26 June 2014
EMA/CHMP/340840/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abasria

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/002835/0000

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AUC_{τ}	Area under the concentration-time curve over the dosing interval
$AUC_{(0-24)}$	Area under the serum insulin glargine concentration-time curve from zero to 24 hours
$AUC_{(0-tlast)}$	Area under the serum insulin glargine concentration curve from time zero to last measured concentration value
BA	Bioavailability
BE	Bioequivalence
BG	Blood glucose
BMI	Body mass index
BMWP	Biosimilar Medicinal Products Working Group
$C_{av,ss}$	Average serum concentration at steady state
CI	Confidence interval
CHMP	Committee for Medicinal products for Human Use
CL	Total body clearance
CL_{ss}	Total body clearance at steady state
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Minimum serum concentration immediately before the next application
$C_{min,ss}$	Minimum serum concentration at steady state
CPK	Creatine phosphokinase
Conc	Concentration
CSR	Clinical study report
CV	Coefficient of Variation
dL	decilitre
DNA	Desoxyribnucleic acid
ECG	Electrocardiogram
EM(E)A	European Medicines Agency
EOI	End of infusion
ESR	Erythrocyte sedimentation rate
EPAR	European Public Assessment Report
EU	European Union
GCP	Good Clinical Practise
EWP	Efficacy Working Group
FBG	Fasting blood glucose
FDA	Food and Drug Administration
GGT	Gamma-glutamyltransferase
GIR	Glucose infusion rate
GIR_{last}	Value of last measurable glucose infusion rate
G_{tot}	Total amount of glucose infused
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
HbA1C	Haemoglobin A1c
HBV	Hepatitis B virus
HS	Healthy subjects

Ig	Immunoglobulin
IGF-1	Insulin growth factor-1
IR	Insulin receptor
IV (i.v.)	Intravenous
ITSQ	Insulin Treatment Satisfaction Questionnaire
ITT	Intention to treat
LLOQ	Lower level of quantitation
LOCF	Last observation carried forward or last postbaseline observation carried forward
LOESS	Locally weighted scatterplot smoothing
LS	Least square
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligramme
MHRA	Medicines and Healthcare products Regulatory Agency
MRT	Mean residence time
MSR	Mean significant ratio
NPH	Neutral protamine hagedorn
N/A	Not applicable
OAM	Oral antihyperglycaemic medications
OR	Odds Ratio
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-protocol population
QC	Quality control
QD	Once daily
QoL	Quality of life
QWP	Quality Working Group
PK	Pharmacokinetic
PT	Preferred term
R	Reference treatment
R_{max}	Maximum glucose infusion rate
RBA	Relative bioavailbility
RIA	Radio-immuno assay
RMP	Reference medicinal product
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SD	Standard deviation
SMBG	self-monitored blood glucose
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SU	sulfonurea
$T_{½}$	Terminal elimination half life
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TID	Three times a day
T_{last}	Time of last measurable glucose infusion rate
T_{max}	Time to reach C_{max}
T_{onset}	Time of first change of glucose infusion rate postdose
TR_{max}	Time to maximum glucose infusion rate
UK	United Kingdom
U	Unit(s)
US	United States
VAS	Visual analogue scale

V_1	V_d in the central compartment
V_2	V_d in the peripheral compartment
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution during the terminal phase after extravenous administration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Regional Operations GmbH. submitted on 3 June 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Abasria, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication;

"Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above."

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products. The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Information on Paediatric requirements

Not applicable

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.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 July 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturers of the active substance

Lilly del Caribe, Inc.
12.3 km 65th Infantry Road
Carolina, PR 00985
Puerto Rico

Eli Lilly and Company
Indianapolis
Indiana 46285
USA

Manufacturer responsible for batch release

Lilly France S.A.S.
2, rue du Colonel Lilly
F-67640 Fegersheim
France

1.3. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings

Co-Rapporteur: Ágnes Gyurasics

- The application was received by the EMA on 3 June 2013.
- The procedure started on 26 June 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2013.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2013.
- During the meeting on 10 October 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 24 October 2014
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 February 2014.
- During the CHMP meeting on 20 March 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 May 2014.
- During the meeting on 26 June 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 Abasria.

2. Scientific discussion

2.1. Introduction

Problem statement

Diabetes mellitus is widely recognized as one of the leading causes of death and disability globally. The International Diabetes Federation (IDF) estimates that more than 371 million adults worldwide have diabetes and that number is projected to increase to 552 million by 2030 (IDF Diabetes Atlas 2012a; IDF Diabetes Atlas 2012b). Diabetes mellitus is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces, resulting in hyperglycaemia. Type 1 diabetes mellitus (T1DM) results from pancreatic islet cell destruction most commonly by an autoimmune process. It is a disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic ß cells fail to respond. Patients are prone to developing ketoacidosis and require exogenous insulin replacement. Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder most commonly associated with insulin resistance in the presence of an associated impairment in insulin secretion. Type 2 diabetes mellitus results from relative insulin deficiency, a mismatch between insulin production and insulin requirements, which is in contrast to the absolute insulin deficiency of patients with T1DM. Insulin is considered the most effective treatment to lower high blood glucose (BG) and is indicated for patients with T1DM and for patients with T2DM, if adequate glycaemic control cannot be achieved through diet, exercise, or other antidiabetes medication. Tight glycaemic control is recommended for most patients with diabetes mellitus to reduce the risk of chronic complications of the disease, and insulin's role in achieving this is well-recognized (DCCT/EDIC 2005).

Long-acting insulin analogues, such as insulin glargine, provide smooth, peakless basal insulin profiles, resulting in a glycaemic profile more similar to normal physiology, potentially enabling patients to achieve normal BG levels. Clinical evidence to date suggests that a long-acting insulin analogue, such as insulin glargine, may provide benefits over prior agents such as neutral protamine Hagedorn (NPH), including reduced frequency of nocturnal hypoglycaemia, better fasting BG control, and improved quality of life when compared with traditional insulins in patients with either T1DM or T2DM (Pieber et al. 2000; Ratner et al. 2000; Rosenstock et al. 2000; Yki-Jarvinen et al. 2000; Schober et al. 2001).

Insulin glargine was first authorised in the EU on 9 June 2000 under the name of Lantus. It is currently approved for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

About the product

Abasria (LY2963016) was submitted as a biosimilar, with Lantus (insulin glargine [rDNA origin] injection) as the chosen reference medicinal product. The reference medicinal product has been marketed in the European Union for over 10 years. *Lantus 100 unit / ml solution for injection* was first authorised in the EU on 9 June 2000 (MA: EMEA/H/C/000284); the Marketing Authorisation Holder is Sanofi-Aventis Deutschland GmbH.

The primary amino acid sequence of LY2963016 is the same as that of the active ingredient in Lantus. Abasria has the same pharmaceutical form and strength as Lantus. Abasria differs from the reference medicinal product with respect to excipients used in the formulation: zinc oxide replaces zinc chloride and Abasria uses 100% glycerol compared with 85% in the reference medicinal product. However, the final quantitative formulation is the same as that of the reference medicinal product.

Abasria (LY2963016) is a long-acting insulin analogue administered as a subcutaneous injection for the treatment of type 1 and type 2 diabetes mellitus. It will be made available in 2 presentations: a 3 mL cartridge,

for delivery by a compatible CE-marked reusable pen injector, and also the same 3 mL cartridge sealed in a prefilled pen injector (KwikPen). The pen injectors differ from those available to administer Lantus cartridges, but are appropriate for use with Lilly insulin cartridges. The pack sizes also differ.

The proposed therapeutic indication and posology for LY2963016 are identical to those for Lantus.

The development programme

The clinical development programme of LY2963016 has specifically considered the EU guidelines for similar biological medicinal products and also indication-specific guidelines (see list below).

Guideline	Document Reference	Topic
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. EMEA, 2006	EMEA/CHMP/BMWP/42832/2005	Development plan
Guideline on Similar Biological Medicinal Products. CHMP, 2005	CHMP/437/04	Development plan
Revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues	EMEA/CHMP/BMWP/32775/2005 Released for consultation December 2012	Development plan
Guideline on the choice of the non-inferiority margin. EMEA, 2005	EMEA/CPMP/EWP/2158/99	Phase 3 clinical trial design
Guideline on the investigation of bioequivalence. EMEA, 2010	CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **	Phase 1 clinical trial design
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. EMEA, 2007	CHMP/EWP/89249/2004	Phase 1 clinical trial design

Although the planning phase of the clinical development programme was completed before the draft guideline on similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005) was published, the clinical programme is broadly in accordance with the principles of this document. During the development of LY2963016 the applicant sought scientific advice at the European Medicines Agency (EMA) in July 2011. The scientific advice procedures covered questions on the pharmaceutical quality, the non-clinical and clinical programme. Broadly, the Scientific Advice recommendations were followed by the applicant and the development has followed a stepwise approach in demonstrating the comparability with the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

Abasria (LY2963016) has the same pharmaceutical form and strength as the reference medicinal product Lantus. It is supplied as a sterile solution for subcutaneous injection. The intended commercial formulation is presented in 3 mL glass cartridges. Each mL of Abasria (insulin glargine injection) contains 100 units of insulin glargine, zinc (zinc oxide), metacresol, glycerol and water for injection, as well as hydrochloric acid and sodium hydroxide (used for pH adjustment). It will be made available in 2 presentations: a 3 mL cartridge, for delivery by a compatible CE-marked reusable pen injector, and the same 3 mL cartridge sealed in a prefilled pen injector

(KwikPen). The pen injectors differ from those available to administer Lantus cartridges, but are appropriate for use with Lilly insulin cartridges.

Overall clinical lots representing two different presentations of LY2963016 finished product produced using the same active substance process material, were used in the clinical program. Both finished product presentations used the same formulation, which was filled into 3 mL cartridges (manufactured at Lilly, France) or 10 mL vials (manufactured at Lilly, Indianapolis).

A comparability exercise has been performed for the proposed LY2963016 biosimilar product with the reference medicinal product, EU-approved Lantus. Data generated with US-approved Lantus has also been presented and is considered supportive.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.2.2. Active Substance

General information

Abasria is formulated from LY2963016 active substance, which is also referred to in the dossier as basal insulin analogue V (BIV). LY2963016 is a two-chain peptide containing 53 amino acids; a 21 amino acid A-chain and a 32 amino acid B-chain that are non-glycosylated.

LY2963016 (INN: insulin glargine) differ from human insulin by the addition of 2 arginine residues to the C-terminus of the B-chain and the replacement of the asparagine at position A21 with a glycine.

Figure 1: Primary Structure of LY2963016

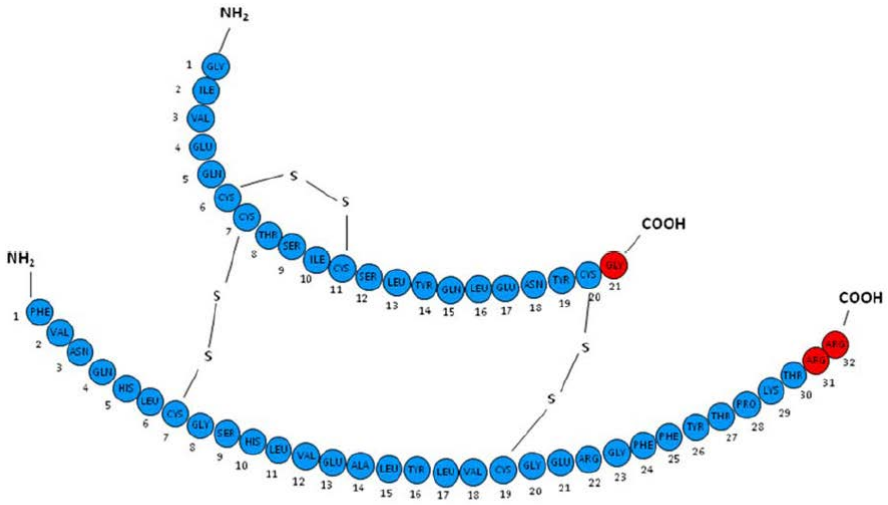


Figure 3.2.S.1.2-1 Primary Structure of LY2963016

These changes shift the isoelectric point such that the analogue is soluble at an acidic pH, but less soluble at neutral physiological pH. Once injected, the insulin analogue precipitates in the neutral pH environment of the subcutaneous injection site, delaying absorption and prolonging the duration-of-action without a pronounced peak in the time action profile. In vivo, the 2 arginines are cleaved and the molecule interacts with the native insulin receptor.

Manufacture, characterisation and process controls

LY2963016 is produced in transformed *Escherichia coli* bacteria, and purified using established biotechnology purification procedures. Fermentation of *E.coli* transformed with the appropriate expression plasmid results in the expression of a pre-pro-protein. Granules of pre-pro-protein are then recovered from the fermentation broth by homogenising the cells prior to removal of cell debris/granule concentration by differential centrifugation.

After isolation, the product undergoes solubilisation and sulfitolysis (opening of disulphide bonds). The product is then re-folded to form a proinsulin-like intermediate with correct disulphide bonds. After re-folding the leader sequence is enzymatically removed. Finally, the active substance, LY2963016 (BIV) is formed by enzymatically removing the connecting peptide (C-peptide).

Subsequent chromatography steps are then employed to remove process and product-related impurities, before the active substance is crystallised, dried and filled into final containers.

LY2963016 active substance is filled in a glass bottle and plastic screw caps. The compatibility and the protection provided by the container closure system have been confirmed by the active substance stability data.

The manufacturing process is well described, and in general the process controls are appropriate.

Information has been provided for the laboratory, pilot and commercial scale operations used in manufacture of Abasria (LY2963016 insulin glargine), to demonstrate the validity of the models used at each of the process steps to determine the acceptance criteria for the manufacturing process. The applicant has provided justification for the claimed proven acceptable ranges (PAR), Critical Process Parameters, Acceptable Ranges for Operational Process Parameters and In-Process Controls, as well as the Normal Operating Ranges, based on laboratory/pilot scale, commercial scale. The application of measurement uncertainty (MU) has been clarified and the use of this to determine the operational PAR is endorsed. Some of the acceptance ranges have been tightened, based on the laboratory, pilot and commercial scale process validation data. This provides reassurance regarding the manufacturing process control.

The applicant has provided information from the process validation study to demonstrate that the loading targets in commercial scale for the Drum Thaw, Transformation and Crystallization are met. The applicant has confirmed that, at all steps, material is controlled within the established intermediate hold times.

The strategy for chromatography resin lifetime monitoring has been explained. Details of the output parameter ranges and actions if those ranges are exceeded have been given. Cleaning and storage details for the resins have also been provided.

Details of the shipping validation have been provided. This demonstrates that the active substance is maintained at less than -39°C, which is acceptable.

Control of materials

The gene was designed with appropriate sequences for ligation into a platform expression plasmid backbone. The plasmid was used to transform the *E. coli* host strain and a clonal recombinant derivative was used to produce the Master and Working Cell Banks.

The development of the transformed host strain and construction and control of the working and master cell banks is considered adequate. Details for stability testing of the MCB and WCB have been provided, including growth of thawed cells and characterisation to confirm retention of the plasmid. Restriction enzyme digest analysis is performed to confirm the correct plasmid banding pattern and the product identity is confirmed by

testing the fermentation culture for potency of product intermediate. Growth data are compared with expected data and fermentation potency data used to demonstrate that the revived cells can be used to manufacture the desired product intermediate.

Manufacturing process development
Several active substance manufacturing processes have been utilised throughout LY2963016 development.

On the whole, comparability between clinically qualified material and proposed commercial material was demonstrated using extensive characterisation of active substance and finished product batches. Additional structural characterization data have been provided, with tests performed directly on active substance batches and some tests performed on finished product batches manufactured using active substance from the two processes and representing both finished product sites (contract manufacturer, USA and Lilly, France).

Comparability was demonstrated for primary structure, secondary structure, tertiary structure and quaternary structure. Stability data under both long term and accelerated conditions was also provided to support the comparability.

Characterisation
The structure of LY2963016 has been elucidated through detailed structural characterization of the primary reference standard ~~a~~nd a commercial-scale finished product demonstration batch. Consistency with the expected LY2963016 amino acid sequence has been demonstrated. Higher order structural characterization has been demonstrated. Additional structural characterization data and biological potency data have been provided, with tests performed directly on active substance batches and some tests performed on finished product batches manufactured using active substance from the two processes and representing both finished product sites (contract manufacturer, USA and Lilly, France).

The biological activity has been characterised utilising several physiologically relevant assays.

LY2963016 related impurities that are seen in the final active substance were isolated and characterized.

Host cell proteins, proinsulin precursor, bacterial endotoxins, iron, and ethanol process related impurities are routinely tested against batch release specifications.

Specification
The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).

The potency assay is an HPLC method. The method has demonstrated specificity for LY2963016. The specification limit is consistent with the specification for total impurities and allows for assay variability. The assay quantifies mg of LY2963016 per mg of total solid and is corrected for any volatiles that may be present via the LOD method. The proposed limit is aligned with the human insulin active substance compendial and registered limits.

The bioidentity method for LY2963016 is a cell-based reporter gene assay.

The analytical procedures used to characterise and control LY2963016 quality are generally appropriate and validated.

Batch data has been presented for multiple validation batches. Data from the validation batches, clinical batches and primary stability batches are all comparable.

Stability

The stability data presented support the proposed shelf-life of 30 months at -10°C. Nine months long term (-10°C) stability data are available for the Process validation and production lots of active substance. Six months accelerated (5°C) stability data are available. Based on stability data comparison, the commercial process and the process used to generate clinically qualified material are comparable in terms of long term (-10°C) and accelerated (5°C) stability.

Stress testing was also done to identify possible degradation pathways. Photostability studies were performed, showing that LY2963016 is light sensitive and is therefore packaged to protect it from light.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Comparability exercise for Active Substance

Please refer to the section "comparability exercise for Finished Product" below.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Abasria finished product will be made available in 2 presentations: a 3 mL cartridge, for delivery by a compatible CE-marked reusable pen injector and the same 3 mL cartridge sealed in a disposable prefilled pen injector (KwikPen). The glass cartridge has an elastomeric disc seal and plunger for administration via subcutaneous injection. The plungers and glass cartridges are siliconized.

Abasria is a clear and colorless solution. It is formulated so that LY2963016 active ingredient is at a concentration of 100 Units/mL. It contains no novel excipients. Excipients include glycerol, metacresol and zinc. Glycerol is added as a tonicity modifier, metcresol as preservative and zinc as a stabiliser. The solution is unbuffered (pH 4).

The LY2963016 Injection finished product formulation is manufactured with no overage of the active substance. For the finished product filling operation, the cartridges are overfilled to ensure the delivery of the minimum volume (3 mL) claimed on the cartridge label.

The LY2963016 Injection formulation development focused on understanding the impact of variation in excipients and formulation composition on key analytical properties of the finished product. The intended commercial formulation of LY2963016 Injection is based on the reference medicinal product. The formulation has been used throughout product development and in all clinical studies.

All excipients are the same chemical compounds and concentrations as those used in Lantus except 2 minor differences. The LY2963016 Injection formulation uses zinc oxide, instead of zinc chloride as in LANTUS. Zinc oxide is chemically converted to zinc chloride by dissolving it in an excess amount of 10% hydrochloric acid before its addition to the formulation solution. Additionally, LY2963016 Injection formulation uses 100% glycerol which is consistent with Lilly insulin manufacturing practice whereas LANTUS uses 85% glycerol. The final levels of zinc and glycerol in LY2963016 Injection and in LANTUS are the same.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

The applicant has adopted an enhanced approach to formulation development and proposes a formulation design space. The stability of the formulation at the target concentration of each component, but also within the region surrounding the target concentration was studied using statistical design of experiments (DoE). The experimental design was a full factorial design with 3 factors and 2 levels for each factor. Critical quality attributes (CQA) have been identified. Data from the DoE evaluation of the Proven Acceptable Ranges (PAR) have been provided to show the impact of process parameters on the CQAs.

Manufacture of the product and process controls

The aseptic manufacturing process for Abasria is a standard formulation, filtration and filling operation. Cartridges are then assembled into pen injectors or packaged in blisters. The cartridge and disc seal components are well-established components having been used with marketed insulin products for several years. The plunger is made of an elastomer formulation selected for improved compatibility properties with this product. The safety of the container closure system components with LY2963016 has been confirmed with compendia compliance and with real time leachables studies. No analytes were measured above the allowable daily intake threshold, indicating a safe toxicological profile.

The process is well described and a detailed risk assessment was carried out to assign critical, non-critical and operational parameters. The process is well controlled.

Finished Product will be manufactured at a contract manufacturer, USA and Lilly, France. Process data is provided for the primary batches and commercial batches produced at Lilly, France and the contract manufacturer, USA. The batch data presented are consistent on the whole for each manufacturing site, with data provided from process validation batches from both sites. Validation for components, equipment and aseptic processing is in place. Media fill program has been validated for sterility at both the contract manufacturer and Lilly France. Compatibility with the non-metal and metal equipment was evaluated and the results are satisfactory.

Injection cartridges manufactured at the 2 sites (contract manufacturer, USA and Lilly, France) were tested for comparability. There was a detailed study which included structural and batch release data comparisons. An assessment of secondary, tertiary and quaternary structure has been made. In conclusion, comparability of the contract manufacturer, USA and Lilly, France batches has been established and stability data has been provided for the process validation batches produced from active substance manufactured using the proposed commercial active substance process.

Details for the cartridge and pen-injector (KwikPen) have been provided. The pen assembly process validation strategy has been described and successful process validation gives assurance that these meet the required quality standards.

Product specification

The control tests proposed for the finished product are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).

The analytical methods are validated and the majority of methods are used to control both the active substance and finished product, except for the metacresol method.

Stability of the product

The proposed shelf life of 24 months at 5°C is supported by data. Stability studies are being conducted for 3 primary batches from each site according to ICH Q5C "*Stability testing of biotechnological/biological products*"

guideline. Stability data show that all analytical properties remained within the proposed specifications at the storage condition of 5°C through the available time points. The patient in-use stability study was conducted using finished product stored under long term conditions for 14 or 24 months. Results were in line with the acceptance criteria and showed no degradation or significant impurity increase.

The finished product is light sensitive, so packaging ensures exposure to light is minimised.

In general, the results support the shelf life and storage conditions as defined in the SPC.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Biosimilar comparability exercise for finished medicinal product

Abasria (LY2963016) has been developed with the same pharmaceutical form and strength as LANTUS, allowing direct comparison of the finished products. The biosimilar comparability testing included structural characterization, physicochemical characterization, biological potency (biological activity), impurity characterization and stability assessment.

The applicant initially proposed to first confirm comparability between US-approved and EU approved Lantus, and between LY2963016 injection that is manufactured at Lilly France and contract manufacturer. Once the two populations of each product were shown to be comparable, it was proposed that comparability would be demonstrated between Lantus and LY2963016 Injection. This approach to the biosimilar comparability exercise was not fully in line with the CHMP guidelines for biosimilars. For the quality biosimilarity exercise, the proposed biosimilar product should be demonstrated to be comparable to the EU reference medicinal product, using multiple batches. In addition, the recommended approach of generating the required quality, safety and efficacy data for the biosimilar comparability study with product manufactured using the final manufacturing process and therefore representing the quality profile of the batches to be commercialised was not followed.

The applicant subsequently provided data for additional batches of EU-approved Lantus and segregated the information derived from EU-approved and US-approved Lantus. Data from LY2963016 batches manufactured by Lilly France and the contract manufacturer has also been presented separately to allow appropriate assessment. Data comparing LY2963016 and EU-approved Lantus side-by-side has been presented and orthogonal methods have been used for the structural analysis of the primary, secondary, tertiary and quaternary structure. The biosimilar comparability exercise has compared the LY2963016 with the EU-approved Lantus, followed by comparison of the EU-approved Lantus with the US-approved Lantus, to demonstrate the validity of the supportive clinical studies carried out with US-approved Lantus. Additional data from the process validation batches has allowed comparison of the final proposed commercial process with the EU-approved Lantus.

Physico-chemical characterisation has demonstrated biosimilar comparability between LY2963016 and the reference medicinal product, EU-approved Lantus, with the only observed difference being the presence of low levels of citrate in the Lantus samples detected by NMR. Reference has been made to data using *in vitro* biological assays with process validation batches and this has been reviewed in the non-clinical assessment. Biological potency has also been evaluated by testing LY2963016 Injection and Lantus in a comparability study. This demonstrated that the average relative potency was comparable for all these batches of LY2963016 Injection and Lantus. The applicant has also provided biological identity test data from LY2963016 Injection and

[2] 26.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Lantus with batches tested concurrently, which were demonstrated to be comparable, showing that the original differences observed were due to analytical variability and diverse testing times for the samples.

Total impurities and HMWP measured by release methods were lower in LY2963016 Injection batches compared with Lantus, which is attributed to the increased age of the reference medicinal product. One impurity, not found in measurable amounts in Lantus but present in LY2963016 Injection clinical trial batches is below the ICH threshold for toxicity. This impurity is controlled and the applicant has discussed potential clinical implications. The assay results between LY2963016 Injection and Lantus indicate that Lantus is formulated to a slightly higher concentration, which did not translate into consistent PK differences.

The Applicant has provided data to support the claim that LY2963016 Injection and Lantus have similar precipitation characteristics under physiological conditions (in phosphate-buffered saline pH 7.4). This demonstrates that these two products have comparable *in vitro* precipitation and the finished products would be expected to behave in a similar manner *in vivo*.

The proposed shelf-life for Abasria is 24 months at 2-8°C, including an in-use period of up to 28 days at 30°C. For Lantus it is also 24 months at 2-8°C, but including an in-use period of up to 28 days at 25°C. Stability is comparable on the whole for LY2963016 Injection and Lantus batches, in terms of rates of degradation.

Both products showed significant degradation on exposure to iron, but the pathway of degradation appeared different. Further studies demonstrated that these differences are likely to be due to citrate, which has been detected in Lantus. Differences were not observed with lower levels of iron, particularly at the levels expected to be present in LY2963016 Injection. Therefore, this discrepancy in iron-induced degradation is not expected to have any impact on the Abasria product under normal conditions.

Overall, comparability between LY2963016 and the reference medicinal product Lantus has been satisfactorily demonstrated from the quality perspective.

Adventitious agents

Biological materials used in the production of LY2963016 have been evaluated for possible sources of bacterial and viral contamination. Biological materials used in the LY2963016 process are of bacterial, microbial or plant sources. No reagents are derived from human or animal sources. Since the *E.coli* host strain is not susceptible to mycoplasma or viruses, no control/reduction measures are required.

GMO

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

During the procedure, a major objection was raised regarding the control strategy for the manufacturing process, which was not clearly explained. In response, the Applicant provided a clearer explanation of the manufacturing process control, based on laboratory, pilot and commercial scale operations used in the manufacture of Abasria.

Justifications for the claimed proven acceptable ranges (PAR), Critical Process Parameters, Acceptable Ranges for Operational Process Parameters and In-Process Controls, as well as the Normal Operating Ranges, based on laboratory/pilot scale, and commercial scale were submitted. This provided reassurance regarding the manufacturing process control and the major objection was considered resolved.

Initially, comparability between different processes was not considered sufficiently demonstrated due to the lack of information provided regarding the nature of some of the process changes implemented and the limited degree of testing applied. The Applicant provided further clarifications and data to demonstrate comparability. This included extensive characterisation of active substance and finished product batches, with tests performed directly on active substance batches and some tests performed on finished product batches manufactured using active substance from different processes and representing both finished product sites (contract manufacturer–USA and Lilly France).

Primary stability data was provided for clinical trial batches, rather than the proposed commercial process. Lack of data from finished product manufactured through a validated process and with the final commercial active substance process gave rise to a major objection on the claimed shelf life of 24 months at +5°C for the finished product. The applicant provided stability data up to 6 months for batches produced via the validated finished product process and from active substance produced via the commercial process. This provided additional assurance regarding the comparability between different processes and consequently the proposed shelf life was found acceptable.

A major objection raised regarding the suitability of the proposed commercial plunger system was thoroughly addressed by the applicant. It was demonstrated that finished product using the commercial plunger system and stored under the long term storage conditions (2-8°C) is sufficiently stable for the patient in-use period (of 28 days at 30°C) if used within its suggested shelf-life of 24 months.

For the demonstration on biosimilar comparability with the reference medicinal product, a major objection was raised regarding the limited techniques applied and insufficient number of batches of reference product (EU-approved Lantus) analysed for several tests. Further data was provided, including side-by-side comparisons between Abasria and EU-approved Lantus using orthogonal methods. Data provided assurance of comparability for primary, secondary, tertiary and quaternary structure. Additional data and clarifications were submitted to satisfactorily demonstrate comparability in terms of potency and biological identity.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

Overall, comparability between LY2963016 and the reference medicinal product Lantus, approved in the EU, has been satisfactorily demonstrated from the quality perspective.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant should reassess the RP-HPLC finished product specifications once further data are generated, including in-use stability data after long term storage of the finished product for 24 months.

2.3. Non-clinical aspects

2.3.1. Pharmacology

The primary aim of the pharmacology package was to demonstrate similarity between the proposed product, Abasria (LY2963016) and the reference medicinal product, Lantus. Studies were first conducted in order to compare the pharmacological activity of a batch of LY2963016 to that of a US-approved batch of Lantus and subsequently, studies were also conducted with EU-approved Lantus (in accordance with CHMP Scientific advice) and with EU and US-formulated LY2963016. The applicant has therefore provided a series of pharmacology studies with EU and US-formulated LY2963016 and EU and US-approved Lantus and has attempted to characterise the binding affinity and functional activity at the relevant insulin receptors. In addition, the potential to stimulate lipogenic activity in adipocytes and mitogenicity in IR and IGF-1 receptor dominant cells has been evaluated.

Primary pharmacodynamic studies

Overall, the general rank orders of affinity to and potency (autophosphorylation) of Lantus and insulin reference compounds at the IGF-1, IR-A and IR-B receptors were in line with that reported previously [Sommerfeld, 2010]. Data from the preliminary study suggest that the affinity and potency (autophosphorylation) of a batch of LY2963016 was similar to that of US-approved Lantus at the IGF-1, IR-A and/or IR-B receptors. In the definitive study, the affinity of batches of LY2963016 evaluated (EU and US-pooled) was considered to be similar to the batches of Lantus (EU and US-pooled). The potency of LY2963016 (EU and US-pooled) at the IR-A was slightly (1.2-fold) lower than Lantus (EU and US pooled) and the potency of US-formulated LY2963016 at the IR-A and IR-B receptor was 1.2 to 1.6-fold higher than that of EU-formulated material. The CHMP notes that the observed difference in potency at the IR-A receptor (between EU and US-LY2963016) correlates with a difference in affinity. Although the observed differences were statistically significant, the applicant did not consider these differences to be of biological significance [as the observed difference was less than the mean significant ratio (MSR); see Discussion].

The applicant suggested that in mouse adipocytes, the lipogenic potency of LY2963016 was similar to that of the reference product, Lantus. In the definitive study, statistical differences were observed when comparing the lipogenic/metabolic potencies (EC_{50}) of pooled LY2963016 and pooled Lantus as well as US-formulated LY2963016 to EU-LY2963016. As the observed differences (1.3-1.4-fold) were below the minimum significant ratio (2.61), the applicant considered that these differences were not biologically significant.

In human osteosarcoma SAOS-2 cells where the mitogenic response is more dependent upon IGF-1R signalling when compared to that of the IR, the rank order of mitogenic potency was in line with the rank order of affinity at the IGF-1 receptor and the rank order of autophosphorylation at the IGF-1 receptor [Sommerfeld, 2010], which would suggest that the assay has been sufficiently characterised. Although the EU-formulated LY2963016 had a slightly higher potency when compared to US formulated LY2963016 (1.3-fold, not significant), overall the data presented from the preliminary and definitive studies would suggest that in the SAOS-2 cell line, the mitogenic potency of the batches of LY2963016 tested is generally similar to that of the reference product, Lantus.

In rat H4IIe hepatoma cells where the mitogenic response is IR-dependent (under serum-free conditions); overall, the mitogenic potency of LY2963016 (pooled) was considered by the applicant to be similar to that of the reference product, Lantus (pooled). It is noted however, that the mitogenic potential of EU-formulated

LY2963016 was higher than that of US-formulated LY2963016 (1.7-fold) and the applicant did not consider the observed difference to be biologically relevant.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted with LY2963016. These are not required for this type of application.

Safety pharmacology programme

No safety pharmacodynamic studies have been conducted with LY2963016. Safety phamacology studies are not required for this type of application.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been submitted, which is acceptable for this type of application.

2.3.2. Pharmacokinetics

In light of the fact that this is a biosimilar application, the absence of distribution, metabolism, excretion and pharmacokinetic drug interaction studies is considered acceptable as the proposed product has the same primary amino acid sequence as the reference product, Lantus, which is currently marketed.

Toxicokinetic analysis was performed during the repeated-dose toxicity studies to clarify whether serum exposures of insulin glargine were similar for LY2963016 and EU- and US-approved Lantus. The analytical methods used for the toxicokinetic analyses of samples from the definitive toxicity studies were validated. Repeated administration of LY2963016 or Lantus caused a dose-related increase in exposures to immunoreactive insulin glargine; however, the observed increase was not considered to be dose-proportional. There was some evidence of accumulation upon repeated dosing. The applicant has suggested that the exposures to insulin glargine are similar following subcutaneous administration of LY2963016 vs Lantus; however, the data as presented during the initial submission were difficult to interpret and further clarification was sought. The applicant subsequently presented the data in a manner which allowed comparison; the exposures to insulin glargine as presented were extremely variable in the LY2963016 and Lantus treated groups and there was no clear difference in exposures between the groups. However, with respect to the determination of exposures to insulin glargine the potential for cross reactivity with rat insulin was noted and clarification was sought as to why C-peptide correction was not applied. The applicant highlighted the technical challenges of measuring C-peptide rat serum levels and referred to clinical PK data which demonstrate that endogenous insulin levels are not a significant confounding factor in the comparison of the pharmacokinetics of Lantus and LY2963016.

2.3.3. Toxicology

Single dose toxicity

Single-dose toxicity studies have not been conducted with LY2963016. This was considered acceptable.

Repeat dose toxicity

In the rat, repeated administration of LY2963016 or Lantus was associated with mortality and clinical signs indicative of severe hypoglycaemia. The mortality rates observed following subcutaneous administration of LY2963016 were generally comparable to that observed with EU or US-approved Lantus. The maximum observed reductions in glucose were observed between 1 to 4 hours post-dose and the duration of hypoglycaemia was dose-related, persisting for up to 2, 8 and 12 to 18 hours post-dose at 0.3, 1.0 and 3.0/2.0 mg/kg, respectively. The applicant considered the glucodynamic profiles for LY2963016 and Lantus (US or EU-approved) to be similar. An increase in body weight/body weight gain and food consumption was also noted and is considered to be secondary to the observed hyperinsulinaemia and hypoglycaemia.

Effects on the central and peripheral nervous system have been reported for agents that induce hypoglycaemia, including insulin glargine [Yasaki and Dyck 1990]. During the repeated-dose studies conducted by the applicant, such effects were limited to the sciatic nerve. The CHMP notes that the incidence of degeneration of axons in the sciatic nerve at 2 mg/kg is higher in animals treated with LY2963016 (females) (when compared to EU-approved Lantus). However, in light of the absence of a similar trend for the study comparing LY2963016 to US-approved Lantus or a clinical correlate, no further action is required.

Increased deep dermal adipose tissue in skin/subcutis sections and at subcutaneous injection sites were observed at 1 mg/kg (LY2963016 and Lantus) which is indicative of lipohypertrophy (typical of insulins). In addition, decreased pancreatic islet cell cytoplasm and vacuolation was noted at ≥1.0 mg/kg/day; this finding is indicative of islet cell atrophy and is consistent with negative feedback in hyperinsulinaemic animals and a subsequent reduction in insulin production. The incidence of these findings appeared to be similar for LY2963016 *vs.* Lantus.

The CHMP also notes that the NOAEL for the 4-week study in the rat was 0.3 mg/kg for LY2963016 or EU/US-approved Lantus. Although the studies conducted by the innovator (as presented by the applicant) did not include a 1-month study, it is acknowledged that the NOAELs for 3 and 6-month studies were of a similar magnitude (0.146 mg/kg and 0.229 mg/kg, respectively).

Genotoxicity

In line with current guidelines on the development of similar biological medicinal products, no genotoxicity studies have been performed.

Carcinogenicity

In line with current guidelines on the development of similar biological medicinal products, no carcinogenicity studies have been performed.

In accordance with the Points to consider document on the non-clinical assessment of the carcinogenic potential of insulin analogues [CPMP/SWP/372/01], the applicant has provided some discussion of the carcinogenic potential of the proposed product and it is agreed that if LY2963016 is considered biosimilar to Lantus, then the carcinogenic risk should be similar to that of Lantus (and therefore acceptable). After review of the initial submission, the potential for LY2963016 (and how this compares to EU-approved Lantus) to cause IR-dependent mitogenesis was not entirely clear as all of the relevant pharmacology studies had not been conducted with material that was representative of the proposed commercial product. Subsequently, the applicant conducted a series of studies with commercial process material (reported within DBT 149), which demonstrated that the mitogenic potential of LY2963016 was similar to that of Lantus. However, further clarification was sought as to why IGF-1 was not included as a reference in the assay conducted in human osteosarcoma SAOS-2 cells where the mitogenic response was said to be IGF-1 dependent. Additional studies

were performed in order to address this and IGF-1 and other reference standards were included in order to characterise the assay, as per regulatory guidance.

In conclusion, taking all of the data submitted into consideration, it is agreed that the carcinogenic risk of the proposed product is similar to that of the currently marketed product, Lantus.

Reproduction Toxicity

In line with current guidelines on the development of similar biological medicinal products, no reproduction toxicity studies have been performed.

Local Tolerance

Local tolerability of LY2963016 was assessed in conjunction with clinical observations and histopathological evaluations of injection sites in the two 4-week repeat-dose toxicity studies. No clinical or histological signs of injection site reactions were noted at the injection sites with either LY2963016 or EU- or US-approved Lantus.

Increased fat was observed in the skin, subcutis and at the injection sites of rats injected with LY2963016 or Lantus. The incidence of this finding was comparable in LY2963016 and Lantus-treated groups.

Other toxicity studies

No other toxicity studies have been submitted.

2.3.4. Ecotoxicity / environmental risk assessment

According to Section 2 of the Guideline on the environmental risk assessment (ERA) of medicinal products for human use [EMEA/CHMP/SWP/4447/00], peptides and proteins are excluded from the need for an environmental risk assessment. An ERA is therefore not required.

2.3.5. Discussion on non-clinical aspects

The non-clinical (pharmacology) studies were conducted with material from a process similar to the process used for the commercial product. A major objection was raised, as the batches of LY2963016 tested were not truly representative of the final commercial product and biocomparability between material from the processes had not been adequately demonstrated. The applicant subsequently performed a series of *in vitro* studies in order to address this issue and the data were submitted in a separate report.

The pharmacology written summary and the text within the study reports suggest that the potency (in terms of the ability to stimulate autophosphorylation at the IR receptors, lipogenesis and mitogenesis) of the test articles was expressed as the EC_{50} relative to a maximum response as observed with an insulin reference standard. Although the data as presented did allow comparison of the respective groups, definitive conclusions as to how LY2963016 compares to Lantus could not be made upon review of the initial submission. The applicant subsequently provided some raw and/or untransformed data which allowed an easier comparison of how the data points were distributed within each individual group and how the data were distributed for the negative controls *vs.* the maximum observed response.

The data from the preliminary and definitive binding affinity and potency (autophosphorylation) studies suggested that when compared to human insulin, the affinity and/or potency for Lantus was 1.4 to 1.7-fold higher at the IR-A receptor and only 1.1 to 1.8-fold higher at the IR-B receptor. As the observed differences as presented in the dossier are slightly smaller than those observed by other investigators, this questioned

(i) the focus on the pivotal study, DBT 134 where the difference between the affinity and potency of human insulin vs. Lantus at the IR-A and IR-B receptor was less pronounced (1.1-1.6-fold) and therefore raised concerns about the ability of this assay to pick up subtle differences in affinity (i.e. are the differences as observed during the pivotal studies actually larger than they appear?)

(ii) the use of the minimum significant ratio, MSR, which ranged from 1.89 to 2.27 (2.61 for the metabolic potency assay) to define whether results were of biological significance. By the applicant's definition the observed difference in affinity and potency between human insulin and Lantus is not biologically relevant as it was less than the MSR; this is in contrast to the overall conclusions in the EPAR summary for Lantus.

In the responses provided, while the applicant maintained that the data generated during the conduct of studies, DBT 93, DBT 134 and those performed by Sommerfeld *and colleagues* are similar, it was still evident from the data presented, that the observed differences between Lantus and the positive control insulin were less pronounced during the pivotal study, DBT 134. However, the applicant conducted a more recent study with commercial process material and implemented a number of measures in order to reduce the extent of variability. Moreover, statistical comparisons were made between LY2963016 and EU-approved Lantus. The observed differences in affinity and potency observed during Study DBT 149 (for insulin vs. Lantus) were closer to those published by Sommerfeld *and colleagues*, despite the differences in the assay systems employed, which was somewhat encouraging. However, it was noted that the magnitude of the differences between the positive controls, insulin and AspB10, (the latter is known to have higher affinity at the IGF-1 and IR receptors) was consistently smaller in the more recent study, DBT 149, when compared to the original study DBT 134. The Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues [EMA/134217/2012] specifically states that it is important that assays used for comparability testing are demonstrated to have appropriate sensitivity to detect minute differences. Given that measures were put in place to improve the assay, the applicant was asked to discuss why the DBT 149 study did not demonstrate a larger difference in potency between the reference standards, insulin and AspB10 at the IR receptors (particularly the IR-A receptor, where the smallest difference was apparent). It is also noted that if the applicant's rationale is to be applied, the difference in potency at the IR-A receptor between insulin and AspB10 was not of biological significance, so yet again, the application of the MSR to decipher whether differences are of biological significance is questionable and even after receipt of the Day 120 responses, use of the MSR in this context was still not adequately justified.

The applicant subsequently clarified that the mean potency ratio for IR-A phosphorylation when comparing the potency of insulin to that of the positive control, AspB10 was lower than that previously reported in the literature and that this was most likely due to spurious results generated during a single run. The overall observed difference in IR-A phosphorylation for LY2963016 *vs* Lantus was simply due to a higher potency ratio again generated during a single run. Given the inherent variability, the Rapporteurs noted that an increased n number should have been considered at the time the studies were conducted. However, when all of the data generated during the 3 separate studies are reviewed as a whole, to produce a larger n number, it is acknowledged that the IR-A phosphorylation assay has the ability to detect differences and the Rapporteurs agreed that the observed difference between the proposed product and the reference product is not of biological significance.

Clarification was also sought with respect to the insulin reference standards used during the binding affinity assays as some discrepancies were noted within study report DBT 134; these were addressed upon submission of the Day 120 responses.

Close examination of the data generated during the preliminary lipogenic potency assay (DBT 93) revealed a considerable amount of variability and in contrast to conclusions drawn by the applicant, the rank order of metabolic potency for the test articles and the reference compounds (Insulin AspB10>human insulin=IGF-1>Lantus) was not in line with that observed for IR autophosphorylation (Insulin Asp B10>human insulin>Lantus>IGF-1), which questioned the ability of the assay to compare the potency of LY2963016 vs. Lantus with respect to their ability of stimulate IR-dependent lipogenesis and the applicant's interpretation of the data generated. The data generated during the more recent study (DBT 149) were less variable and no differences in lipogenic potency were apparent for LY2963016 vs. Lantus. However, it is noted that IGF-1 was not included as a reference.

In rat H4IIe hepatoma cells where the mitogenic response is IR-dependent (under serum-free conditions), results from the preliminary study showed that the rank order of potency for rat H4IIe hepatocyte proliferation was similar to that observed for IR autophosphorylation activity (insulin Asp-B10 > human insulin > LY2963016 or Lantus >>> IGF-1). However, the rank order of mitogenic potency as demonstrated during the definitive study was not in line with that observed for IR autophosphorylation, (the potency of insulin was ≥ Insulin AspB10 and the effects of IGF-1 were not evaluated). Once again, this suggests limitations of the assay used with respect to the mapping of potency at the IR receptor and a functional response (the mitogenic response was previously described by the applicant to be IR-dependent). In the more recent study (DBT 149), the applicant demonstrated that insulin AspB10 was more potent than insulin in both the IR-A phosphorylation and the mitogenic assay in rat hepatoma cells which is reassuring. However, concerns remained as to why the reference IGF-1 was omitted during Study 149 considering that current regulatory guidance recommends its inclusion; hence, the applicant was invited to address whether the assays (particularly the SAO2-cell assay where mitogenesis is said to be IGF-1 dependent) were sufficiently characterised. In response to the concerns raised by the CHMP, the applicant conducted a number of additional studies which included the comparison of the binding and activity of insulin, AspB10, IGF-1 and a range of other related compounds. Overall, the order of potency of the standards was similar to that published previously and it was acknowledged that the SAO2 cell assay along with the other *in vitro* assays used had been adequately characterised in line with regulatory guidance. However, the applicant should submit all of the new data generated as a formal report after marketing authorisation.

It is evident that throughout the initial dossier, small but significant differences in affinity and potency (autophosphorylation, lipogenesis, mitogenesis) were noted when comparing LY2963016 to Lantus or US-formulated LY2963016 to EU-formulated LY2963016 for example. However, the applicant suggested that these differences were not of biological significance. In adition, the applicant has stated that the affinity and potency of LY2963016 and Lantus are independent of the source of test article. Consequently, the results with US and EU-material (for both LY2963016 and Lantus) have been pooled for subsequent analyses. The use of the MSR to demonstrate whether differences are biologically significant was not accepted and it was the view of the CHMP that datasets (generated with US and EU product) displaying significant differences should not be pooled in order to facilitate further statistical evaluations. Moreover, it was requested that all comparisons should be made to the EU-approved Lantus (as opposed to EU and US-pooled data for Lantus). In the Day 120 responses, the applicant provided the statistical comparisons to the EU-approved reference product, as requested: In the study conducted previously, i.e. DBT 134; it is evident that significant differences were noted between US (contract manufacturer)-LY2963016 and EU-approved Lantus in the IR-A phosphorylation, IR-B phosphorylation and lipogenesis assays. It is agreed that the observed differences were largely due to the fact

that the US-LY2963016 samples were not evaluated in the same run as the Lantus, EU LY2963016 and the relevant positive control samples.

As described previously, an additional study (DBT 149) was conducted and the assays were improved to minimise the variability observed previously. In this study, a statistical difference was noted in a single assay only, whereby the potency of EU-LY2963016 to phosphorylate the IR-A receptor was higher than that of EU-approved Lantus. On the basis of the numerical/fold difference in potency (1.16-fold) and on the basis of the fact that no statistical differences were noted in any of the other assays, it is agreed that overall, the pharmacological profile of LY2963016 (US or EU) is similar to that of EU-approved Lantus.

Hence, the overarching Major Objection was resolved, as the data presented suggest that overall; the *in vitro* pharmacological profile of LY2963016 is similar to that of EU-approved Lantus. In addition, the concerns with respect to the ability of the IR-A phosphorylation assay and its ability to detect subtle differences along with the omission of IGF-1 as a reference have all been addressed.

The pharmacokinetic data submitted were quite limited and somewhat variable. Two studies were performed which involved a comparison of LY2963016 to either US-approved Lantus or EU-approved Lantus. The applicant was asked to present all parameters in the same manner to allow easier comparison of the datasets generated for both studies; to allow definitive conclusions with respect to similarity to be made. The standard errors and deviations were fairly large and it was evident that there were no apparent differences in the exposure to insulin glargine when comparing LY2963016 to Lantus. However, it is noted that the serum levels of insulin glargine were determined using a validated radioimmunoassay (RIA) method which did not appear to be highly specific for insulin glargine and cross reactivity with rat insulin was likely. C-peptide was not measured, which suggests that no correction of data has been made to exclude physiological insulin; hence, further clarification was sought, especially in light of the observed variability. The applicant maintained that measuring C-peptide levels was not required during the rat toxicology studies, as the contributions of endogenous insulin to the overall immunoreactive insulin glargine response are considered minimal. In light of the technical challenges of measuring C-peptide rat serum levels, the applicant has referred to clinical data which provides further support that endogenous insulin levels are not a significant confounding factor in the comparison of the pharmacokinetics of Lantus and LY2963016.

In the rat, following repeated dosing for up to 4 weeks, the applicant considered the glucodynamic profiles for LY2963016 and Lantus (US or EU-approved) to be similar. However, the CHMP noted that there was a trend for the rebound increase in glucose levels at the end of the study (on Day 30) to occur at higher doses of LY2963016 (2 mg/kg) when compared to EU-approved Lantus (≥1 mg/kg). In addition, close examination of the tabulated Summary for Study 8259267 suggested that at the maximum dose tested (2 mg/kg), the increase in body weight gain with EU-approved Lantus was more pronounced than that observed with LY2963016. Taken together with the *in vitro* data initially submitted, these data suggested that LY2963016 could be slightly less potent than EU-approved Lantus. However, the applicant has clarified that the magnitude of the increase in serum glucose and the incidence of pancreatic islet cell atrophy following repeated administration of LY2963016 are similar to that observed following treatment with EU-approved Lantus. In addition, the applicant has suggested that when the absolute weights are plotted over time, it is evident that there is good agreement in the growth curves for LY2963016 and EU-approved Lantus.

2.3.6. Conclusion on the non-clinical aspects

In response to the Day 120 List of Questions, the applicant has repeated the *in vitro* pharmacology studies with batches of LY2963016 that are considered to be representative of the commercial product. The methods used

have been improved, the data appear to be less variable than that observed for the previous studies and the batches of LY2963016 tested appear to have a similar *in vitro* pharmacological profile to that of EU-approved Lantus. However, there were still some concerns with respect to the ability of the IR-A phosphorylation assay to detect subtle differences, along with the omission of IGF-1 as a reference. The applicant has admitted that the inherent variability contributed to the lack of a substantial difference between reference compounds and it is evident that a larger number of experiments should have been performed in order to overcome this. The applicant has also performed a series of additional in vitro binding and functional studies to include IGF-1 and other related compounds as reference standards in order to characterise the methods further. Taken together, these measures help to demonstrate that the assays used have the inherent ability to detect subtle differences.

Following the evaluation of the latest submission of data, there were no non-clinical objections to the approval of Abasria; however, the CHMP recommended that the new data provided as responses during the procedure are submitted in a report within 6 months of marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme to show biosimilarity between LY2963016 and Lantus is based on five phase I and two phase III studies.

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

Study Alias	Objective	Study Population	Number of Subjects Randomised
Phase I Studies			
ABEA	Comparison of the PK and PD of LY2963016 and EU-approved Lantus	Healthy subjects	80
ABEE	Comparison of the PD of LY2963016 and EU-approved Lantus	Patients with T1DM	20
ABEI	Relative bioavailability of LY2963016 to EU-approved Lantus	Healthy subjects	16
ABEM	Relative bioavailability of LY2963016 to EU-approved Lantus	Healthy subjects	24
ABEN[a]	Comparison of the PK and PD of EU- and US-approved Lantus	Healthy subjects	40
Phase III Studies			
ABEB	Comparison of LY2963016 with Lantus (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with pre-meal insulin lispro	Patients with T1DM (open-label)	536

ABEC	Comparison of LY2963016 with Lantus (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759

[a] *Study ABEN was a comparison of EU- and US-approved Lantus; no LY2963016 was administered.*

The biosimilar clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) comparative studies versus the chosen reference medicinal product. For Abasria, PK and PD data have been generated in four trials submitted in this application. Two studies encompassed pivotal evidence and three trials were conducted to generate supplemental evidence. It should be noted that Study ABEN was carried out entirely for PK/PD comparability of US and EU approved Lantus reference product. Study ABEM was conducted following CHMP SAWP recommendation to determine dose-dependent pattern of comparability.

According to CHMP guidance PK/PD insulin clamp studies represent the mainstay of the proof of similar efficacy of the biosimilar and the reference insulin medicinal product. There is no anticipated need for specific efficacy studies since endpoints used in such studies, e.g. HBA1c, are not considered sufficiently sensitive for the purpose of showing biosimilarity. The applicant has carried out two efficacy trials provided within the current MAA. Apart from primary evaluation of the non-inferiority of LY2963016 once-daily (QD) to Lantus (QD), as measured by the change in HbA1c from baseline to 24 weeks, these studies included 7-point self-monitored blood glucose [SMBG] profiles and the data on intra-patient blood-glucose (BG) variability, basal and prandial (separately and as total daily) insulin dose, and weight. These comparability data constitute supportive evidence of clinical biosimilarity.

2.4.2. Pharmacokinetics

PK and PD data on LY2963016 have been generated in four trials submitted in this application (ABEA, ABEI, ABEM, and ABEE). In addition, a 5th study (ABEO) was conducted for the purpose of a US submission in comparison to the US-reference product. Finally, the 6th study (ABEN) was a comparison of the US and EU-reference product with no data on LY2963016.

Overview of PK/PD studies

Pivotal PK/PD studies						
Study	**Objectives**	**Treatment**	**Study design**	**Population**	**Number of subjects**	**Treatment duration**
I4L-MC-ABEA (ABEA)	Evaluate PK equivalence of LY2963016 and EU-approved Lantus	Single 0.5 U/kg doses of LY2963016 and EU-approved Lantus administered by SC injection	Single-center, randomized, double-blind, 2-treatment, 4-period, replicate crossover, 24-hour euglycaemic glucose clamp studies.	Healthy males or females, aged between 18 and 60 years, inclusive, with screening BMI between 18.5 and 32.0 kg/m2.	80 randomized 78 completed	Four 24-hour periods, with a 7-day washout between each period.
I4L-MC-ABEN (ABEN)	Evaluate PK equivalence between EU-approved Lantus and US-approved Lantus	Single 0.5 U/kg doses of EU-approved Lantus and US-approved Lantus administered by SC injection	Single-center, randomized, double-blind, 2-treatment, 4-period, replicate crossover, 24-hour euglycaemic glucose clamp studies.	Subjects aged between 21 and 65 years, inclusive, with BMI between 18.5 and 29.9 kg/m2, inclusive.	40 randomized 34 completed	Four 24-hour periods, with a 7-day washout between each period.

I4L-MC-ABEO (ABEO) (on-going to support US submis-sion)	Evaluate PK similarity of LY2963016 to US-approved Lantus in HS following single 0.5-U/kg dose, administered SC.	Single 0.5 U/kg doses of LY2963016 and US-approved Lantus administered by SC injection	Single-center, randomized, double-blind, 2-treatment, 4-period, replicate crossover, 24-hour euglycaemic glucose clamp studies.	Healthy males or females, aged between 21 and 65 years, inclusive, with screening BMI between 18.5 and 29.9 kg/m2, inclusive, and screening fasting glucose <6.0 mmol/L.	91 randomized 82 completed First patient visit: 20 Sep2012 Last Patient Visit: 16 Feb 2013	Four 24-hour periods, with a 7-day washout between each period.
Supportive PK/PD studies						
I4L-MC-ABEI (ABEI)	Evaluate relative bioavailability and PD response of LY2963016 compared to EU-approved Lantus	Single 0.5 U/kg doses of LY2963016 and EU-approved Lantus administered by SC injection	Single center, open-label, randomized, 2-treatment, 2-period, crossover, 24-hour euglycaemic glucose clamp studies.	Healthy men and women, with a body mass index (BMI) between 18.5 and 29.9 kg/m2 and an age range between 21 to 60 years.	16 randomized 13 completed	Two 24-hour treatment periods, with a 7-day washout between treatment periods.
I4L-MC-ABEM (ABEM)	Compare PK of LY2963016 and Lantus in HS following 0.3- and 0.6-U/kg single-dose SC administration.	Single 0.3 U/kg and 0.6 U/kg doses of LY2963016 and EU-approved Lantus administered by SC injection	Single-center, randomized, subject- and investigator-blind, 4-treatment, 4-period, crossover, 24-hour euglycaemic glucose clamp studies.	Healthy males or females, aged between 21 and 65 years, inclusive, with BMI between 18.5 and 29.9 kg/m2, inclusive.	24 randomized 23 completed	Four 24-hour periods, with a 6-day washout between each period.
I4L-MC-ABEE (ABEE)	Assess the duration of action of LY2963016 compared to Lantus in subjects with T1DM.	Single 0.3 U/kg doses of LY2963016 and EU-approved Lantus administered by SC injection	Single-center, randomized, subject- and investigator-blind, single-dose, 2-period, crossover, 42-hour postdose euglycaemic glucose clamp studies.	Males and females, aged between 18 and 60 years, inclusive, with T1DM for ≥1 year, HbA1c ≤10.0%, fasting C-peptide ≤0.3 nmol/L, and BMI ≤29 kg/m2.	20 randomized 20 completed	Two 2-day treatment periods, with a washout from 7 to 21 days between treatment periods.

Analytical methods

Analytical methods applied during the clinical development are summarised below.

1. Methods for measuring human immunoreactive insulin glargine

A radioimmunoassay (RIA) was used to measure the "free" immunoreactive insulin (i.e., insulin and insulin analogues not bound to endogenous anti-insulin antibodies) in human serum. It is not selective for insulin glargine as the immunoreactive insulin response is a summative response to insulin glargine, its metabolites M1 and M2, and endogenous insulin. The RIA assay has complete cross-reactivity to insulin glargine and endogenous insulin and is also expected to have complete reactivity to M1 and M2 given their molecular sequences. In a published study supported by Sanofi-Aventis a selective LC/MS/MS method provided the same results for M1 than the immunoreactive insulin measured with an unselective RIA assay since M1 appeared the predominant metabolite and insulin glargine and M2 concentrations were below the lower limit of quantitation (Lucidi, 2012). The LLOQ of the RIA assay is 50 pM and its percentage to the C_{max} is approximately 30%, higher than 5% as recommended in the Guideline on the Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009). However, the assay is sufficiently sensitive to fully characterize the flat profile of the active drug over the 24-hour PK sampling window.

The endogenous insulin concentration was separately estimated by measuring C-peptide using a commercial sandwich immunoassay approved by the FDA with additional validation by the central laboratory performing the analysis. The total measured insulin concentration was corrected with the endogenous insulin concentration using the method of Owens (1986). This is a well-established method that has been widely used ever since its

introduction and was also used for the estimation of endogenous insulin for all studies conducted by Sanofi-Aventis with the reference product in healthy subjects. More recent methods have been proposed but are not devoid of limitations. As there is no gold standard, this method was considered acceptable by the CHMP.

2. Method for measuring anti-insulin antibodies

The immunogenicity assay was developed as a conventional radioligand binding assay. After adding a radiolabeled tracer (LY2963016) to a serum sample, percent binding represents the percent of the total amount of tracer that co-precipitates with the antibodies. Similar to titres, it is a method of quantifying the amount of antibody in a sample; unlike titres, it is a continuous variable. Antibodies to native human insulin and insulin analogues will also cross-react with LY2963016. Hence, antibodies to LY2963016, insulin glargine, native insulin, and insulin analogues are measured using the same assay. The assay was adequately validated for antibodies against LY2963016 and antibodies cross-reactive to insulin. The sensitivity of the method was considered acceptable.

Methodology of PK/PD studies

The clinical pharmacological development programme was designed to follow the recommendations of the draft revised Guideline on Biosimilar Insulins (EMEA/CHMP/BMWP/32775/2005_Rev. 1). It should be demonstrated that the pharmacokinetic profiles are similar after single administration and that the differences between the PD parameters are below a tight limit. Regarding PD measurements, this guideline asserts that the euglycaemic clamp technique is the best available method for the measurement of insulin action. In these clamp experiments, the plasma insulin concentration is raised (e.g. by subcutaneous injection of insulin) and the blood-glucose level maintained ("clamped") at a pre-defined level by means of a variable infusion of glucose. Measurements of the plasma insulin concentration and glucose infusion rate (GIR) allow an estimation of the time-concentration and time-action profile. The primary variables are GIR_{AUC} and GIR_{max} which are denoted as G_{tot} and R_{max} in this submission.

All studies (except for ABEI) had a double-blind cross-over design. PK and PD profiling was carried out synchronously and was confined to 24-hour monitoring in studies ABEI, ABEN, ABEM and ABEA and up to 42-hour of euglycaemic clamp in Study ABEE. Hence the PK/PD evaluations covered a 24-42 hour period. Furthermore, to take into account the high variability of the parameters, replicate designs have been used in the main studies with four periods (2 on each product).

All studies except for ABEE were conducted in healthy volunteers without prior endogenous insulin suppression. The adjustment to background C-peptide levels was done in a consistent way across all studies using Owen's method. Studies in healthy volunteers provided a much more homogenous and sensitive PK comparability model, as prior insulin treatment with lispro was shown to interfere with the performance of immunoreactive detection of insulin glargine concentrations in Study ABEE (patients with T1DM). The determination of PK equivalence was based on comparing C-peptide corrected insulin concentration-time data: AUC from zero to 24 hours ($AUC_{[0-24]}$), the maximum serum study drug concentration (C_{max}), and AUC from time zero to infinity ($AUC_{[0-\infty)}$). The primary use of AUC is accepted as with relatively flat time-concentration profile, the use of C_{max} for demonstrating PK equivalence of long-acting insulin products has lower sensitivity in detecting subtle differences.

The CHMP had some concerns because the applicant initially planned to carry out studies only in healthy volunteers while endogenous insulin levels can have a significant confounding effect. The CHMP suggested two additional studies to address this concern:

- a clamp study with two different doses "to increase the sensitivity of the study and help judge the magnitude of the observed differences, as similar dose-response would add strength to the evidence of biosimilarity". Study ABEM was therefore carried out with the applicant opting to compare the PK/PD response at two additional dose levels. This study was powered on the basis of estimates precision and not for any formal statistical comparison.
- a study showing similar duration of action in diabetic patients. Study ABEE was therefore conducted in patients with T1DM but without formal statistical criteria.

All formal statistical evaluation for PK comparability was carried out using pre-specified statistical plans and conventional objectives to declare PK equivalence only if 90% CI for AUC and other appropriate parameters were completely contained within the interval of 0.8-1.25.

In addition to PK sampling, glucodynamic evaluations using the euglycaemic clamp method were carried out. The subjects underwent preparation for the euglycaemic clamp procedure commencing up to 2 hours prior to dosing and continued the clamp for up to 24 hours post-dose. The glucose infusion rates (GIRs) required for maintaining euglycaemia and blood glucose concentrations as a measure of PD effect were documented throughout the procedure. The methodology for automated or manual glucodynamic parameter recording and statistical analysis applied to all submitted studies was satisfactory from planning and blinding perspectives. The analyses were performed using a locally weighted scatterplot smoothing (LOESS) function applied to all individual GIR versus time profiles in each treatment group. The fitted data for each subject were used to calculate the primary PD parameters: maximum glucose infusion rate (R_{max}) and total amount of glucose infused (G_{tot}) over the duration of the clamp procedure. For long-acting insulins, clamp duration of at least 24 hours is expected but it is agreed that the primary endpoint should be the GIR-AUC over the dosing interval, i.e. 24 hours in this case. Therefore, the duration of the clamp studies in healthy volunteers was considered acceptable by the CHMP.

The primary PD parameters (R_{max} and G_{tot}) were log-transformed prior to analysis. For each PD parameter, the difference in least-square means along with the 90% CI was back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to Lantus. PD comparability was concluded if the 90% CI was completely contained within the interval of 0.80 to 1.25. This margin was first chosen for feasibility reasons as the choice of a tighter equivalence margin would have resulted in too large sample size, which would not be feasible in a single centre; indeed, clamp methodology is specific to clinical sites. Furthermore, due to the considerable variation in insulin needs and individual dose adjustment, a tighter equivalence margin is not required from a clinical perspective. CHMP guidance requires 95% CIs for PD parameters and statistical analyses that exclude the subjects who do not provide evaluable data for both the test and reference products. This analysis was initially presented only for the pivotal PK/PD trial, but subsequently for supportive studies as well.

Results of PK/PD data

The results are presented in Tables 5 & 6

Table 5: Summary of the primary PK & PD results from pivotal PK/PD studies

Studies and dose	Ratio of LS Geometric Means (90% Confidence Interval for PK; 95% Confidence Interval for PD)

		PK Parameters			PD Parameters	
Study	**Dose U/kg**	**$AUC_{(0-24)}$ (pmol·hr/L)**	**$AUC_{(0-inf)}$ (pmol·hr/L)**	**C_{max} (pmol/L)**	**G_{tot} (mg/kg)**	**R_{max} (mg/kg/min)**
Results for Completers						
ABEA	0.5	0.91 (0.87, 0.96)	0.94 (0.88, 1.00)	0.95 (0.91, 1.00)	0.95 (0.90, 1.01)	0.99 (0.93, 1.05)
ABEN	0.5	0.97 (0.89, 1.04)	0.96 (0.87, 1.05)	0.97 (0.90, 1.04)	1.02 (0.88, 1.19)	0.98 (0.87, 1.11)
Results for All Subjects						
ABEA	0.5	0.91 (0.87, 0.96)	0.96 (0.90, 1.02)	0.95 (0.90, 1.00)	0.95 (0.90, 1.01)	0.99 (0.93, 1.05)
ABEN	0.5	0.98 (0.91, 1.05)	0.98 (0.89, 1.07)	0.99 (0.92, 1.06)	1.00 (0.87, 1.15)	0.97 (0.86, 1.09)

Table 6: Summary of the PK & PD results of the supportive PK/PD studies

Study ABEI

Parameters (units)	Treatment (0.5 U/kg)	All Subjects[a]			Completers[b]			
		n	LS Geometric Mean	Ratio of LS Geometric Means[a] (90% CI)	n	LS Geometric Mean	Ratio of LS Geometric Means[a] (90% CI)	95% CI
$AUC_{(0-24)}$ (pmol·hr/L)	LY2963016	16	1934.2	0.94 (0.83, 1.06)	13	1969.63	0.95 (0.84, 1.07)	—
	EU-LANTUS®	13	2061.8		13	2075.83		
C_{max} (pmol/L)	LY2963016	16	112.8	0.93 (0.83, 1.04)	13	115.33	0.94 (0.83, 1.06)	—
	EU-LANTUS®	13	121.5		13	123.06		
G_{tot} (mg/kg)	LY2963016	16	2227.37	0.95 (0.74, 1.21)	13	2256.64	0.95 (0.73, 1.24)	(0.69, 1.32)
	EU-LANTUS®	13	2355.25		13	2366.13		
R_{max} (mg/kg/min)	LY2963016	16	2.62	0.94 (0.73, 1.20)	13	2.63	0.94 (0.72, 1.22)	(0.68, 1.30)
	EU-LANTUS®	13	2.79		13	2.80		

Study ABEM

Parameters (units)	Treatment	All Subjects[a]			Completers[b]			
		n	LS Geometric Mean	Ratio of LS Geometric Means[a] (90% CI)	n	LS Geometric Mean	Ratio of LS Geometric Means[a] (90% CI)	95% CI
0.3 U/kg								
$AUC_{(0-24)}$ (pmol·hr/L)	LY2963016	23	1727	1.03 (0.91, 1,16)	23	1738	1.03 (0.92, 1.15)	—
	EU-LANTUS®	23	1684		23	1690		
C_{max} (pmol/L)	LY2963016	23	108	1.03 (0.92, 1.15)	23	108	1.03 (0.89, 1.19)	—
	EU-LANTUS®	23	105		23	105		
G_{tot} (mg/kg)	LY2963016	23	1028	0.98 (0.78, 1.24)	23	1084	1.01 (0.80, 1.28)	(0.76, 1.34)
	EU-LANTUS®	23	1046		23	1074		
R_{max} (mg/kg/min)	LY2963016	23	1.78	1.04 (0.87, 1.25)	23	1.83	1.05 (0.88, 1.27)	(0.84, 1.32)
	EU-LANTUS®	23	1.71		23	1.74		
0.6 U/kg								
$AUC_{(0-24)}$ (pmol·hr/L)	LY2963016	24	3160	1.07 (0.95, 1.21)	23	3181	1.07 (0.90, 1.27)	—
	EU-LANTUS®	24	2944		23	2978		
C_{max} (pmol/L)	LY2963016	24	180	1.03 (0.92, 1.16)	23	181	1.03 (0.89, 1.20)	—
	EU-LANTUS®	24	174		23	176		
G_{tot} (mg/kg)	LY2963016	24	2255	0.87 (0.70, 1.09)	23	2306	0.84 (0.65, 1.08)	(0.61, 1.14)
	EU-LANTUS®	24	2589		23	2761		
R_{max} (mg/kg/min)	LY2963016	24	3.05	0.94 (0.79 1.12)	23	3.10	0.92 (0.75, 1.12)	(0.72, 1.17)
	EU-LANTUS®	24	3.25		23	3.38		

Abbreviations: AUC(0-24) = area under the serum concentration versus time curve from zero to 24 hours; AUC(0-inf) = area under the serum concentration versus time curve from time zero to infinity; Cmax = maximum serum concentration; Gtot = total amount of glucose infused during the clamp procedure; LS = least-squares; Rmax = maximum glucose infusion rate during the clamp procedure.
[a] Ratio is Test/Reference where Test = LY2963016 and Reference = EU-approved Lantus
[b] subjects who completed all periods of the study and had evaluable data in those periods

Study **ABEI** was the first study, which demonstrated a similar relative bioavailability and a comparable PD profile for LY2963016 and Lantus at the dose of 0.5 U/kg. The relative bioavailability analysis, based on statistical comparisons of AUCs and C_{max} established that both PK parameters using correction for baseline C-peptide levels were similar but the values derived for LY2963016 were slightly lower than those with Lantus. The 90%CI $AUC_{0-\infty}$ ratio was slightly outside the targeted 0.8-1.25 limits (0.77-1.07) but this is not surprising given the small sample size of this pilot study and the variability of the half-life determination for a long-acting analogue. Likewise, the statistical comparisons of G_{tot} and R_{max} showed 95%CI outside the pre-defined 0.80-1.25 limits with the ratios of least-square geometric means of 0.95 (0.69-1.32) and 0.94 (90% CI: 0.68-1.30), respectively.

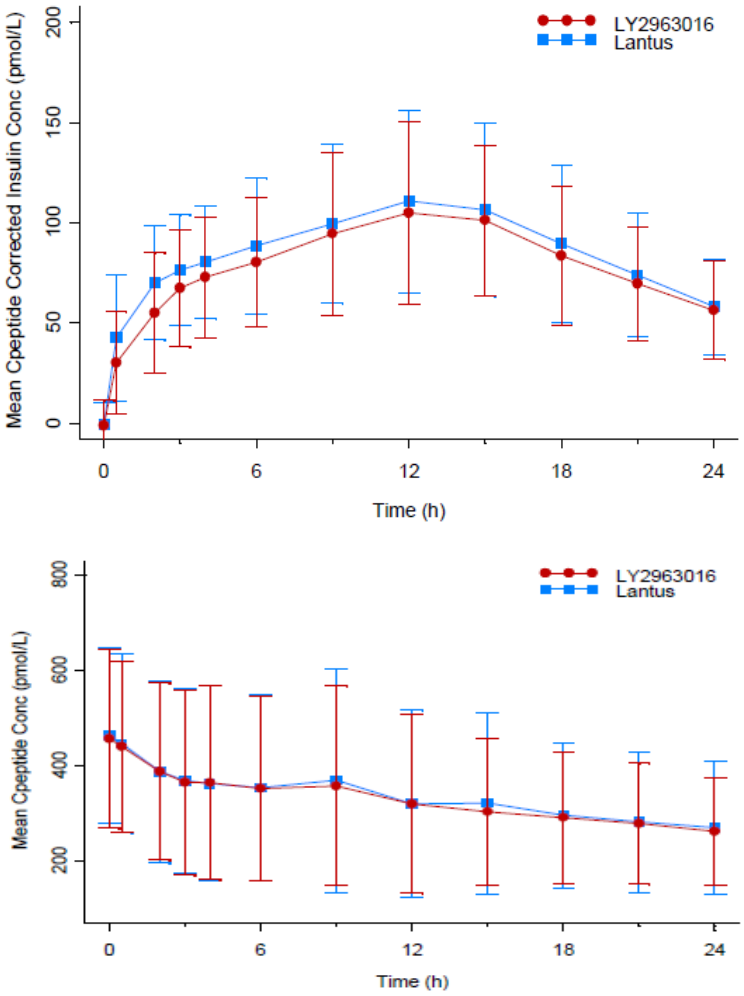
Study **ABEN** was conducted in order to fulfil the purpose of achieving biosimilarity claims for LY2963016 in both the EU and US regions and comparing the EU and US reference Lantus materials. The study showed unequivocally that AUCs and C_{max} were similar between EU and US-approved Lantus products, with ratios of LS geometric means between 0.96 to 0.99 for all PK parameters (in all subjects and in completers defined as those who completed all treatment periods) and 90%CIs for these parameters fully contained within the pre-specified interval 0.80 to 1.25. Furthermore, EU- and US-approved Lantus reference products were shown to be PD equivalent in terms of total amount of glucose infused and maximum glucose infusion rate during the 24 hour clamp procedure. Hence, the EU and US Lantus reference products were shown to be comparable from the PK and PD perspective, thus supporting the use of both products in the efficacy/safety studies.

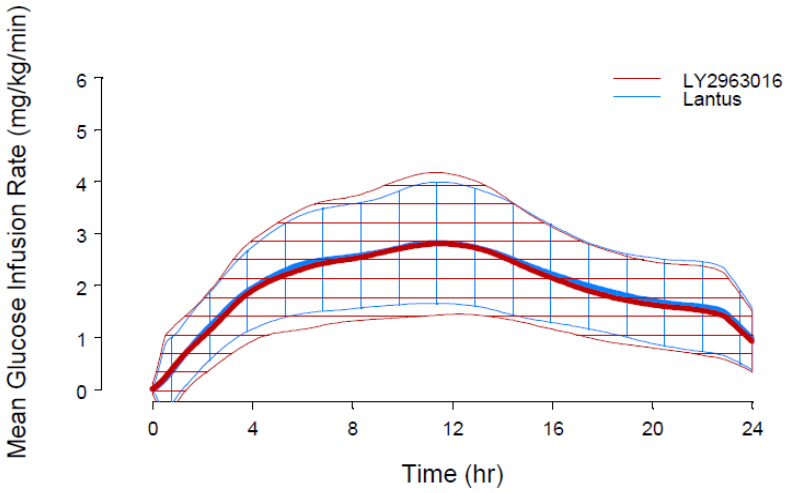
Study **ABEA** was the pivotal trial conducted to demonstrate PK equivalence between 0.5 U/kg SC doses of LY2963016 and Lantus. Based on statistical comparisons of AUCs and C_{max}, the PK profiles were shown to be

similar with ratios of LS geometric means of 0.91 and 0.95 for the primary parameters $AUC_{(0-24)}$ and C_{max}, and 90% CIs completely contained within the pre-specified interval 0.80 to 1.25.

Importantly, PK similarity between LY2963016 and Lantus was apparent when either the concentration-time data for immunoreactive insulin or C-peptide corrected insulin using Owens method were used for the analysis. Additionally, the C-peptide concentration-time profiles were superimposable between LY2963016 and Lantus with comparable standard deviations (Figure 5), showing a similar level of suppression of endogenous insulin following LY2963016 or Lantus administration and reducing potential errors introduced by any C-peptide correction method.

Figure 5: PK & PD profiles in pivotal study ABEA (healthy volunteers; 0.5 U/kg)





Euglycaemic comparisons of G_{tot} and R_{max} demonstrated similarity in the 24-hour PD profile between LY2963016 and Lantus with ratios of LS geometric means (0.95 and 0.99, respectively) and 95% CIs (ranging between 0.90 and 1.05) well contained within 0.80-1.25. Partial GIR-AUCs are meaningful additional PD parameters, which were presented following CHMP request; these further confirmed the PD equivalence of both products (data not shown).

In study **ABEM**, the PK parameters essentially overlapped between LY2963016 and Lantus. Similar PK profiles were observed at both 0.3 U/kg and 0.6 U/kg doses. The ratios of geometric LS means for the primary PK parameters, $AUC_{(0-24)}$ and C_{max}, were 1.03 for both parameters following a 0.3 U/kg dose, and 1.07 and 1.03, respectively, following a 0.6 U/kg dose. All the corresponding 90% CIs limits, which ranged between 0.91 and 1.21, were contained within the interval of 0.80-1.25 when all subjects were considered; however, in the analysis of completers, the upper limit of the equivalence interval for the AUC ratio was marginally above it (1.27), a result which is compatible with a large confidence interval around a point estimate of 1.07 due to small sample size.

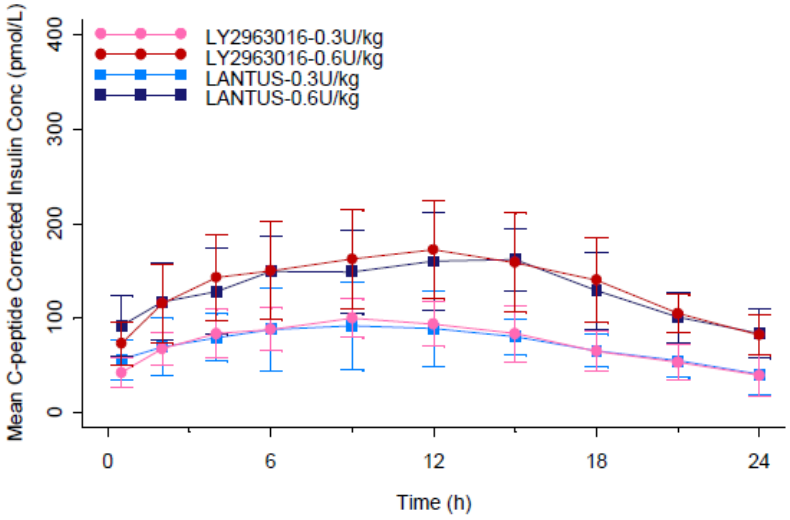
The ratios of the geometric means for the primary PD parameters (G_{tot} and R_{max}) following administration of LY2963016 versus Lantus were 1.01 and 1.05, respectively, after a 0.3 U/kg dose, and 0.84 and 0.92, respectively, after a 0.6 U/kg dose. The 95% CIs limits ranged between 0.76 and 1.34 for the low dose and 0.61 to 1.17 for the high dose. While it is acknowledged that the study was not powered to show PK and PD equivalence, the results at the low dose (0.3 U/kg) with point estimates close to 1.0 appeared compatible with similarity of the test and reference products. In contrast, the results at the high dose (0.6 U/kg) in the same subjects suggested a lower effect of LY2963016 compared to Lantus; the comparison of partial GIR-AUCs showed that the difference was essentially apparent during the early absorption phase (first 6 hours) with a ratio of 0.66 (95%CI 0.44, 1.08) as shown in Table 7.

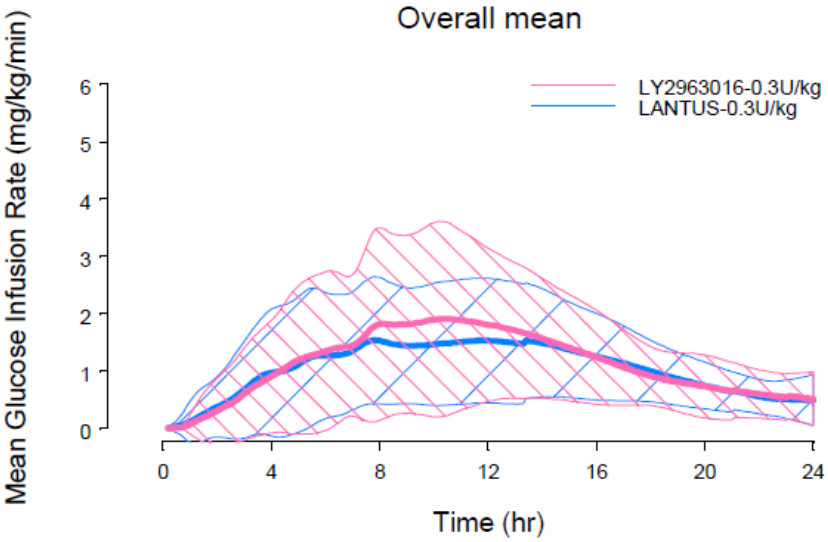
After further investigation following CHMP request, the applicant showed that this difference was mainly driven by a single subject with an aberrant GIR profile, for which no plausible physiological explanation could be found (clamp data at the 0.3 U/kg dose within expected range and PK profile reflecting insulin absorption). A post-hoc analysis excluding this single outlier provided ratios of the GIR-AUC geometric means close to 1, except in the first 6 hours, but a ratio of 0.77 in the beginning of the clamp experiment was considered by the CHMP to be within acceptable limits given the small size of the trial (Table 7).

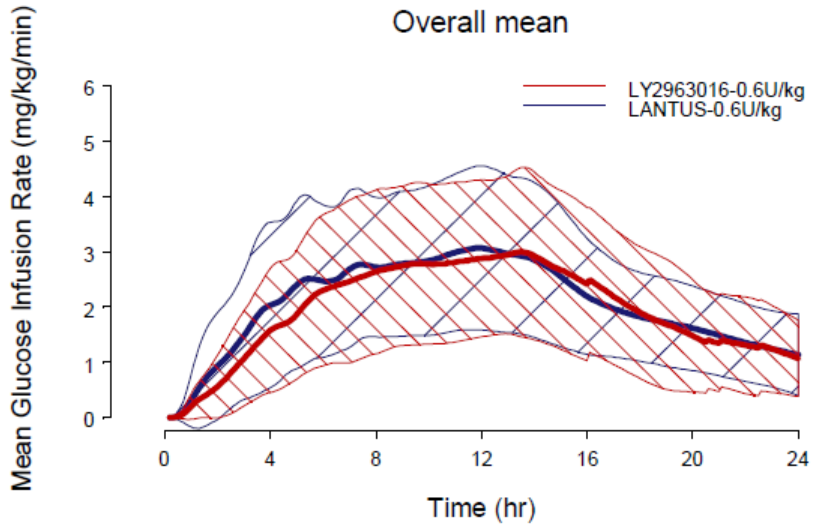
Table 7: Partial G_{tot} analyses of Study ABEM (healthy volunteers; 0.3 & 0.6 U/kg)

		Analysis *With* Outlier Data			Analysis *Excluding* Outlier Data		
Dose Level	**Treatment**	**N**	**LS Geometric Mean**	**Ratio of LS Geometric Mean (95% CI)**	**N**	**LS Geometric Mean**	**Ratio of LS Geometric Mean (95% CI)**
$Gtot_{(0-6)}$							
0.3 U/kg	LY2963016	18	172	0.97 (0.59, 1.60)	17	189	0.98 (0.61, 1.56)
	LANTUS®	18	177		17	194	
0.6 U/kg	LY2963016	18	377	**0.66** (0.44, 1.08)	17	426	**0.77** (0.48, 1.23)
	LANTUS®	18	573		17	553	
$Gtot_{(0-12)}$							
0.3 U/kg	LY2963016	21	625	1.16 (0.74, 1.82)	20	672	1.18 (0.78, 1.79)
	LANTUS®	21	537		20	571	
0.6 U/kg	LY2963016	21	1231	**0.82** (0.52, 1.28)	20	1447	**0.96** (0.64, 1.46)
	LANTUS®	21	1505		20	1501	
$Gtot_{(0-18)}$							
0.3 U/kg	LY2963016	22	744	0.98 (0.57, 1.70)	21	795	1.01 (0.59, 1.76)
	LANTUS®	22	757		21	784	
0.6 U/kg	LY2963016	22	1984	**0.85** (0.49, 1.47)	21	2257	**0.97** (0.56, 1.67)
	LANTUS®	22	2326		21	2337	
$Gtot_{(0-24)}$							
0.3 U/kg	LY2963016	23	1084	1.01 (0.76, 1.34)	22	1145	1.03 (0.78, 1.35)
	LANTUS®	23	1074		22	1113	
0.6 U/kg	LY2963016	23	2306	**0.84** (0.61, 1.14)	22	2543	**0.92** (0.70, 1.21)
	LANTUS®	23	2761		22	2756	

Figure 6: PK & PD profiles in study ABEM (healthy volunteers; 0.3 & 0.6 U/kg)





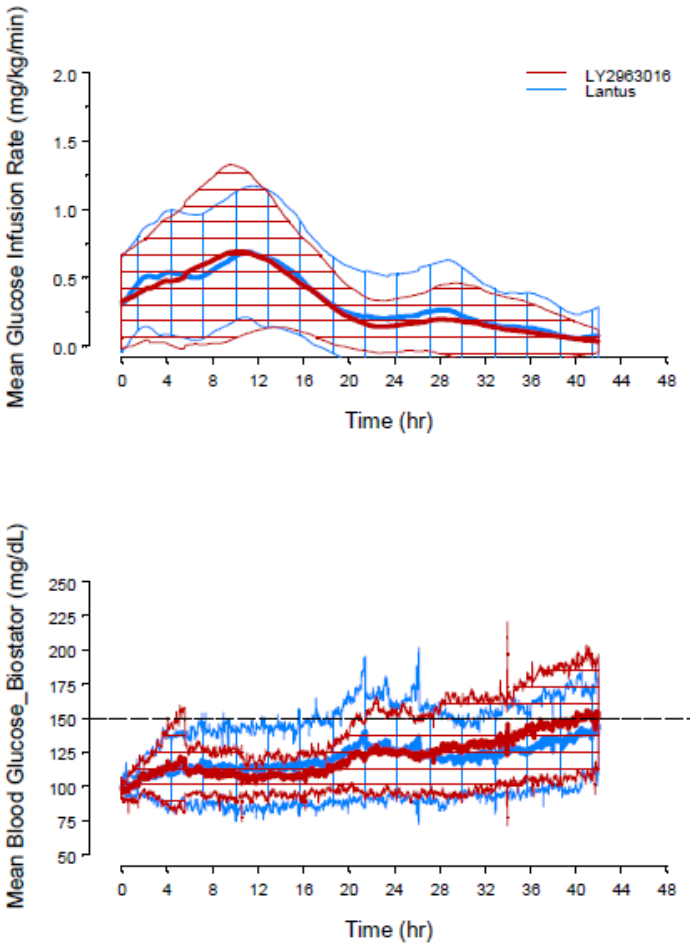


Study **ABEE** was carried out in stable T1DM patients who were receiving baseline insulin treatment. The study yielded limited PK data and its interpretation was hampered by cross-reactivity with the carried over background insulin (especially in the initial portion of the time-concentration curve). The profiles of the concentration curves appeared to be similar but no formal PK equivalence was declared as the study was primarily PD in nature and its primary objective was to compare the duration of action of LY2963016 and Lantus. Individual patient PK profiles appeared similar but not fully overlapping and accompanied with a high degree of variability. PD comparability was carried out via the assessment of several parameters describing the duration of action. A substantial number (35%) of clamps were terminated at 42 hours, before the end of action was reached. Nevertheless, the median duration of action was estimated to be 37.1 and 40.0 hours for LY2963016 and Lantus, respectively. A survival type of analysis was carried out and, using a Cox proportional hazard model, the hazard ratio (LY2963016/Lantus) was 1.063 with a p-value = 0.8777, supporting the conclusion that there does not appear to be a significant difference in the duration of action between LY2963016 and Lantus.

Statistical analyses of G_{tot} and R_{max} generated ratios of LS geometric means (90% CI) of 0.77 (0.46, 1.30) and 0.91 (0.52, 1.61), respectively. Although no justification for the width of an acceptable margin was provided, the 90% CIs overlapped and appeared to support similarity. Other PD parameters characterizing the time profile for

GIR (such as late $TR_{max50\%}$, late $TR_{max75\%}$, and T_{last}) appeared comparable between LY2963016 and Lantus although T_{onset} (observed time of the first positive GIR post-dose) appeared slightly longer for LY2963016 compared to Lantus; however, this measure is not accurate as it may be influenced by the effect of the insulin lispro infusion during the pre-clamp and early clamp periods.

Figure 7: PD profile in study ABEE (T1DM patients; 0.3 U/kg)



Absorption

Abasria is only administered subcutaneously. Its prolonged duration of action is dependent on its injection into subcutaneous tissue, which results in a slow and prolonged absorption, similar to the reference product Lantus.

Distribution

As a result of slow absorption, the distribution phase of insulin glargine is long-lasting. No estimate of the volume of distribution is available.

Elimination

After subcutaneous injection of Abasria, insulin glargine is rapidly metabolized at the carboxyl terminus of the beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1.

The median half-life of immunoreactive insulin associated with the terminal rate constant in non-compartmental analysis was estimated to be approximately 10 hours.

Dose proportionality and time dependencies

Pharmacokinetics appeared approximately dose-proportional over the dose range tested (0.3 to 0.6 U/kg).

Pharmacokinetic interaction studies

No PK interaction studies were performed as these are not required for a similar biological medicinal product.

2.4.3. Pharmacodynamics

Mechanism of action

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the Abasria injection solution. After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

In vitro studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin.

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Primary and Secondary pharmacology

The similarity of the pharmacodynamic actions was investigated using the euglycaemic clamp technique. In this assessment report the PD results were summarized and assessed together with PK data.

2.4.4. Discussion on clinical pharmacology

The assay format (RIA) employed by the applicant for the measurement of insulin glargine concentration is considered acceptable; it has recently been published by the manufacturer of Lantus that the response to M1 (the predominant metabolite) in a selective LC/MS/MS assay measuring separately insulin glargine, M1, and M2 was similar to that of the combined immunoreactive insulin response of the RIA assay. Furthermore, the assay is considered sufficiently sensitive to measure insulin concentrations over 24 hours given the flat PK profile of insulin glargine.

The design of five completed PK/PD studies ABEI, ABEN, ABEM, ABEA and ABEE appears to be satisfactory and overall complies with CHMP biosimilar insulin guideline and recommendations given in the CHMP Scientific

Advice. Although an evaluation over 24 hours does not cover the full PK/PD profile of long-acting insulins, and thus, clamp duration of at least 24 hours is expected, the primary endpoints should be the insulin AUC and GIR-AUC over the dosing interval, i.e. 24 hours in this case. Therefore, the duration of the clamp studies in healthy volunteers is considered acceptable; moreover, the supportive study in patients with T1DM was extended well beyond (up to 42 hours).

PK and PD comparability is the cornerstone on which the biosimilarity is established for new biosimilar insulin products and glucodynamic studies using euglycaemic clamp evaluations represent a key tool in achieving this objective. PK equivalence of LY2963016 and Lantus has been convincingly demonstrated across all studies and all doses using methodology in line with CHMP guidance, including analyses with outliers.

As for the PD assessment, the pivotal trial demonstrated that LY2963016 has similar effects to Lantus at 0.5 U/kg based on primary and secondary parameters. Importantly, the actual 95%CIs for the primary parameters (G_{tot} and R_{max}) ratios were contained within a much tighter interval (1.0 ± 0.1) than predefined. The comparison of the duration of action in patients with T1DM showed high variability but provided supportive evidence of similarity. The results from the supportive study requested by the CHMP to investigate two further doses (0.3 U/kg and 0.6 U/kg) appeared also compatible with a similar PD response, acknowledging that this trial was not powered to formally demonstrate PD equivalence.

In additional analyses provided by the applicant following CHMP request, both PK and PD appeared approximately dose-proportional. From these analyses combined with data from the literature, it is likely that the 0.5 U/kg dose level is in the linear portion of the dose-response curve. Based on the comparison of the slopes of the dose-response relationship for PK or PD parameters, G_{tot} seemed to be the most sensitive parameter to detect differences between the two products.

2.4.5. Conclusions on clinical pharmacology

PK and PD equivalence of LY2963016 and Lantus has been established based on an extensive comparability exercise performed in five studies, which tested several dose levels and were conducted in healthy volunteers as well as patients with type 1 diabetes.

2.5. Clinical efficacy

Two Phase III clinical studies have been conducted with a similar design, randomised, parallel-group, active-comparator, multicentre, multinational studies. Study ABEB is a 52 week study (24-week treatment period and 28-week extension period) in patients with T1DM and study ABEC is a 24-week study in T2DM. In each respective study, the primary outcome was assessed at the end of the 24-week treatment period. Both studies used treat-to-target approaches to achieve the protocol-specified glycaemic goals (for example, HbA1c <7.0%, fasting plasma glucose (FPG) ≤6.0 mmol/L, other pre-prandial capillary BG 3.9 to 7.2 mmol/L without incurring hypoglycaemia in Study ABEB; FPG <5.6 mmol/L, HbA1c <7.0% without incurring hypoglycaemia in Study ABEC).

The details of both studies are summarized below.

Summary of phase III comparative studies with LY2963016

Study	Objectives	Study design	Dose regimen	Population	Number of subjects	Treatment duration
I4L-MC-ABEB (ABEB)	- LY2963016 QD is noninferior to Lantus QD, as measured by change in HbA1c from baseline to 24 weeks, when used subcutaneously in combination with premeal insulin lispro TID. - Immunogenicity and safety	Phase 3, prospective, randomized, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study with a 28-week active control, open label extension period and 4-week posttreatment follow-up in patients with T1DM.	Test: LY2963016 QD, administered SC. LY2963016 was started at the same dose and administered at same timing (ie, daytime or night-time) as the patient's prestudy QD basal insulin. Control: Lantus QD, administered SC. Lantus was started at the same dose and administered at same timing (ie, daytime or nighttime) as the patient's prestudy QD basal insulin.	Males and females with T1DM ≥1 year, aged ≥18, BMI ≤35 kg/m2, HbA1c ≤11%, on basal-bolus insulin therapy for >1 year. Basal insulin must be QD injection of NPH, Lantus, or detemir ≥3 months prior to study entry and combined with mealtime injections of human regular insulin, insulin analog lispro, aspart, or glulisine.	536 randomized 509 completed 24-week treatment period 490 completed treatment in 28-week extension period	24-week treatment, with a 28-week extension period
I4L-MC-ABEC (ABEC)	- LY2963016 QD is noninferior to Lantus QD, as measured by change in HbA1c from baseline to 24 weeks, when used in combination with OAMs. - Immunogenicity and safety	Phase 3, prospective, randomized, multicenter, 2-arm, active-control, double-blind, parallel, 24-week treatment, and 4-week posttreatment follow-up study in adult patients with T2DM.	Test: LY2963016 QD; Patients on prestudy Lantus: Starting LY2963016, at same dose as prestudy Lantus, administered SC. Insulin-naïve patients: Starting LY2963016 QD 10-U dose, administered SC. Control: Lantus QD; Patients on prestudy Lantus: Starting Lantus QD, at same dose as prestudy Lantus, administered SC. Insulin-naïve patients: Starting Lantus QD 10-U dose, administered SC.	Patients with T2DM, aged ≥18, with BMI ≤45 kg/m2, and on 2 or more OAMs (with or without Lantus) for ≥12 weeks prior to study entry. Insulin-naïve patients: HbA1c between ≥7.0% and ≤11.0%. Prestudy Lantus patients: HbA1c ≤11.0%.	759 randomized 662 completed	24-week treatment

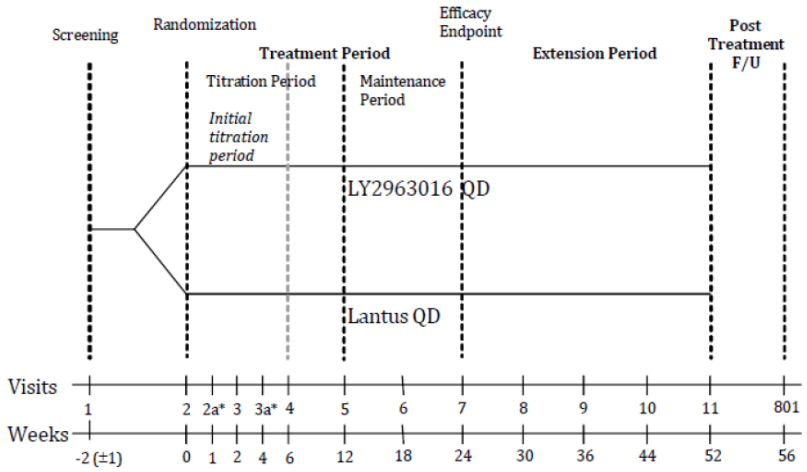
2.5.1. Main studies

Methods

ABEB

ABEB was a randomized, multinational, multicentre, 2-arm, active-controlled, open-label 52-week treatment study in patients with type 1 diabetes mellitus (T1DM) and 4-week post-treatment follow-up. The objective of the study was a comparison of LY2963016 to Lantus in combination with mealtime insulin lispro in adult patients with T1DM: the ELEMENT 1 Study. This study was conducted at 59 study centres in 9 countries.

Figure 8: Illustration of design for study ABEB

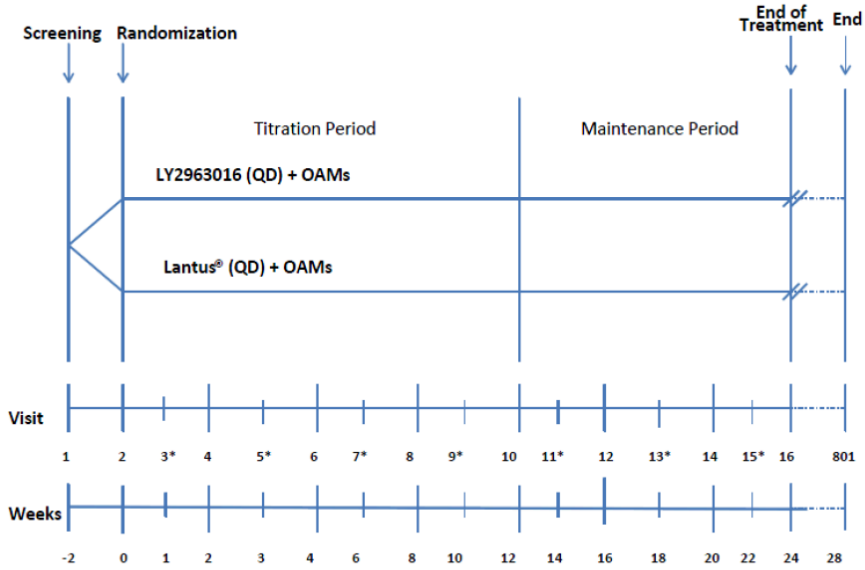


QD = once-daily administration; * = telephone visits; F/U = follow up.

ABEC

Study ABEC was a randomized, multinational, multicentre, 2-arm, active-controlled, double-blind, parallel, 24-week study with a 4-week post-treatment follow-up in patients with type 2 diabetes mellitus (T2DM). The objective of the study was a comparison of LY2963016 to Lantus in combination with oral anti-hyperglycaemic medications (OAMs): the ELEMENT 2 Study. The study was conducted at 88 centres in 13 countries.

Figure 9: Illustration of design for study ABEC



QD = Once daily; OAM = Oral antihyperglycemic medication; * = Telephone visit

Study Participants

ABEB

Eligible patients had T1DM for at least 1 year based on the disease diagnostic criteria described by the WHO and were at least 18 years of age with a body mass index (BMI) of ≤35 kg/m2. Patients had an HbA1c ≤11.0% and had been treated with basal-bolus insulin for at least 1 year. Basal insulin had to be once daily injection of human insulin isophane suspension (NPH), LANTUS, or detemir for at least 3 months prior to Visit 1 and combined with mealtime injections of human regular insulin, or insulin analog lispro, aspart, or glulisine.

ABEC

Eligible patients had T2DM based on the disease diagnostic criteria described by the WHO and were at least 18 years of age with a body mass index of ≤45 kg/m2. Patients had been treated with 2 or more OAMs at stable doses for 12 weeks prior to Visit 1, with or without Lantus, and had an HbA1c ≥7.0% and ≤11.0% if insulin naïve, or an HbA1c ≤11.0% if previously on Lantus.

Treatments

ABEB

Clinical lots produced in cartridges of LY2963016 were employed in study ABEB. Insulin glargine once-daily was started at the same dose and administered at same timing (i.e., daytime or night-time) as the patient's pre-study once daily basal insulin. Insulin lispro was administered with meals at the same dose as the patient's pre-study insulin dose while avoiding hypoglycaemia. The basal and bolus insulin doses were adjusted during the study to achieve glycaemic targets (HbA1c <7%, FPG ≤108 mg/dL [6.0 mmol/L], other preprandial capillary blood glucose 70 to 130 mg/dL), without incurring hypoglycaemia. The mode of administration was subcutaneous. The treatment duration was 52 weeks.

ABEC

Clinical lots produced in vials of LY2963016 were employed in study ABEC. Patients previously on Lantus started LY2963016 QD at an equivalent dose as pre-study Lantus. Insulin naïve patients had a starting dose of 10 U LY2963016 QD. All patients then followed a patient-driven dosing algorithm while being supervised by investigators through the course of the study to maintain the fasting blood glucose (FBG) ⩽100 mg/dL (5.6 mmol/L) while avoiding hypoglycaemia.

Objectives

ABEB

The primary objective of this study was to test the hypothesis that LY2963016 once-daily was non-inferior to LANTUS (once-daily), as measured by change in HbA1c from baseline to 24 weeks, when used in combination with pre-meal insulin lispro administered thrice daily (TID).

The main secondary objectives of the study were:

- To compare safety of LY2963016 relative to LANTUS (e.g., incidence of anti-insulin antibodies, hypoglycemia, adverse events [AEs]) when used in combination with pre-meal insulin lispro.
- To compare LY2963016 relative to LANTUS for other efficacy variables (e.g., change in HbA1c at 6 weeks, 12 weeks, 36 weeks, and 52 weeks; 7-point self-monitored blood glucose [SMBG] profiles; percentage of patients with HbA1c <7%, percentage of patients with HbA1c ≤6.5%).
- To compare LY2963016 relative to LANTUS with regard to intra-patient blood-glucose (BG) variability, basal and prandial (separately and as total daily) insulin dose, and weight when used in combination with pre-meal insulin lispro.

ABEC

The primary objective of this study was to test the hypothesis that LY2963016 administered once daily

(QD) was noninferior to LANTUS administered QD, as measured by change in HbA1c from baseline to 24 weeks, when used in combination with oral antihyperglycaemic medications (OAMs).

The main secondary objectives of the study were:

- To compare safety of LY2963016 relative to Lantus (e.g., incidence of anti-insulin antibodies, hypoglycemia, adverse events [AEs]) when used in combination with OAMs.
- To compare LY2963016 relative to Lantus for other efficacy variables (e.g., change in HbA1c at 4, 8, 12, 16, and 20 weeks, 7-point self-monitored blood glucose [SMBG] profiles [as plasma equivalent values], percentage of patients with HbA1c <7%, the percentage of patients with HbA1c ≤6.5%).
- To compare LY2963016 relative to Lantus with regard to intrapatient blood glucose (BG) variability, basal insulin dose, and weight, when used in combination with OAMs.

Sample size

ABEB

Based on the primary objective, to show non-inferiority of LY2963016 to Lantus at the 0.4% non-inferiority margin, 184 (368 total) completers per arm were needed at 24 weeks. This calculation assumed no treatment difference in HbA1c between LY2963016 and LANTUS, common SD of 0.884% for change from baseline in HbA1c, 0.05 two-sided significance level, and over 99% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients was 216 per arm (432 total). The same sample size was needed to show non-inferiority of LY2963016 to LANTUS at the 0.3% noninferiority margin with 90% power. Blinded sample-size re-estimation was performed before the last patient had been enrolled in the study. The re-estimation used a Bayesian longitudinal model (Fu and Manner 2010) to estimate the variability in the change in HbA1c from baseline to the 24-week endpoint using all available patient HbA1c values at the time of data cut-off. Since no data was available at 24 weeks, the model was used to impute a final 24-week value for each patient; using all early measures of HbA1c that were available. The estimate of 24-week variability was then used to recalculate the sample size that was needed to have 90% power for a non-inferiority margin of 0.3%,

assuming no difference between treatments. Although the algorithm predicted that only 400 patients would be required, the planned sample size was set to 500 to provide a sufficient number of patients in the safety database.

ABEC

Based on the primary objective, to show non-inferiority of LY2963016 to Lantus at the 0.4% non-inferiority margin, 284 (568 total) completers per arm were needed at 24 weeks. This calculation assumed no treatment difference in HbA1c between LY2963016 and Lantus, common SD of 1.1% for change from baseline in HbA1c, 0.05 two-sided significance level, and over 99% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients was 334 per arm (668 total). The same sample size was needed to show non-inferiority of LY2963016 to Lantus at the 0.3% non-inferiority margin with 90% power. Blinded sample-size re-estimation was performed before the last patient had been enrolled in the study following the same methodology as in ABEB.

Statistical methods

Efficacy and safety analyses were conducted using the full analysis set (FAS), which included all patients who were randomized and had taken at least 1 dose of study medication.

The primary analysis model was an ANCOVA for the change from baseline HbA1c to endpoint with the randomisation stratification factors and treatment as fixed effects and baseline HbA1c as a covariate.

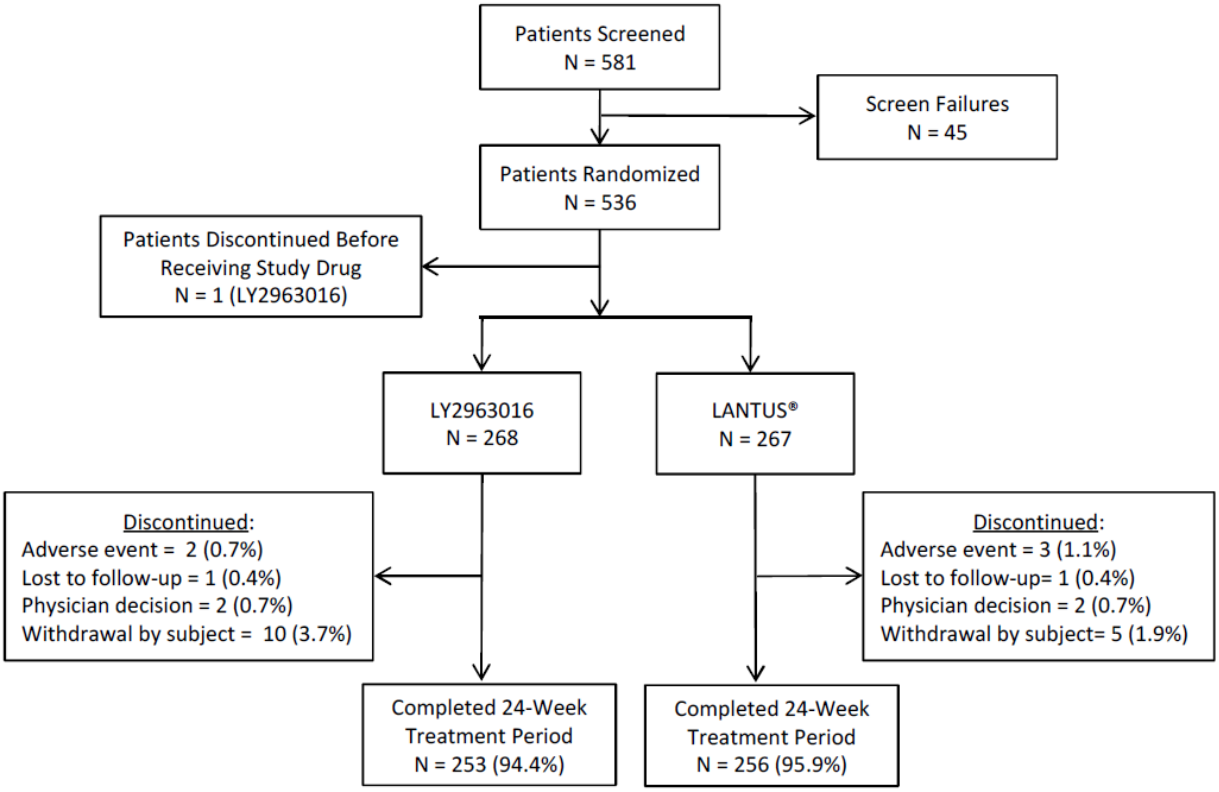
Results

Participant flow

ABEB

The disposition of patients in study ABEB has been illustrated in Figure 10.

Figure 10: Patient disposition in ABEB study

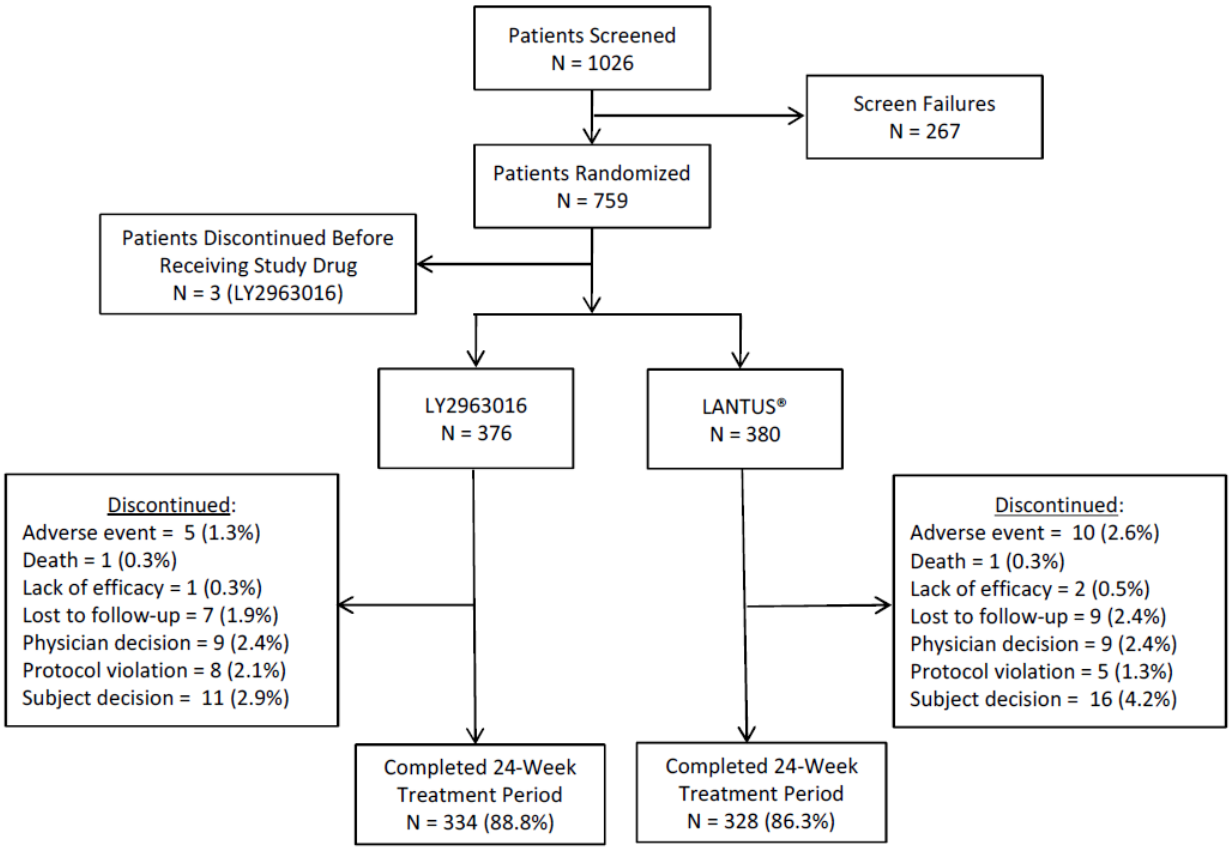


Overall, the incidence of discontinuations in the LY2963016 arm (15 patients [5.6%]) was similar to the LANTUS arm (11 patients [4.1%]), p=0.547). The most common reason for study discontinuation in both arms was withdrawal by subject.

ABEC

The disposition of patients in ABEC study has been illustrated in Figure 11.

Figure 11: Patient disposition in ABEC study



Overall, the incidence of discontinuations in the LY2963016 arm (42 patients [11.2%]) was similar to the LANTUS arm (52 patients [13.7%]), p=0.322. The most common reason for study discontinuation in both groups was subject decision (LY2963016: 11 patients [2.9%]; LANTUS: 16 patients [4.2%]).

Baseline data

For both studies, demographic and baseline characteristics were generally balanced between treatment arms.

Table 8: Patient demographics in Studies ABEB and ABEC (FAS population)

	Study ABEB (T1DM) N=535		Study ABEC (T2DM) N=756	
Variable Statistic	**LY2963016 n=268**	**LANTUS® n=267**	**LY2963016 n=376**	**LANTUS® n=380**
Age (years)				
Mean (SD)	41.0 (13.7)	41.4 (13.3)	59.0 (10.2)	58.7 (10.0)
Minimum, Maximum	18.3, 81.4	19.5, 71.5	23.4, 84.3	26.5, 82.4
Age Group (n [%])				
<65 years	254 (94.8)	256 (95.9)	264 (70.2)	278 (73.2)
≥65 years	14 (5.2)	11 (4.1)	112 (29.8)	102 (26.8)
Age Group (n [%])				
<75 years	266 (99.3)	267 (100.0)	355 (94.4)	367 (96.6)
≥75 years	2 (0.7)	0 (0.0)	21 (5.6)	13 (3.4)
Race; (n [%])[a]				
American Indian or Alaska Native	11 (4.1)	12 (4.5)	17 (4.5)	21 (5.5)
Asian	49 (18.4)	51 (19.1)	29 (7.7)	35 (9.2)
Black or African American	9 (3.4)	2 (0.7)	26 (6.9)	32 (8.4)
Multiple	1 (0.4)	1 (0.4)	2 (0.5)	1 (0.3)
White	197 (73.8)	201 (75.3)	302 (80.3)	291 (76.6)
Gender (n [%])				
Female	113 (42.2)	112 (41.9)	197 (52.4)	181 (47.6)
Male	155 (57.8)	155 (58.1)	179 (47.6)	199 (52.4)
Duration of Diabetes (years)				
Mean (SD)	16.2 (11.0)	16.7 (11.0)	11.7 (6.8)	11.2 (6.8)
Minimum, Maximum	1.0, 54.3	1.1, 55.2	0.5, 40.4	0.4, 33.5
Body Weight (kg)				
Mean (SD)	75.8 (16.8)	74.8 (15.4)	90.4 (20.0)	89.8 (19.3)
Minimum, Maximum	42.4, 117.7	43.4, 120.0	49.5, 165.4	44.2, 176.0
BMI (kg/m^2)				
Mean (SD)	25.7 (4.2)	25.4 (3.7)	31.9 (5.5)	31.9 (5.4)
Minimum, Maximum	16.9, 38.0	18.5, 35.5	20.0, 45.5	19.6, 45.7
HbA_{1c} (%)				
Mean (SD)	7.8 (1.1)	7.8 (1.0)	8.3 (1.1)	8.3 (1.1)
Minimum, Maximum	4.8, 11.5	5.2, 10.3	4.9, 11.3	5.9, 11.2
Entry HbA1c Group (n [%])[b]				
<8.5%	190 (70.9)	186 (69.7)	209 (55.6)	210 (55.3)
≥8.5%	78 (29.1)	81 (30.3)	167 (44.4)	170 (44.7)
Entry HbA1c Group (n [%])[b,c]				
<7.0%	72 (27.8)	49 (19.0)	19 (5.1)	25 (6.6)
≥7.0%	187 (72.2)	209 (81.0)	357 (94.9)	355 (93.4)
Fasting Glucose (mmol/L)[d]				
Mean (SD)	8.37 (3.01)	8.18 (2.99)	8.82 (2.50)	8.86 (2.42)
Minimum, Maximum	3.15, 19.02	2.66, 20.37	3.02, 18.73	3.28, 18.15

Variable Statistic	Study ABEB (T1DM) N=535 LY2963016 n=268	Study ABEB (T1DM) N=535 LANTUS® n=267	Study ABEC (T2DM) N=756 LY2963016 n=376	Study ABEC (T2DM) N=756 LANTUS® n=380
Entry Basal Insulin (n [%])				
LANTUS®	218 (81.3)	234 (87.6)	155 (41.2)	144 (37.9)
None	0 (0.0%)	0 (0.0%)	221 (58.8)	236 (62.1)
Other	50 (18.7)	33 (12.4)	(0.0%)	(0.0%)
Basal Insulin Dose (U/kg/d), Mean (SD)[d]				
Prior Insulin Users	0.33 (0.14)	0.31 (0.13)	0.39 (0.26)	0.35 (0.21)
Insulin-naïve	NA	NA	0.0 (0.0)	0.0 (0.0)

Abbreviations: DM= diabetes mellitus; N = total number of patients; NA = not applicable; SD = standard deviation; U/kg/d = units per kilogram per day.

[a] One patient in the LY2963016-treatment group of Study ABEB did not declare a race; thus, the percentages are based on N=267 for this variable.

[b] Entry hemoglobin A1c (HbA1c) Group (<8.5%, ≥8.5%) is from interactive voice response system (IVRS) used as stratification variable for randomization of patients upon study entry. Entry HbA1c Group (<7%, ≥7%) is the HbA1c value at Visit 1.

[c] The difference between treatment groups was statistically significant (p=0.022) in Study ABEB.

[d] Fasting blood glucose and basal insulin dose and values in this table represent the baseline values for the respective analysis; thus, the N for these variables can be found in Table 2.7.3.5.

Summary of phase III 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 ABEB

Title: A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS in Combination with Mealtime Insulin Lispro in Adult Patients with Type 1 Diabetes Mellitus: The ELEMENT 1 Study			
Study Identifier	I4L-MC-ABEB		
Design	Phase 3, randomized, multicenter, 2-arm, active-control, open-label, parallel study		
	Duration of Main phase:	24 weeks	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	28 weeks	
Hypothesis	Non-inferiority of LY2963016 to LANTUS QD, as measured by change in HbA1c from baseline (BL) at 24 weeks, when used in combination with premeal insulin lispro administered thrice daily		
Treatment groups	LY2963016	QD subcutaneous (SC) injection, individually variable dose titrated to achieve glycemic targets (e.g., FBG ≤6.0 mmol/L); 52 weeks; 269 Randomized. Patients were on basal bolus insulin regimen for ≥1 year at entry.	
	LANTUS	QD SC injection, individually variable dose titrated to achieve glycemic targets (e.g., FBG ≤6.0 mmol/L); 52 weeks; 267 Randomized. Patients were on basal bolus insulin regimen for ≥1 year at entry.	
Endpoints and Definitions	Primary Endpoint	Change in HbA1c (%) from BL	Non-inferiority of LY2963016 to LANTUS® using a non-inferiority margin (NIM) of 0.4% (and if met, of 0.3%) at 24 weeks

		HbA1c targets (%)	% of patients achieving glycemic target <7.0% or ≤6.5% at 24 weeks
		Body weight (kg)	Actual body weight and change from BL at 24 weeks
		7-point SMBG mean (mmol/L)	Daily mean of 7-point self-monitored BG (SMBG) measurements at 24 weeks
		FBG (mmol/L)	Fasting mean (morning premeal time point of SMBG profile) at 24 weeks
		Basal insulin dose (U/kg/day)	Actual basal insulin dose and change from BL at 24 weeks
		Total insulin dose (U/kg/day)	Actual total insulin dose and change from BL at 24 weeks

Database Lock (24-week treatment period): 7 November 2012. Final lock: July 2013				
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS) at 24-week endpoint (EP) using last observation carried forward (LOCF). The FAS, based on the intent-to-treat (ITT) principle, included all randomized patients who took at least 1 dose of study medication.			
Descriptive statistics and estimate variability	**Treatment group (Number of Subjects)**		**LY2963016 (268)**	**LANTUS (267)**
	LS mean change in HbA1c (%) from BL ± SE		-0.350 ± 0.053	-0.456 ± 0.054
	HbA1c target <7.0%/≤6.5%		34.5%/20.2%	32.2%/18.4%
	LS mean body weight (kg) ± SE		73.92 ± 1.17	72.84 ± 1.19
	LS mean change in body weight (kg) ± SE		0.36 ± 0.23	0.12 ± 0.23
	Daily LS mean SMBG (mmol/L) ± SE		8.32 ± 0.13	8.31 ± 0.13
	LS mean FBG (mmol/L) ± SE		7.99 ± 0.19	7.82 ± 0.20
	LS mean basal insulin dose (U/kg/d) ± SE		0.37 ± 0.01	0.36 ± 0.01
	LS mean change in basal insulin dose (U/kg/d) ± SE		0.02 ± 0.01	0.03 ± 0.01
	LS mean total insulin dose (U/kg/d) ± SE		0.72 ± 0.02	0.70 ± 0.02
	LS mean change in total insulin dose (U/kg/d) ± SE		0.01 ± 0.02	0.0 ± 0.02
Effect estimate per comparison	**Primary Endpoint***	**Comparison groups**	**LY2963016 - LANTUS** LS mean treatment difference (95% confidence interval [CI])	
		HbA1c (%) change from BL	0.106 (-0.005, 0.217)	
	Secondary Endpoints*	**Comparison groups**	**LY2963016 - LANTUS**	
		Body weight (kg)	1.08 (-1.37, 3.53)	
		Change in body weight (kg)	0.24 (-0.23, 0.71)	
		Daily mean 7-point SMBG profile (mmol/L)	0.01 (-0.26, 0.28)	
		FBG (mmol/L)	0.16 (-0.24, 0.57)	
		Basal insulin dose (U/kg/d)	0.01 (-0.01, 0.04)	
		Change in basal insulin dose (U/kg/d)	0.00 (-0.02, 0.01)	
		Total insulin dose (U/kg/d)	0.02 (-0.02, 0.06)	
		Change in total insulin dose (U/kg/d)	0.01 (-0.03, 0.04)	
Notes				
Analysis description	**Per-Protocol Analysis**			
Analysis population and time point description	Per-Protocol (PP) at 24-week EP (LOCF). The PP population included all FAS/ITT patients who had no violations of inclusion/exclusion criteria, had not discontinued from the study prior to 24 weeks, had not been off study medication for more than 10 consecutive days during the treatment period, and had not received chronic (lasting longer than 14 days) systemic glucocorticoid therapy (excluding topical, intra-articular, intraocular, and inhaled			

	preparations).			
Descriptive statistics and estimate variability	**Treatment Group (Number of Subjects)**		**LY2963016 (251)**	**LANTUS (256)**
	LS mean change in HbA1c (%) from BL ± SE		-0.370 ± 0.054	-0.468 ± .054
Effect estimate per comparison	**Primary Endpoint**	**Comparison groups**	**LY2963016 - LANTUS**	
		HbA1c (%) change from BL	0.098 (-0.014, 0.209)	

* There were no statistically significant ($p<0.05$) differences between treatment groups at the Week 24 endpoint.

An updated analysis at 52 weeks was subsequently submitted for study ABEB. The LS mean change in HbA1c from baseline to the 52-week endpoint (LOCF) was -0.256% in the LY2963016 arm and -0.276% in the Lantus arm, respectively (FAS analysis); the LS mean treatment difference was 0.020% (95% CI: -0.099%, 0.140%), therefore non-inferiority was maintained after 1 year of treatment.

Table 10: Summary of Efficacy for trial ABEC

Title: A Prospective, Randomized, Double-Blind Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS® in Adult Patients with Type 2 Diabetes Mellitus: The ELEMENT 2 Study				
Study Identifier	I4L-MC-ABEC			
Design	Phase 3, randomized, multicenter, 2-arm, active-control, double-blind, parallel study			
	Duration of Main phase:		24 weeks	
	Duration of Run-in phase:		Not applicable	
	Duration of Extension phase:		Not applicable	
Hypothesis	Non-inferiority of LY2963016 to LANTUS® QD, as measured by change in HbA1c from baseline (BL) at 24 weeks, when used in combination with OAMs			
Treatment groups	LY2963016	QD SC injection, individually variable dose titrated to achieve glycemic targets (e.g., ≤5.6 mmol/L); 24 weeks; 376 Randomized.		
	LANTUS®	QD SC injection, individually variable dose titrated to achieve glycemic targets (e.g., ≤5.6 mmol/L); 24 weeks; 380 Randomized		
	Pre-Treatment	Patients were taking 2 or more oral antihyperglycemic medications (OAMs) and may have been insulin-naïve with inadequate glycemic control or taking LANTUS® with adequate or inadequate glycemic control.		
Endpoints and Definitions	Primary Endpoint	Change in HbA1c (%) from BL	Non-inferiority of LY2963016 to LANTUS® using a non-inferiority margin (NIM) of 0.4% (and if met, of 0.3%) at 24 weeks	
		HbA1c targets (%)	% of patients achieving glycemic target <7.0% or ≤6.5% at 24 weeks	
		Body weight (kg)	Actual body weight and change from BL at 24 weeks	
		7-point SMBG mean (mmol/L)	Daily mean of 7-point self-monitored BG (SMBG) measurements at 24 weeks	
		FBG (mmol/L)	Fasting mean (morning premeal time point of SMBG profile) at 24 weeks	
		Basal insulin dose (U/kg/day)	Actual basal insulin dose and change from BL at 24 weeks	
Database Lock (24-week treatment period): 16 January 2013				
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS) at 24-week endpoint (EP) using last observation carried forward (LOCF). The FAS, based on the intent-to-treat (ITT) principle, included all randomized patients who took at least 1 dose of study medication.			
Descriptive statistics and estimate variability	**Treatment group (Number of Subjects)**		**LY2963016 (369)**	**LANTUS® (375)**
	LS mean change in HbA1c (%) from BL ± SE		-1.286 ± 0.06	-1.338 ± 0.06
	HbA1c target <7.0%/≤6.5%		48.8%/26.8%	52.5%/30.4%
	LS mean body weight (kg) ± SE		85.51 ± 1.32	84.93 ± 1.32

	LS mean change in body weight (kg) ± SE		1.78 ± 0.25	2.02 ± 0.25
	Daily LS mean SMBG (mmol/L) ± SE		7.57 ± 0.13	7.67 ± 0.13
	LS mean FBG (mmol/L) ± SE		5.94 ± 0.11	6.06 ± 0.11
	LS mean basal insulin dose (U/kg/d) ± SE		0.50 ± 0.03	0.48 ± 0.03
	LS mean change in basal dose (U/kg/d) ± SE		0.36 ± 0.02	0.37 ± 0.02
Effect estimate per comparison	**Primary Endpoint***	**Comparison groups**	**LY2963016 - LANTUS®** LS mean treatment difference (95% confidence interval [CI])	
		HbA1c (%) change from BL	0.052 (-0.070, 0.175)	
	Secondary Endpoints*	**Comparison groups**	**LY2963016 - LANTUS®**	
		Body weight (kg)	0.576 (-2.02, 3.17)	
		Change in body weight (kg)	-0.243 (-0.74, 0.25)	
		Daily mean 7-point SMBG profile (mmol/L)	-0.10 (-0.33, 0.13)	
		FBG (mmol/L)	-0.12 (-0.33, 0.09)	
		Basal insulin dose (U/kg/d)	0.02 (-0.03, 0.07)	
		Change in basal insulin dose (U/kg/d)	-0.01 (-0.05, 0.04)	
Notes				
Analysis description	**Per-Protocol Analysis**			
Analysis population and time point description	Per-Protocol (PP) at 24-week EP (LOCF). The PP population included all FAS/ITT patients who had no violations of inclusion/exclusion criteria, had not discontinued from the study prior to 24 weeks, had not been off study medication for more than 14 consecutive days during the treatment period, and had not received chronic (lasting longer than 14 days) systemic glucocorticoid therapy (excluding topical, intra-articular, intraocular, and inhaled preparations).			
Descriptive statistics and estimate variability	**Treatment Group (Number of Subjects)**		**LY2963016 (251)**	**LANTUS® (256)**
	LS mean change in HbA1c (%) from BL ± SE		-1.332 (0.07)	-1.448 (0.07)
Effect estimate per comparison	**Primary Endpoint**	**Comparison groups**	**LY2963016 - LANTUS®**	
		HbA1c (%) change from BL	0.116 (-0.010, 0.242)	

*There were no statistically significant ($p<0.05$) differences between treatment groups at the Week 24 endpoint.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

For the purpose of the clinical biosimilarity exercise for biosimilar insulin products, the CHMP is of the view that the evaluation of HBA1c is not a sensitive endpoint and therefore efficacy studies evaluating HBA1c are not generally anticipated (EMEA/CHMP/BMWP/32775/2005). However, the applicant has conducted two phase III non-inferiority studies comparing the test and reference product in order to investigate how PK/PD features of the biosimilar product translate into clinical parameters relevant for the management of patients with Type 1 and 2 DM. Furthermore, both efficacy studies provide the safety and immunogenicity datasets that are still required by the CHMP guideline.

In general, according to EU biosimilar guidelines, equivalence trials are expected but subject to appropriate clinical and scientific justifications, a non-inferiority approach can be accepted. The applicant has adequately

justified the non-inferiority margin of 0.3% for HbA1c, both from a statistical and clinical standpoint. Given the supportive role of these phase III studies in the biosimilar programme, the statistical methodology for these studies does not raise major concerns.

The choice of the patient population, i.e. well-controlled Type 1 DM managed on Lantus, NPH insulin or insulin detemir for at least 1 year (study ABEB) and well-controlled patients with Type 2 DM managed on oral antiglycaemic agents and who were either insulin-naïve or previously treated with Lantus patients (study ABEC), sufficiently covers and represents the paradigm of current management of diabetes with long-acting insulins.

Given the primary endpoint at 24 weeks and that collection of self-monitored blood glucose levels and insulin dosages were carried out, these studies provide additional supportive value to the PK/PD comparability programme conducted in healthy volunteers and T1DM patients.

Both trials were conducted in numerous European and US sites but also included sites in Japan, Mexico, South Korea, and Taiwan. Provided results are shown to be similar across geographical regions, this is acceptable in the context of a biosimilar application. Overall, the conduct of both studies was acceptable and there were no notable findings that could have impacted on the robustness of clinical findings and conclusions.

Efficacy data and additional analyses

Patient demographics and disease characteristics were well balanced across treatment arms, except for a statistically significant imbalance in the proportion of patients with HbA1c >7% in the LY2963016 arm compared to the Lantus arm in study ABEB. In order to account for this baseline imbalance, the applicant has carried out post-hoc analysis of the primary endpoint with similar non-inferiority conclusion as in the pre-specified analysis. Based on the data provided, non-inferiority of LY2963016 to Lantus was demonstrated in both studies using both FAS and PP datasets. Actual results showed an upper limit of the 95% CI being less than 0.25% in both clinical trials, which is substantially less than 0.3%.

Overall, the results of other secondary endpoints were consistent with the results of the primary endpoint. Some differences were identified in both studies but they were not considered clinically relevant when the results of the two studies were taken together.

Study ABEB

Patients in the LY2963016 arm had statistically significantly lower mean BG values at bedtime and 3 am compared with the Lantus arm; however, the mean difference between treatment arms was small and unlikely to result in clinically meaningful differences, as reflected by no difference in nocturnal hypoglycaemia. There were no statistically significant differences between treatment arms in mean FBG (morning pre-meal) values, daily mean pre-meal or post-prandial BG values, and the daily mean BG values. Additionally, this finding was not replicated in study ABEC.

Study ABEC

- The LS mean BG value was lower in the LY2963016 arm at the morning 2-hour post-prandial time point and statistically significantly lower at the midday pre-meal time point compared with the Lantus arm although there were no statistically significant differences between treatment arms in the morning pre-meal BG values, the daily mean BG values, the daily mean pre-meal and post-prandial BG values, or in the bedtime to 3 am excursion.
- The increases in LS mean body weight from baseline were statistically significantly smaller in the LY2963016 arm compared with the Lantus arm at Week 2, Week 4 and Week 20. There were no statistically significant

differences in body weight changes at any other visit or endpoint (LOCF). Baseline differences in body weight and insulin doses may have confounded early weight gain at Week 2 and 4. Furthermore, the differences were small (< 0.5 kg) and this finding was not replicated in patients with T1DM.

- At 24 weeks, the proportion of patients achieving HbA1c <6.5% was 26.8% in LY2963016 and 30.4% in Lantus groups respectively, whilst at the baseline the proportions were 3.5% and 2.4%, respectively. Similarly at baseline in study ABEC, the proportion of patients with <7.0% HBA1c was 6.2% in LY2963016 and 7.2% in Lantus arms but at 24 weeks there was a modest trend for reduction of the proportion in LY2963016 group (48.8% vs. 52.5%). A supplemental subgroup analysis of HbA1c evolution according to baseline HbA1c levels (< 7% and ≥ 7%), considered more sensitive than the responder analysis, was provided. In the largest subgroup of subjects with baseline HbA1c level ≥7%, the difference in HbA1c decrease was very small (mean 0.02%; 95%CI -0.13%, +0.18%) and clearly below differences that can be considered clinically meaningful.

Finally, to further support the similarity of the PD effects at high doses, an additional analysis of the self-monitored blood glucose profiles was performed in both clinical studies; it showed comparable glucose levels with LY2963016 and Lantus in the subgroup of patients receiving doses of insulin glargine ≥ 0.6 U/kg/d, in particular during the first hours following the injection.

2.5.3. Conclusions on the clinical efficacy

Two clinical studies conducted in patients with type 1 and 2 diabetes demonstrated that LY2963016 is non-inferior to Lantus in achieving HBA1c at week 24 and therefore provided strong supportive evidence about the comparability of the two products. Importantly, both studies provided data on patients switching from Lantus to LY2963016 at the same dose regimen; no difference in dose changes after titration to tighten glucose blood control was reported between the two treatment arms. The study in type 1 diabetes was pursued up to 52 weeks and non-inferiority of LY2963016 to Lantus was confirmed at this further time point.

2.6. Clinical safety

Patient exposure

Overall, 446 patients with T1DM and T2DM were exposed for at least 6 months within the integrated dataset composed of ABEB and ABEC studies. The total amount of comparative data up to 6 months is adequate. In addition, 499/643 patients were of Caucasian origin and there was a substantial subset of patients ≥65 years of age with only few patients exposed in the age group of >75 years.

Table 11: Overall patient exposure in studies ABEB & ABEC

Total Patient Population				
Integrated Dataset of Studies ABEB and ABEC	LY2963016		LANTUS®	
Duration of Exposure (at least)	Persons	Person-Time (Weeks)[a]	Persons	Person-Time (Weeks)[a]
<2 weeks	9	8.57	7	5.43
≥2 and <6 weeks	12	35.29	18	61.00
≥6 and <12 weeks	17	149.29	12	110.29
≥12 and <18 weeks	11	150.57	16	224.86
≥18 and <24 weeks	149	3474.00	134	3122.86
≥24 weeks	446	10847.57	460	11201.43
Total person time	644	14665.29	647	14725.86

Table 12: Exposure by Age Group, Gender, and Medicinal Product

Study ABEB: Total Population by LY2963016				
Age Group	Persons		Person-Time (Weeks)[a]	
	Male	Female	Male	Female
<65 years	147	107	3435.29	2501.00
≥65 years	8	6	174.57	139.00
<75 years	155	111	3609.86	2598.00
≥75 years	-	2	-	42.00
Study ABEB: Total Population by LANTUS®				
Age Group	Persons		Person-Time (Weeks)[a]	
	Male	Female	Male	Female
<65 years	151	105	3581.14	2470.71
≥65 years	4	7	96.00	169.00
<75 years	155	112	3677.14	2639.71
≥75 years	-	-	-	-
Study ABEC: Total Population by LY2963016				
Age Group	Persons		Person-Time (Weeks)[a]	
	Male	Female	Male	Female
<65 years	129	135	2807.14	3128.57
≥65 years	50	62	1121.57	1358.14
<75 years	169	186	3699.43	4244.86
≥75 years	10	11	229.29	241.86
Study ABEC: Total Population by LANTUS®				
Age Group	Persons		Person-Time (Weeks)[a]	
	Male	Female	Male	Female
<65 years	146	132	3227.43	2902.29
≥65 years	53	49	1172.00	1107.29
<75 years	193	174	4256.57	3840.00
≥75 years	6	7	142.86	169.57

The 52-week safety data of study ABEB were subsequently submitted. The mean exposure to study drug was 49.3 weeks for the LY2963016 arm and 49.9 weeks for the Lantus arm.

Adverse events

There were no imbalances in the presentation of adverse events, treatment-related adverse events, study discontinuations, hypoglycaemic episodes and injection site reactions between LY2963016 and Lantus arms in the phase I studies (ABEA, ABEM, ABEE and ABEI). The preliminary safety profile of LY2963016 established during the phase I studies appeared very similar that of Lantus and was considered acceptable.

Subsequently, the safety profile of LY2963016 was comprehensively evaluated during the 6-month comparative phase of studies ABEB and ABEC.

Table 13: Overall summary of adverse events in studies ABEB & ABEC (FAS)

	ABEB (T1DM)		ABEC (T2DM)	
	LY2963016 (N=268)	LANTUS (N=267)	LY2963016 (N=376)	LANTUS (N= 380)
Adverse Events[a]	n (%)	n (%)	n (%)	n (%)
Deaths[b]	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Serious adverse events	9 (3.4)	16 (6.0)	15 (4.0)	18 (4.7)
Discontinuations due to an adverse event	2 (0.7)	3 (1.1)	6 (1.6)	11 (2.9)
Patients with ≥1 TEAE	132 (49.3)	128 (47.9)	196 (52.1)	184 (48.4)
Possibly related to study drug[c]	12 (4.5)	11 (4.1)	26 (6.9)	23 (6.1)
Special topic assessment of allergic events	11 (4.1)	9 (3.4)	21 (5.6)	27 (7.1)
Injection site adverse events	5 (1.9)	3 (1.1)	13 (3.5)	11 (2.9)

Abbreviations: N = total number of patients; n = number of patients in specified category; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

a Patients may be counted in more than 1 category.

b Deaths are also included as serious adverse events and discontinuations due to adverse events.

c As assessed by the investigator.

The incidence and the pattern of identified AEs and TEAEs with LY2963016 appeared to be very similar to those with Lantus. The incidence of hypoglycaemic, allergic and post-injection site reactions was well balanced between treatment arms in each study.

The analysis of hypoglycaemic events was very comprehensive and followed the framework of both US and EU diabetes guidelines. The analysis included asymptomatic, relative, and nocturnal hypoglycaemic events. The total number of hypoglycaemic events was numerically lower with LY2963016 compared to Lantus in both studies, including the number of severe hypoglycaemic events. The total number of nocturnal hypoglycaemic events was also numerically lower with LY2963016 compared to Lantus in both studies: ABEB: 2301 events with LY2963016 in 222 patients vs. 2347 events in 216 patients on Lantus; ABEC: 1248 events with LY2963016 in 212 patients vs. 1386 events in 203 patients on Lantus. Of note, the total incidence of hypoglycaemic attacks was found to be greater in study ABEB where all patients were insulin-dependent and this is expected as opposed to a lower incidence of these events in T2DM patients of study ABEC where a significant proportion of patients were insulin-naïve at entry into the study.

In the 52-week report of study ABEB, an estimated difference of ~3 events/year of hypoglycaemia with BG ≤70 mg/dL was not considered clinically meaningful. Of note, the baseline hypoglycaemia rates were also lower in the LY2963016 arm (8.4/month) than in the Lantus arm (9.3/month). With a more stringent definition (<54 mg/dL), no difference between the two treatment arms was observed. Likewise, in the double-blind study ABEC,

the estimated difference at 24 weeks was even smaller (~1 event/year of hypoglycaemia with BG ≤70 mg/dL) with no difference in documented symptomatic hypoglycaemia.

The pattern of allergic events was evaluated in a blinded fashion and was based on a thorough skin evaluation questionnaire. The number of allergic events and injection site-related abnormalities appeared similar between the two insulins and considered acceptable. In the 52-week follow-up of study ABEB, 20 patients (7.5%) in the LY2963016 arm and 11 patients (4.1%) in the Lantus arm reported treatment-emergent allergic events.

The applicant tabulated all cases of neoplasia reported during the development programme and there were no imbalances that would raise any new concerns. The theoretical risk of tumorogenicity with Lantus has been evaluated in numerous post-marketing studies and extensively discussed at CHMP and PRAC in the past. It was agreed that no new studies are required but that the risk has to be monitored and included in the RMP. The applicant has implemented the risk of neoplasia into the RMP and based on the lack of any unanticipated signals in studies ABEC and ABEB, it is considered that passive post-marketing surveillance for neoplastic events with biosimilar LY2963016 will be sufficient.

The only imbalance identified in the main studies was a higher number of events in the vascular SOC with LY2963016 and this observation was confined entirely to study ABEC: 21 patients (5.6%) vs. 9 patients (2.4%). This imbalance was driven by a baseline imbalance in the number of patients with pre-existing hypertension randomised into the LY2963016 arm of study ABEC. The applicant has conducted a number of safety analyses including evaluations of systolic and diastolic blood pressure and thorough examination of pre-existing medical histories of affected patients. It is evident that, in the absence of mechanistic association between insulin signalling pathways and vascular tone, the lack of documented risk with the reference product and therefore an absence of plausible biological and clinical causal link, there is a high probability of confounding of the safety profile of insulin products with numerous co-morbidities well-recognised in diabetes mellitus. Finally, the slightly lower frequency of vascular AEs in study ABEB over 52 weeks of follow-up (27.6% with LY2963016 vs. 29.6% with Lantus) also suggests that the finding in study ABEC is a chance finding possibly driven by the baseline imbalance of patients with pre-existing hypertension.

In summary, the safety profile of LY2963016 appeared to be similar to that of Lantus and in line with the safety characteristics expected from an insulin product.

Serious adverse event / deaths / other significant events

There were no imbalances in the number of SAEs and deaths reported. The number of SAEs with LY2963016 was numerically lower than with Lantus. The occurrence of hypoglycaemia, the most frequent SAE, was similar with both treatments.

There were a total of 3 deaths in the Phase III studies. In study ABEB, one death was reported at Week 30 in a patient on Lantus. Two deaths were reported in study ABEC: 1 case on Lantus and 1 case on LY2963016. The narratives do not raise any treatment-related concerns.

Laboratory findings

Laboratory measurements were collected at baseline and Week 24 in both studies. None of the differences were found to be clinically relevant or raised new concerns. There were no AEs related to changes in vital signs and ECG findings.

Immunological events

In studies ABEB and ABEC, patient samples were analysed for anti-insulin antibodies, including those cross-reacting with human insulin. In study ABEB, the proportion of patients with detectable anti-insulin antibodies at any time over the 24-week period was 29.8% in the LY2963016 arm vs. 33.7% in the Lantus arm; in study ABEC, 15.3% in the LY2963016 arm vs. 11.0% in the Lantus arm (see Table 14).

Table 14: Proportion of patients with detectable antibodies: Summary at baseline, 24-week endpoint (LOCF), and overall in studies ABEB & ABEC

	ABEB (T1DM)		ABEC (T2DM)	
Visit	LY2963016 (N=268) n (%)	LANTUS® (N=267) n (%)	LY2963016 (N=376) n (%)	LANTUS® (N=380) n (%)
Baseline				
Number of patients	265	267	365	365
Patients with detectable antibodies	45 (17.0)	55 (20.6)	20 (5.5)	13 (3.6)
Endpoint (LOCF)				
Number of patients	265	267	365	365
Patients with detectable antibodies	50 (18.9)	51 (19.1)	30 (8.2)	22 (6.0)
Overall[a]				
Number of patients	265	267	365	365
Patients with detectable antibodies	79 (29.8)	90 (33.7)	56 (15.3)	40 (11.0)

Abbreviations: LOCF = last observation carried forward; N = total number of patients; n= number of patients in the specified category; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Overall includes all patients with detectable antibodies at any point over the 24-week treatment period (does not include baseline).

The applicant presented further analyses of treatment-emergent immune responses using arbitrarily pre-defined definitions, which suggested potential differences between LY2963016 and Lantus.

The CHMP considered that, for the purpose of comparing the immunogenicity of the test and reference products, the evaluation of the incidence and quantitative measurement of antibodies over time using the continuous variable of percent binding (% B/T) is more informative and accurate than an assessment of the immune response based on arbitrarily selected criteria. Therefore, additional antibody analyses were requested to further compare the immunogenicity profile of the two products up to 52 weeks in study ABEB, to present data separately in patients already treated with Lantus prior to trial entry vs. other basal insulin (study ABEB) or insulin-naïve patients (study ABEC), and to present a quantitative evaluation of total and cross-reactive antibody levels over time (% B/T).

The proportion of patients with detectable antibodies was comparable throughout both studies, with the exception of a significant overall difference in the subgroup of patients with T2DM that were previously treated with Lantus (see Table 15).

The median antibody levels remained low throughout both studies, with no significant differences between treatment arms regardless of previous insulin treatment. Figure 12 presents these data for the subgroup of patients treated with Lantus prior to study entry in both trials.

The data for cross-reactive antibodies appeared similar to that of total antibodies. The majority (approximately 70% to 100%) of detectable antibodies in both treatment arms were cross-reactive throughout the studies (data not shown).

Table 15: Proportion of patients with detectable antibodies: Summary at baseline, endpoint (LOCF), and overall in studies ABEB & ABEC - by baseline insulin status

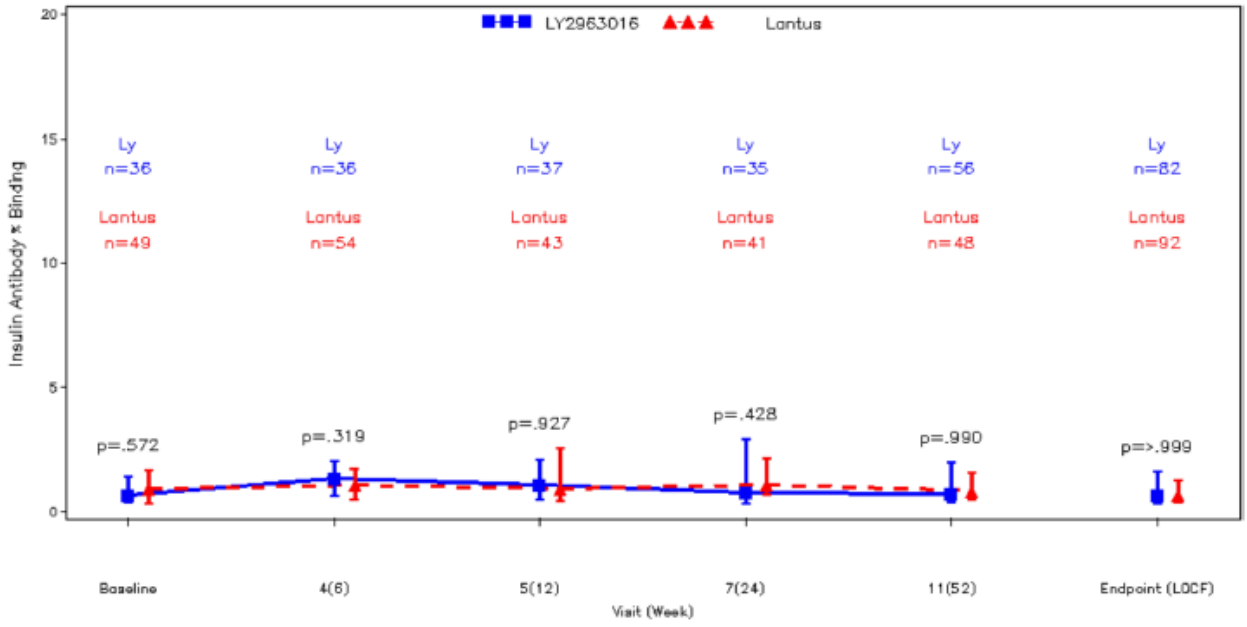
Population	Study ABEB (T1DM)			
	LY2963016		LANTUS®	
	Number of Patients	Number (%) Patients with detectable antibodies	Number of Patients	Number (%) Patients with detectable antibodies
Total				
FAS (baseline)	265	45 (17.0)	267	55 (20.6)
FAS (endpoint)	265	73 (27.5)	267	59 (22.1)
FAS (overall 52 wks)	265	107 (40.4)	267	105 (39.3)
Prior LANTUS® (baseline)	217	36 (16.6)	234	49 (20.9)
Prior LANTUS® (endpoint)	217	58 (26.7)	234	53 (22.6)
Prior LANTUS® (overall 52 wks)	217	82 (37.8)	234	92 (39.3)
Cross-Reactive				
FAS (baseline)	264	27 (10.2)	267	40 (15.0)
FAS (overall 52 wks)	264	56 (21.2)	267	54 (20.2)
Prior LANTUS® (baseline)	216	21 (9.7)	234	35 (15.0)
Prior LANTUS® (overall 52 wks)	216	43 (19.9)	234	49 (20.9)

Population	Study ABEC (T2DM)			
	LY2963016		LANTUS®	
	Number of Patients	Number (%) Patients with detectable antibodies	Number of Patients	Number (%) Patients with detectable antibodies
Total				
FAS (baseline)	365	20 (5.5)	365	13 (3.6)
FAS (endpoint)	365	30 (8.2)	365	22 (6.0)
FAS (overall 24 wks)	365	56 (15.3)	365	40 (11.0)
Prior LANTUS® (baseline)	151	10 (6.6)	139	6 (4.3)
Prior LANTUS® (endpoint)	151	13 (8.6)	139	5 (3.6)
Prior LANTUS® (overall 24 wks) *	151	29 (19.2)	139	11 (7.9)
Insulin-naive (baseline)	214	10 (4.7)	226	7 (3.1)
Insulin-naive (endpoint)	214	17 (7.9)	226	17 (7.5)
Insulin-naive (overall 24 wks)	214	27 (12.6)	226	29 (12.8)

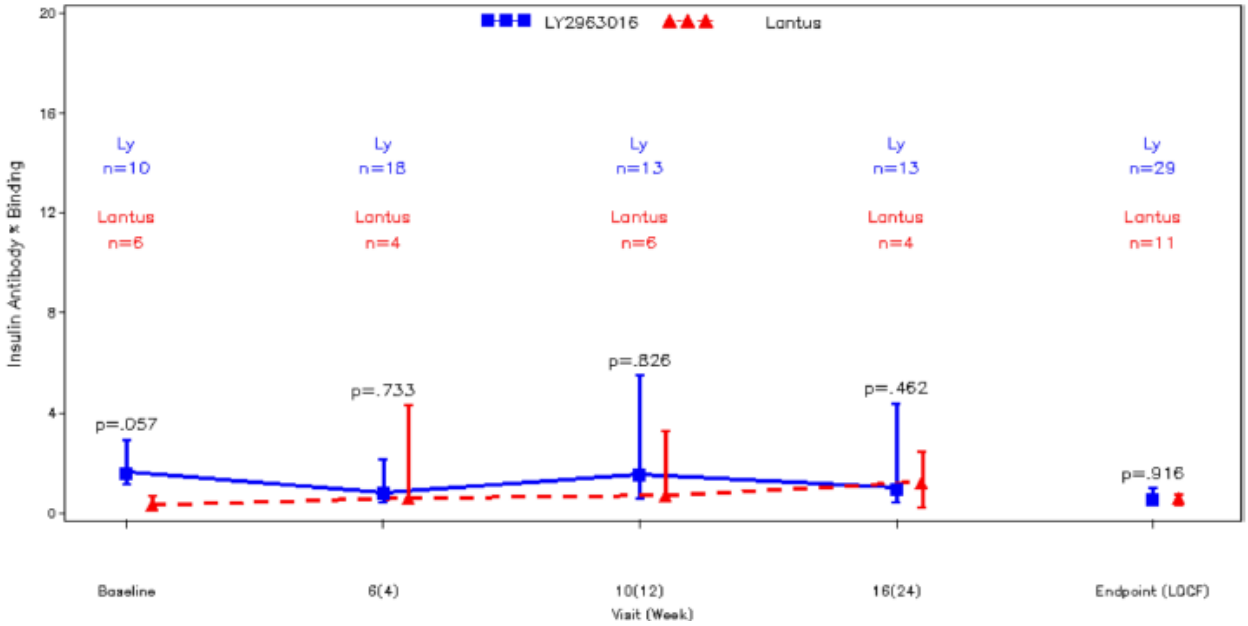
*statistical difference p = 0.006

Figure 12: Antibody level (% B/T - Median +/- interquartile range) in studies ABEB and ABEC Patients with Lantus prior to study entry

Study ABEB



Study ABEC



Finally, there was no evidence that these antibodies had any impact on efficacy and safety outcomes (HbA1c, weight, insulin dose, hypoglycaemic episodes, allergic or injection site reactions) and no consistent differences between the two products were observed.

Safety related to drug-drug interactions and other interactions

There is no expectation that a development programme for a biosimilar candidate would evaluate various drug-drug interactions previously reported with the reference medicinal product. The section 4.5 of Lantus SmPC contains a number of potential drug-related effects on treatment with Lantus. These are equally relevant and are transferrable into the SmPC of Abasria.

Discontinuation due to adverse events

The discontinuations due to treatment-related AEs were numerically higher with Lantus compared to LY2963016. There was no unusual pattern that warrants further action.

2.6.1. Discussion on clinical safety

Extensive comparative safety data have been provided, up to 6 months in one study and 12 months in the other study. There was a substantial subset of patients ≥65 years of age, especially with T2DM, with only few patients exposed in the age group of >75 years. This is acceptable as there is no expectation that all different age groups or special populations should be included into the biosimilar development programme. The objective of the biosimilar development is to demonstrate the similarity in safety profile but not to reassess the safety profile of the reference medicinal product.

The incidence and pattern of identified AEs and TEAEs to LY2963016 appeared to be very similar to those with Lantus; the incidence of hypoglycaemic, allergic and post-injection site reactions was well balanced between treatment arms in each study.

Although the total number of hypoglycaemic events was numerically lower with LY2963016 compared to Lantus in both studies, the estimated difference in the 52-week update of study ABEB was approximately 3 events per year, which is not considered clinically meaningful. Likewise, in the double-blind study ABEC, the estimated difference at 24 weeks was smaller (~1 event/year) with no difference in documented symptomatic hypoglycaemia.

The number of allergic reactions and injection site-related abnormalities appeared broadly similar between the two insulins and considered acceptable. There were no severe or life-threatening allergic reactions reported. There were several cases of malignancies, which were balanced between treatment arms. There were no imbalances in the number of SAEs and deaths.

The most sensitive population with regard to immunogenicity is the population of patients with type 1 diabetes. Study ABEB showed that LY2963016 and Lantus had comparable immunogenicity profiles up to 52 weeks, in terms of incidence and level of anti-insulin antibodies (both total and cross-reactive with human insulin). Patients with type 2 diabetes tend to develop anti-insulin antibodies infrequently, and therefore, the numbers involved in study ABEC were much smaller. While no difference in immune response was shown in insulin-naïve patients, a difference in antibody incidence was detected in the subgroup of patients that were on Lantus prior to study entry. However, this is likely a chance finding as there was already a difference at baseline, no difference in antibody levels was detected, and this observation was not corroborated by the data from study ABEB in a larger and more sensitive population.

For insulin analogues in general, an impact of anti-insulin antibodies on efficacy or safety has only been occasionally reported. In the two clinical studies, antibodies did not appear to have any influence on efficacy and

safety outcomes (HbA1c, weight, insulin dose, hypoglycaemic episodes, allergic or injection site reactions) and no consistent differences between the two products were observed.

2.6.2. Conclusions on the clinical safety

The safety profile of LY2963016 has been well characterised in the context of the biosimilarity exercise. It appeared comparable to the safety profile of Lantus in the clinical studies and in line with the profile established and documented with the reference product. There were no major safety findings or signals identified in the clinical programme.

Furthermore, extensive immunogenicity evaluation in two large studies, which covered both types of diabetic population, showed that the antibody profiles of LY2963016 and Lantus were comparable.

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:

Based on the PRAC review of the Risk Management Plan version 1.4, the PRAC considers by consensus that the risk management system for insulin glargine LY2963016 (Abasria) in the treatment of proposed indication is acceptable.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the Risk Management Plan as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.4 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Hypoglycaemia • Hypersensitivity reactions • Injection site reactions • Medication errors (incorrect insulin)
Important potential risks	• Malignancies • Immunogenicity
Missing information	• Use in pregnancy

Summary of safety concerns	
	• Use in children younger than 2 years of age

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

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

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypoglycaemia	Education through SmPC, package leaflet	*None*
Hypersensitivity reactions	Education through SmPC, package leaflet	*None*
Injection site reactions	Education through SmPC, package leaflet	*None*
Medication errors (incorrect insulin)	Education through SmPC, package leaflet	*None*
Malignancies	Education through SmPC, package leaflet	*None*
Immunogenicity	Education through SmPC, package leaflet	*None*
Use in pregnancy	Education through SmPC, package leaflet	*None*
Use in children less than 2 years age	Education through SmPC, package leaflet	*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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lantus. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient *per se* as this has been shown for the reference product. The benefits and risks are inferred from the similarity of the test product to the reference product in terms of quality, efficacy and safety.

Benefits

Beneficial effects

From a quality perspective:

- Physico-chemical characterisation has demonstrated biosimilar comparability between LY2963016 and the reference medicinal product (EU-approved Lantus) for the primary, secondary, tertiary and quaternary structure.
- LY2963016 and Lantus were comparable in the average relative potency assay when batches of LY2963016 from Lilly (France) and a contract manufacturer (USA) were compared directly with EU-approved Lantus or US-approved Lantus. Biological identity test data from LY2963016 finished product and Lantus were also demonstrated to be comparable in batches tested concurrently.
- LY2963016 has the same quantitative formulation as Lantus, with comparable levels of metacresol and zinc, also similar pH.
- Levels of total impurities and HMWP were comparable in LY2963016 and Lantus.
- Comparable chromatographic profiles were demonstrated for LY2963016 and Lantus, except for low levels of an impurity in LY2963016. This product-related impurity was shown to be active in the reporter gene assay and was qualified in toxicology studies. This impurity is controlled in the purification process.
- LY2963016 finished product and Lantus have similar *in vitro* precipitation characteristics under physiological conditions.

From a non-clinical perspective:

- The data from the binding affinity, functional, metabolic potency and rat hepatoma mitogenesis assays showed that LY2963016 is similar to EU-approved Lantus.

From a clinical perspective:

- In single dose cross-over studies ABEA and ABEM conducted in healthy volunteers the PK parameters for LY2963016 and Lantus adjusted for baseline C-peptide levels established biosimilarity based on 90% confidence intervals for the ratios of both primary parameters (C_{max} and AUC_{0-24}), which were well contained within the standard bioequivalence interval of 0.80 – 1.25.
- In the pivotal ABEA study, euglycaemic clamp glucodynamic evaluations established PD similarity following a single dose of 0.5 U/kg based on 95% confidence intervals for the ratios of both primary parameters (G_{tot} and R_{max}), which were well contained within 0.80-1.25.
- These pivotal PD data were supported by similar PD results at the dose of 0.3 U/kg in study ABEM (despite insufficient study power) and similar duration of action in patients with T1DM.

- Both efficacy studies in type 1 and 2 diabetes mellitus met their primary objective, i.e. showed that LY2963016 was non-inferior to Lantus based on the change in HbA1c from baseline to the 24-week time point using an acceptable margin of 0.3% in both the FAS and PP populations. In both studies, significant ($p<0.001$) reductions in HbA1c at 24 weeks were achieved with the two products. Likewise, non-inferiority of LY2963016 to Lantus was confirmed at the final time point (52 weeks) of study ABEB in T1DM patients.

Uncertainty in the knowledge about the beneficial effects.

From a quality perspective:

- Low levels of citrate were detected in the Lantus samples (both EU and US Lantus) by NMR, which is not present in LY2963016.
- Differences were observed in the degradation pathways under accelerated conditions, although no differences were observed under long term storage conditions.

From a non-clinical perspective:

- Differences were initially observed in the functional activity for stimulating auto-phosphorylation of the human insulin receptor IR-A, but pooling of datasets from several studies has indicated that the differences observed with this sensitive assay were not of biological significance.

From a clinical perspective:

- At the highest dose tested (0.6 U/kg), PD results in healthy volunteers suggested potentially lower activity of LY2963016 compared to Lantus, especially in the first hours following injection. However, this observation was largely driven by a single subject, for whom no plausible physiological explanation could be found, and a post-hoc analysis without this single outlier showed comparable effects taking into account the small size of this supportive study.
- To further confirm the similarity of the PD effects at high doses, an additional analysis of the self-monitored blood glucose profiles was performed in both clinical studies; it showed comparable glucose levels with LY2963016 and Lantus in the subgroup of patients receiving insulin doses ≥ 0.6 U/kg/d, in particular during the first hours following the injection.

Risks

Unfavourable effects

LY2963016 exhibited a safety profile comparable to that of Lantus in large clinical trials up to 52 weeks. The type and incidence of ADRs were broadly comparable and in line with those expected on the basis of the Lantus SmPC.

Uncertainty in the knowledge about the unfavourable effects

The initial immunogenicity assessment suggested that LY2963016 might be slightly more immunogenic than Lantus but this was based on an arbitrary definition of immune response. Extensive and more relevant analyses

of the incidence and quantitative measurement of anti-insulin antibodies did not show any meaningful difference in the immunogenicity profile of the two products, especially in the most sensitive population of patients with type 1 diabetes followed up to 12 months. Furthermore, these antibodies did not show any impact on efficacy and safety outcomes.

Benefit-risk balance

Importance of favourable and unfavourable effects

Minor quality differences are expected to be observed between a biosimilar and its reference product; they are acceptable as long as they do not impact on efficacy and safety.

All major physicochemical characteristics and biological activities of LY2963016 were shown to be comparable to those of Lantus, with only small differences observed which are attributed to the presence of low levels of citrate in Lantus.

Furthermore, an extensive clinical programme, including five PK/PD studies and two efficacy/safety studies, did not reveal any relevant difference between LY2963016 and Lantus.

Benefit-risk balance

For a biosimilar, the benefit-risk balance is based on the totality of evidence collected from the quality, non-clinical, and clinical comparability exercise.

Discussion on the benefit-risk balance

Several PK/PD studies, which are considered the cornerstone of the clinical comparability exercise for insulin analogues, have established equivalence between the PK and PD profiles of LY2963016 and Lantus. In addition, two clinical studies conducted in patients with both types of diabetes mellitus have confirmed that the efficacy, safety and immunogenicity profiles of the two products were comparable.

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 Abasria in the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above 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 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.

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

Not applicable.