to other GLP-1 antagonists. Only a small number of patients with severe renal impairment were included in phase 3 studies and since a potential increase in exposure to albiglutide when renal function decreases was noted in the population pharmacokinetic evaluation and the use of albiglutide is not recommended in patients with severe renal impairment.

With regard to the long-term safety, the cardiovascular safety evaluation was found to be sufficient by CHMP despite a slight increase in heart rate and imbalance in atrial fibrillation/flutter in the clinical studies. TIA occurred in a larger proportion of patients receiving albiglutide compared with all comparators. Events of TIA/stroke will be monitored in pharmacovigilance activities for the identified risk of atrial fibrillation and the potential risk of cardiovascular safety of antidiabetic therapy.

Otherwise, the long-term safety concerns are the same as for the other GLP-1 receptor agonist, i.e. potential increased risk for pancreatitis and thyroid and pancreatic tumours. Pancreatitis is included as an identified risk and pancreatic and medullary thyroid cancer, respectively, as potential risks in the RMP.

Process 3 albiglutide has been investigated in an adequate number of patients and there appears to be no clinically relevant differences in the safety profile between Process 2 and Process 3 albiglutide. Especially, no difference in immunogenicity has been observed, which was found to be reassuring by CHMP.

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:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 03, the PRAC considers by consensus that the risk management system for albiglutide (Eperzan) in the treatment of type II diabetes in adults could be acceptable provided an updated risk management plan and satisfactory responses to the List of Outstanding Issues are submitted.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 29 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Acute Pancreatitis Gastrointestinal events

	Hypoglycaemia Injection Site Reactions Immunogenicity Pneumonia Atrial fibrillation/flutter
Important potential risks	Cardiovascular safety of antidiabetic therapy Medullary Thyroid Cancer (Thyroid C-cell Tumours nonclinical) Hepatotoxicity Pancreatic cancers Intestinal Obstruction Foetal & neonatal developmental toxicity-nonclinical Accelerated sexual maturation in juveniles-nonclinical
Missing information	Use in pregnancy and lactation Use in paediatric population Use in hepatic impairment Use in very elderly (age ≥ 75 years) Use in severe renal impairment (eGFR < 30 ml/ by MDRD) Use in NYHA Class III/ IV heart failure

The PRAC considers that the following issues should be addressed:

The Applicant should either include 'Malignancy' as an important potential risk (in which the influence of insulin use can be investigated further) or should include 'Malignant neoplasms following combination treatment with insulin' as an important potential risk.

In addition, the Applicant has included 'intestinal obstruction' as an important potential risk as requested but following further PRAC discussion it is agreed this term can be included amongst the terms covered by the important identified risk of 'gastrointestinal events' and does not need to be separately included as an important potential risk.

- **Pharmacovigilance plans**

Table 30: Ongoing and planned studies in the PhV development 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)
Phase IV Observational database study (non- interventional cohort, 3)	To assess the risk of pancreatitis with albiglutide and other incretin based therapies in observational databases	Acute Pancreatitis	Planned (pending post approval feasibility assessments)	TBD
V30016 and V70310N In vitro binding study to evaluate GLP-1R distribution in thyroid cells from healthy untreated rodents and monkeys compared to humans (nonclinical, 3)	Determine GLP-1R distribution in thyroid cells from healthy untreated rodents and monkeys compared to humans	Thyroid C-cell Tumours (Medullary Thyroid Cancer)	Started	December 2014
Phase IV Observational database study (non- interventional cohort, 3)	To assess the risk of thyroid and pancreatic cancers in observational databases of sufficient size that provides long term longitudinal follow up of patients	Thyroid and pancreatic cancers	Planned (pending post approval feasibility assessments)	TBD
Juvenile toxicity study in mice treated with albiglutide (nonclinical, 3)	Determine if albiglutide has effects on sexual maturation and CNS/behaviour in juvenile mice	Use in paediatric population	Planned	December 2014
Phase IV Observational drug utilization study (non- interventional cohort, 3)	1) To assess the proportion and characteristic of type 2 diabetic women of child-bearing potential who are prescribed albiglutide 2) To assess the proportion and characteristics of type 2 diabetic women who are exposed to albiglutide during pregnancy.	Pregnancy	Planned	TBD

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, is of the opinion that there are still outstanding issues regarding the RMP but a preliminary view is that the proposed post-authorisation Pharmacovigilance development plan is not sufficient to identify and characterise the risks of the product and the Applicant should propose PhV studies/activities as detailed in section 4.

The PRAC also considered that routine Pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

The applicant proposes routine risk minimisation for all safety concern and missing information:

Table 31: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Acute pancreatitis	Special warning and precaution in section 4.4 regarding use in patients with history of pancreatitis and guidance on actions to take if pancreatitis is suspected or confirmed Listed in section 4.8 Undesirable effects Prescription only medicine	None
Gastrointestinal events (i.e., nausea, vomiting, diarrhoea, constipation, dyspepsia, and gastro-oesophageal reflux)	Special warning and precaution in section 4.4 regarding use in patients with severe gastrointestinal disease and in patients with renal impairment Listed in section 4.8 Undesirable effects Prescription only medicine	None
Hypoglycaemia	Reduction in dose of concomitant sulphonylurea or insulin and blood glucose self-monitoring may be needed aredescribed in section 4.2 Posology and method of administration Special warning and precaution in section 4.4 precautionary guidance regarding possible need to reduce dose of concurrent SU or insulin Listed in section 4.8 Undesirable effects Prescription only medicine	None
Injection site reactions	Listed in section 4.8 Undesirable effects Discussed in section 5.1 Pharmacodynamic properties, Immunogenicity Prescription only medicine	None
Immunogenicity (e.g., clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, other immune related events)	Section 4.3 Contraindication for use in patients with hypersensitivity to active ingredient or excipients Discussed in Section 5.1 Pharmacodynamic properties, Immunogenicity Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pneumonia	Listed in section 4.8 Undesirable effects Prescription only medicine	None
Atrial fibrillation/flutter	Listed in section 4.8 Undesirable effects Prescription only medicine	None
Cardiovascular safety of antidiabetic therapy	None Prescription only medicine	None
Medullary thyroid cancer	Special warning and precaution in section 4.4 discuss nonclinical finding and uncertain relevance to man, precautionary guidance for use in patients with personal or family history MTC Discussed in section 5.3 Preclinical safety data Prescription only medicine	None
Hepatotoxicity	None Prescription only medicine	None
Pancreatic cancers	None Prescription only medicine	None
Intestinal obstruction	None Prescription only medicine	None
Foetal/neonatal developmental toxicity	Discussed in Section 4.6 Pregnancy, lactation and fertility with guidance regarding use during pregnancy and breast feeding; guidance regarding lead time to discontinue use before planned pregnancy Discussed in Section 5.3 Preclinical safety data Prescription only medicine	None
Accelerated sexual maturation in juveniles	Section 4.1 Therapeutic indication states for use in adults Section 4.2 Posology and method of administration, Special Populations and Section 5.2 Pharmacokinetics indicates absence of information Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in pregnancy and lactation	Discussed in Section 4.6 Pregnancy, lactation and fertility with guidance regarding use during pregnancy and breast feeding; guidance regarding lead time to discontinue use before planned pregnancy Discussed in Section 5.3 Preclinical safety data Prescription only medicine	None
Use in paediatric population	Section 4.1 Therapeutic indication states for use in adults Section 4.2 Posology and method of administration, Special Populations and Section 5.2 Pharmacokinetics indicates absence of information Prescription only medicine	None
Use in hepatic impairment	Section 4.2 Posology and method of administration, Special Populations – no dose adjustment needed Discussed in Section 5.2 Pharmacokinetics, notes no clinical studies and rationale for no need to dose adjust Prescription only medicine	None
Use in very elderly (≥75 years old)	Section 4.2 Posology and method of administration, Special Populations – no dose adjustment needed and very limited experience Discussed in Section 5.2 Pharmacokinetics, notes clinical studies and rationale for no need to dose adjust Prescription only medicine	None
Severe renal impairment (eGFR< 30 mL/min/1.73m²)	Section 4.2 Posology and method of administration, Special Populations limited experience and not recommeded Discussed in Section 5.1, Pharmacodynamic Properties and 5.2 Pharmacokinetics, notes clinical studies and rationale for no need to dose adjust Prescription only medicine	None
NYHA class III/IV heart failure	Section 4.4, Special Warnings and Precautions- Population not studied Prescription only medicine	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice with the changes in the summary of safety concerns as well as the proposed post-authorisation Pharmacovigilance development plan.

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The CHMP justified these changes as follows:

In response to the PRAC Advice, the MAH has incorporated all changes as requested by the PRAC and submitted an updated version of the RMP, i.e. version 04, accordingly. This has been evaluated by the PRAC (Co)Rapporteurs, who consider that the outstanding issues have been resolved.

The final summary of safety concerns in the latest version 04 of the RMP is as follows:

Summary of safety concerns	
Important identified risks	Acute Pancreatitis Gastrointestinal events Hypoglycaemia Injection Site Reactions Immunogenicity Pneumonia Atrial fibrillation/flutter
Important potential risks	Cardiovascular safety of antidiabetic therapy Medullary Thyroid Cancer (Thyroid C-cell Tumours-nonclinical) Hepatotoxicity Pancreatic cancers Malignant neoplasms following combination treatment with insulin Foetal & neonatal developmental toxicity-nonclinical Accelerated sexual maturation in juvenilles-nonclinical
Missing information	Use in pregnancy and lactation

Summary of safety concerns	
	Use in paediatric population Use in hepatic impairment Use in very elderly (age ≥ 75 years) Use in severe renal impairment (eGFR < 30 ml/ by MDRD) Use in NYHA Class III/ IV heart failure

The CHMP agreed.

In the updated RMP, the MAH proposed the following **ongoing and planned studies in the PhV development 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)**
Phase IV Observational database study (non- interventional cohort, 3)	To assess the risk of pancreatitis with albiglutide and other incretin based therapies in observational databases	Acute Pancreatitis	Planned (pending post approval feasibility assessments)	TBD
Phase IV CV Outcome Trial (randomized, controlled trial, 3)	To assess the risk of Major Adverse Cardiovascular events (composite primary endpoint) and additional adjudicated events (e.g. TIA)	CV safety of antidiabetic therapy TIA/stroke related to atrial fibrillation concern	Planned	TBD
V30016 and V70310N In vitro binding study to evaluate GLP-1R distribution in thyroid cells from healthy untreated rodents and monkeys compared to humans (nonclinical, 3)	Determine GLP-1R distribution in thyroid cells from healthy untreated rodents and monkeys compared to humans	Thyroid C-cell Tumours (Medullary Thyroid Cancer)	Started	December 2014
Phase IV	To assess the risk of thyroid and	Thyroid and	Planned	TBD

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)
Observational database study (non- interventional cohort, 3)	pancreatic cancers, and malignancy when used in combination with insulins in observational databases of sufficient size that provides long term longitudinal follow up of patients	pancreatic cancers and malignancy when used in combination with insulin	(pending post approval feasibility assessments)	
Juvenile toxicity study in mice treated with albiglutide (nonclinical, 3)	Determine if albiglutide has effects on sexual maturation and CNS/behaviour in juvenile mice	Use in paediatric population	Planned	December 2014
Phase IV Observational drug utilization and foetal outcome study (non- interventional cohort, 3)	1) To assess the proportion and characteristic of type 2 diabetic women of child-bearing potential who are prescribed albiglutide 2) To assess the proportion and characteristics of type 2 diabetic women who are exposed to albiglutide during pregnancy. 3) To assess frequency and types of adverse foetal outcomes	Pregnancy	Planned (assessment of foetal outcomes pending post approval feasibility assessments)	TBD

The CHMP, having considered the data submitted, was of the opinion that the proposed post-authorisation Pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

In the updated RMP, the MAH proposed the following risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Acute pancreatitis	Special warning and precaution in section 4.4 regarding use in patients with history of pancreatitis and guidance on actions to take if pancreatitis is suspected or confirmed Listed in section 4.8 Undesirable effects Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Gastrointestinal events (i.e., nausea, vomiting, diarrhoea, constipation, dyspepsia, and gastro-oesophageal reflux)	Special warning and precaution in section 4.4 regarding use in patients with severe gastrointestinal disease and in patients with renal impairment Listed in section 4.8 Undesirable effects Prescription only medicine	None
Hypoglycaemia	Reduction in dose of concomitant sulphonylurea or insulin and blood glucose self-monitoring may be needed are described in section 4.2 Posology and method of administration Special warning and precaution in section 4.4 precautionary guidance regarding possible need to reduce dose of concurrent SU or insulin Listed in section 4.8 Undesirable effects Prescription only medicine	None
Injection site reactions	Listed in section 4.8 Undesirable effects Prescription only medicine	None
Immunogenicity (e.g., clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, other immune related events)	Section 4.3 Contraindication for use in patients with hypersensitivity to active ingredient or excipients Discussed in Section 4.8 Undesirable effects Prescription only medicine	None
Pneumonia	Listed in section 4.8 Undesirable effects Prescription only medicine	None
Atrial fibrillation/flutter	Listed in section 4.8 Undesirable effects Prescription only medicine	None
Cardiovascular safety of antidiabetic therapy	None Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medullary thyroid cancer	Special warning and precaution in section 4.4 discuss nonclinical finding and uncertain relevance to man, precautionary guidance for use in patients with personal or family history MTC Discussed in section 5.3 Preclinical safety data Prescription only medicine	None
Hepatotoxicity	None Prescription only medicine	None
Pancreatic cancers	None Prescription only medicine	None
Malignant neoplasms following combination treatment with insulin	None Prescription medicine only	None
Foetal/neonatal developmental toxicity	Discussed in Section 4.6 Pregnancy, lactation and fertility with guidance regarding use during pregnancy and breast feeding; guidance regarding lead time to discontinue use before planned pregnancy Discussed in Section 5.3 Preclinical safety data Prescription only medicine	None
Accelerated sexual maturation in juveniles	Section 4.1 Therapeutic indication states for use in adults Section 4.2 Posology and method of administration, Special Populations and Section 5.2 Pharmacokinetics indicates absence of information Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in pregnancy and lactation	Discussed in Section 4.6 Pregnancy, lactation and fertility with guidance regarding use during pregnancy and breast feeding; guidance regarding lead time to discontinue use before planned pregnancy Discussed in Section 5.3 Preclinical safety data Prescription only medicine	None
Use in paediatric population	Section 4.1 Therapeutic indication states for use in adults Section 4.2 Posology and method of administration, Special Populations and Section 5.2 Pharmacokinetics indicates absence of information Prescription only medicine	None
Use in hepatic impairment	Section 4.2 Posology and method of administration, Special Populations – no dose adjustment needed Discussed in Section 5.2 Pharmacokinetics, notes no clinical studies and rationale for no need to dose adjust Prescription only medicine	None
Use in very elderly (≥75 years old)	Section 4.2 Posology and method of administration, Special Populations – no dose adjustment needed and very limited experience Discussed in Section 5.2 Pharmacokinetics, notes clinical studies and rationale for no need to dose adjust Prescription only medicine	None
Severe renal impairment (eGFR< 30 mL/min/1.73m^2)	Section 4.2 Posology and method of administration, Special Populations limited experience and not recommended Discussed in Section 5.1, Pharmacodynamic Properties and 5.2 Pharmacokinetics, notes clinical studies and rationale for no need to dose adjust Prescription only medicine	None
NYHA class III/IV heart failure	Section 4.4, Special Warnings and Precautions- Population not studied Prescription only medicine	None

The CHMP, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. 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

Benefits

Beneficial effects

It is well known that patients with type 2 diabetes are at increased risk of developing macro- and microvascular complications including cardiovascular morbidity and mortality. A major purpose of using glucose lowering agents is to reduce and mitigate these risks. HbA1c is generally accepted as surrogate marker for treatment effect and was included as the primary endpoint in the pivotal studies. Other important endpoints in studies of patients with type 2 diabetes (T2DM) are changes in body weight, fasting glucose, postprandial glucose as well as the possible effect on other cardiovascular risk factors.

The use of albiglutide 30 mg weekly (with optional uptitration to 50 mg weekly) has been studied in a well-conducted clinical program consisting of 8 Phase III studies including 6043 subjects out of which 3358 were treated with albiglutide. The choice of dose was based on non-clinical and clinical Phase II data and has been adequately justified. The program investigated albiglutide both as monotherapy and in various combinations with OADs and basal insulin. The study program includes a number of comparisons with both OADs, basal and bolus insulin as well as with another GLP-1 receptor agonist (liraglutide). Less than 5 % of subjects were recruited in Europe, whereas the vast majority were recruited in the US. The subgroup analyses, however, did not reveal any difference in treatment effect by region, race/ethnicity or BMI and extrapolation of the results from the study program to a European population therefore is deemed adequate.

The pivotal study with regards to the monotherapy indication compared both the 30 mg and 50 mg weekly dose of albiglutide to placebo in drug-naïve patients. Consistent placebo-corrected reductions of baseline HbA1c was observed for both doses with a slightly higher placebo-corrected decrease with the higher dose (-0.84 % vs -1.04 % for the lower and higher dose, respectively). This was supported by a decrease in FPG. The rate of responders (subjects achieving HbA1c < 7.0 %) was higher in the low dose group (49.0 %) compared to the high dose group (40.2 %) whereas the responder rate in the placebo group was 21.4 %. This may be explained by a difference in baseline HbA1c. In the low dose treated group, weight reduction was numerically less (-0.39 kg) than observed in the placebo treated group (-0.66 kg), whereas a

numerically greater weight reduction compared to placebo was observed in the high dose group (-0.86 kg).

Three studies investigated the use of albiglutide as add-on to metformin, add-on to TZD +/- metformin or add-on to metformin and SU. In all three studies, statistically significant placebo-corrected reductions in baseline HbA1c were observed (-0.91 %, -0.75 % and -0.87 %, for the three studies respectively). This was supported by reductions in FPG. Responder rates were significantly higher in all three studies compared to placebo, with differences to placebo ranging from 21 - 30 %. Weight reduction (-0.42 to -1.21 kg) did not differ from that observed with placebo treatment (-0.40 to -1.0 kg) and, in the study investigating add-on to TZD, a weight increase was observed in both groups (+0.28 kg for albiglutide and +0.45 kg for placebo).

Five studies included one or two active comparators added to various background therapies. Superiority could be shown for albiglutide versus both sitagliptin (treatment difference -0.35 %; 95 % CI -0.53, -0.17) and glimepiride (treatment difference -0.27 %; 95 % CI -0.45, -0.09). The weight reduction was numerically less with sitagliptin than with albiglutide whereas a weight increase was observed with glimepiride as expected.

Albiglutide was compared to pioglitazone as add-on to metformin and SU. Pioglitazone was shown to be superior to albiglutide with a treatment difference in reduction of baseline HbA1c of 0.25 % (95 % CI, 0.10, 0.40). This was supported by the rates of responders and outcome of FPG. An increase in weight was observed in the pioglitazone treated group whereas a slight weight reduction was observed in the albiglutide treated group, comparable to that observed in the placebo treated group included in the study.

In the study comparing albiglutide with insulin glargine as add-on to metformin +/- SU, non-inferiority for albiglutide vs insulin glargine could be shown with regards to the reduction of baseline HbA1c (0.11 %; 95 % CI; -0.04, 0.27, thus the upper limit of the 95 % CI below the 0.3 % non-inferiority margin). Responder rates were comparable between the two groups (about 32 % in both groups). Treatment with insulin glargine resulted in a significantly lower FPG compared to albiglutide treatment. Albiglutide treatment resulted in a modest weight reduction of 1.05 kg whereas insulin glargine treatment resulted in a weight increase of 1.56 kg. The patients in the insulin glargine treated group appears to have been adequately dosed, thus the data showing non-inferiority appear robust.

One study compared albiglutide with insulin lispro as add-on to insulin glargine + OADs. In this study, a wide variety of background treatment was allowed. The absolute HbA1c reduction was slightly higher in the albiglutide treated group (-0.82 % vs -0.66 %) and non-inferiority versus insulin lispro was shown. Comparable outcomes with regards to rate of responders and FPG supported the primary endpoint. Responder rates were somewhat lower than in the other studies, which may be explained by the fact that this study included patients with a longer diabetes duration and a higher baseline HbA1c.

In the study where albiglutide was compared with liraglutide as add-on to metformin, SU and TZD (either alone or in combination), liraglutide was statistically superior to albiglutide with an absolute difference in reduction of baseline HbA1c of 0.21 %. This was supported by a higher rate of responders and a significantly higher reduction of FPG. A statistically significant, larger reduction in body weight was observed with liraglutide (1.55 kg).

As hyperglycaemia rescue was allowed in all studies, time to hyperglycaemia rescue was included as a secondary efficacy endpoint. Albiglutide treatment resulted in a significant longer time to hyperglycaemia rescue when compared to placebo, whereas no difference was observed between albiglutide and insulin glargine.

A durability of effect up to 156 weeks could be demonstrated. This was observed both in the study were no uptitration was allowed and in studies with optional or forced uptitration. Although discontinuation rates were in the range of 40 %, a lower proportion needed rescue in the albiglutide treated groups compared to placebo. Comparable rescue rates were observed for albiglutide and active comparators.

The effect of albiglutide in patients with moderate to severe renal impairment was investigated in a dedicated renal study which included 98 subjects with moderate renal impairment and 19 subjects with severe renal impairment treated with albiglutide. In this study, albiglutide again was shown to be superior to sitagliptin treatment (HbA1c reduction -0.83 % vs -0.52 % for albiglutide and sitagliptin, respectively) and the treatment effect with sitagliptin was as expected (-0.52 %). For both treatments there was an increased effect with decreasing renal function. The effect was maintained over the 52 week treatment period. More patients in the sitagliptin group needed rescue or withdrew from the study. The outcome of FPG and responder rates supported the primary outcome. The body weight reduction was modest in both groups and higher in the albiglutide treated group.

Further to this, a subgroup analysis of 173 patients with impaired renal function defined as eGFR 60-90 mL/min/1.73 m^2 included in the 7 phase III studies give no indication of a difference in treatment effect due to renal function.

Sufficient data have been provided to support the dosing recommendations given in the SmPC. It is noted that in studies with optional uptitration of albiglutide from 30 mg weekly to 50 mg weekly, a total of 77.0% of albiglutide subjects had their dose uptitrated from 30 mg to 50 mg indicating that the 30 mg dose may not be sufficient in the majority of the patients.

Clinical data in a total of 456 patients that have received the drug product intended for commercial use (Process 3) for on average 35 weeks has been provided and is deemed sufficient to conclude that this drug product is comparable to the drug product used in the clinical program with regards to efficacy.

Uncertainty in the knowledge about the beneficial effects

The number of patients above the age of 75 or with severe renal impairment is limited and thus the data has to be interpreted with caution. Available data, however, does not indicate a different treatment effect in these groups.

Risks

Unfavourable effects

The most common short-term safety issue is gastrointestinal side effects. Nausea (13 %) and diarrhoea (12 %) were mostly mild to moderate in intensity. In the study comparing albiglutide to liraglutide, the proportions of patients with nausea were 7.2 and 35.3%, respectively. Albiglutide was also compared to exenatide BID in a phase II dose finding study. In this study

the incidences of nausea were 40 and 26% in the exenatide and albiglutide groups, respectively. However, few patients were included in each group.

The proportion of patients with hypersensitivity reactions including injection site reactions was 8.8% compared to 2.0% for all comparators at week 104. In the study comparing albiglutide to liraglutide, the proportions of patients with injection site reaction were 6.9 and 0.7%, respectively. Antibody positive status was detected in 4.4% of patients on-therapy. The development of antibodies was associated with a slightly higher incidence of injection site reactions.

Hypoglycaemia is mainly seen when albiglutide treatment is combined with SU or basal insulin, but the incidence is not increased compared to comparators. The product information states that when albiglutide is added to SU therapy or basal insulin a reduction of dose of the SU or the basal insulin may be considered to reduce the risk of hypoglycaemia. Triple combination with insulin and SU has not been evaluated.

During the clinical development a new manufacturing process (Process 3) was introduced. No pre-clinical data is available for this Process 3 (which is the proposed process for commercialization). Due to an increase in methionine oxidation of the albumin moiety observed when changing from Process 2 to Process 3 there were concerns that this could potentially lead to serious immunological adverse events (e.g.an increased development of anti-albumin antibodies). A total of 456 patients have been switched from Process 2 to Process 3 and the average time of exposure is 35 weeks (range 8-65 weeks). The safety data provided do not indicate a substantial and clinically relevant difference in the safety profile of Process 2 and Process 3 albiglutide. Especially, no difference in immunogenicity has been observed. Thus the comparability between two processes was considered by CHMP to be demonstrated from a clinical point of view.

There is limited data in some patient groups with contraindications to metformin (i.e patients with severe hepatic and severe renal impairment as well as patients with CHF); however, albiglutide could be an alternative in patients with moderate renal impairment, with hepatic impairment and with heart failure NYHA class I-II and the SmPC has been amended with adequate warnings and recommendations.

Uncertainty in the knowledge about the unfavourable effects

Albiglutide treatment was associated with a higher frequency of atrial fibrillation/flutter compared to all comparators (1.3 % vs. 0.5 %). There is no indication of QT prolongation in study GLP107085, although an increased heart rate was seen in this study. In the Phase III integrated analysis the mean heart rate was numerically higher (approx 1-2 bpm), at each integrated analysis visit over time for the albiglutide group compared with the all comparators group. No consistent effect on blood pressure was found in any of the groups and the variation between baseline and end of treatment was small (within 1 mmHg of the baseline value). A limited increase in heart rate has also been found with other products in the class.

TIAs occurred in a larger proportion of patients receiving albiglutide (0.6%) compared with all comparators (0.2%). Atrial fibrillation is a strong risk factor for TIA/CVA; however atrial fibrillation occurred prior to a TIA/CVA event in only 2 out of 20 patients with a TIA/CVA event.

The 3 year meta-analysis of CV events (MACE+; CV death, non-fatal myocardial infarction, hospitalization for unstable angina and stroke) when evaluated to the all comparator group resulted in a HR of 1.00, (95% confidence interval 0.68; 1.49).

As for other GLP-1 receptor agonist, the clinical relevance of the thyroid C cell tumours in rats cannot be excluded. In the clinical development program 2 cases of medullary thyroid carcinoma (MTC) were diagnosed (one exposed to albiglutide). This patient had an increased calcitonin baseline value as well as the diagnosis of MEN 2 and therefore, the case was not considered as related to the use of albiglutide. There were no differences in calcitonin levels between albiglutide and comparators.

There were 2 cases of pancreatic carcinoma of which one was exposed to albiglutide. In addition, one subject randomized to albiglutide had a benign neuroendocrine tumour located in the pancreas. In line with all GLP-1 based therapies and in accordance with the finalised review of GLP-1-based therapies under the Article 5(3), pancreatic cancer is included as a potential risk in the RMP.

Criteria for assessing the probability of pancreatitis (symptoms, lipase measurements and imaging) were predefined. According to these criteria, the incidence rate of probable/definite pancreatitis was 2.1 for albiglutide (n=7) compared to 0 for comparators. Pancreatitis is included in the RMP as an identified risk and a warning is included in the SmPC.

Intestinal obstruction is associated with the GLP-1 receptor agonists liraglutide and exenatide and was observed at a slightly higher frequency for albiglutide (0.3 %) vs all comparators (0.2 %; no cases with placebo), therefore information on intestinal obstruction is included in section 4.8 of the SmPC.

Acarbose is contraindicated in patients with partial intestinal obstruction or in patients predisposed to intestinal obstruction. Thus based on theoretical considerations, information on the risk of intestinal obstruction when albiglutide is co-administrated with acarbose is included in the SmPC.

Pneumonia was infrequent but more common in albiglutide treated subjects. Previously upper respiratory infections have been reported more frequently in patients treated with GLP-1 receptor agonists and this is included in the product information. An association between other GLP-1 receptor agonists and pneumonia has not previously been described. A potential mechanism for pneumonia associated to albiglutide has been discussed by the Applicant; however no mechanism has been identified.

Due to the slow elimination of albiglutide, clinically relevant systemic concentrations may be maintained for up to 4 to 5 weeks following cessation of dosing. In this context, when discontinuing the product, the long time for elimination could pose additional problems in association with the occurrence of serious adverse events. The evaluation of time to resolution of common on-therapy AEs and SAEs following cessation of therapy did not indicate concerns regarding the long elimination half-life of albiglutide.

The teratogenic potential of albiglutide was only studied in one species. An embryo-fetal toxicity study in mice showed developmental toxicity, similar to that seen with other members of the class. Considering the cautious recommendation in the SmPC, based on the long washout of albiglutide, the absence of data in a second species is well justified.

Benefit-risk balance

Importance of favourable and unfavourable effects

The clinical data provided show that albiglutide treatment results in a clinically relevant lowering of baseline HbA1c in a representative T2DM patient population, both when given as monotherapy and in combination with metformin, SU, TZD and basal insulin. Durability of the effect over a study period of 3 years has been shown. The study program includes a larger number of comparisons with other treatments than usually seen, which is welcomed. Albiglutide appears to provide a larger effect on HbA1c than sitagliptin and glimepiride. On the other hand, albiglutide was shown less efficient than pioglitazone and liraglutide. The effect of albiglutide appears comparable to that of basal or bolus insulin treatment.

The effect on body weight appears less pronounced than previously described for some of the other GLP-1 receptor agonists and no difference when compared to placebo was observed. However, body weight decreased slightly or remained stable during treatment which is of benefit considering that continuous weight gain is a clinical problem in this patient group. Maintaining body weight while decreasing HbA1c is therefore considered a beneficial effect of importance.

When compared to other GLP-1 receptor agonists which are administered once or twice daily, administration once weekly may be of benefit in some patients.

Albiglutide could be an alternative in patients with moderate renal impairment, with hepatic impairment and with heart failure NYHA class I-II. Consequently, albiglutide might be a useful option for many patients in whom metformin is contraindicated.

Overall, the safety profile of albiglutide is largely comparable to other GLP-1 receptor agonists. In direct comparison with liraglutide, gastrointestinal events were less pronounced but the proportion of injection site reactions higher. With regard to the long-term safety, the results of the meta-analysis of MACE+ show no trend to a higher risk for CV events versus the comparator groups.

Concerning immunological events an overrepresentation of injection site reactions observed with albiglutide compared to liraglutide; however the severity of injection site reactions with albiglutide was generally mild and moderate in nature and none were considered an SAE. Information regarding injection site reactions is included in 4.8 of the SPC, which is considered sufficient.

Otherwise, the potential long-term safety concerns are the same as for the other GLP-1 receptor agonist, i.e. identified risk for pancreatitis and potential risks for pancreas and thyroid tumours. These events will be followed in post approval safety studies

Benefit-risk balance

The absolute glucose lowering effect of albiglutide is considered to be of clinical relevance. The weight reduction is modest, however, in this patient group stabilising body weight is also considered beneficial. The safety profile is largely similar to other products in the class. There are potential risks associated with a propensity to induce increased heart rate, pancreatitis and injections site reactions.

Considering the relative benefit/risk balance comparing albiglutide to other products in the class, the study including liraglutide as a comparator indicates that both the glucose and weight

lowering effects are less pronounced for albiglutide compared to liraglutide. However, the incidence of nausea is considerably lower with albiglutide compared to liraglutide and exenatide BID (albeit in a small sample size) and there may be advantages with respect to the weekly dosing. No studies with a direct comparison of albiglutide to other products in the class of GLP-1 receptor agonists are available. However, a comparison with similarly designed studies of other GLP-1 receptor agonists, while having many limitations, might indicate the strength of the benefit/risk balance of albiglutide to be similar to lixisenatide. The efficacy may seem to be lower compared to the other product available for once weekly dosing (exenatide QW), but on the other hand, the incidences of nausea and immunogenicity are lower for albiglutide.

However, even if the relative benefit/risk balance might be somewhat weaker compared to e.g. liraglutide and exenatide, the absolute benefit/risk balance of albiglutide is positive.

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 Eperzan in the treatment of type 2 diabetes mellitus 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.

Conditions and requirements of the Marketing Authorisation

- **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 agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that albiglutide is qualified as a new active substance.