25 July 2013
EMA/CHMP/207158/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Vipdomet

International non-proprietary name: alogliptin / metformin

Procedure No. EMEA/H/C/002654/0000

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List of abbreviations

niddBCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DoE	Design of Experiments
DPP4	Dipeptidyl peptidase-4
EU	European Union
FDC	Fixed Dose Combination
FMEA	Failure Mode Effects Analysis
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
IR	Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance Spectroscopy
NMT	Not More Than
PCTFE	Polychlorotrifluoroethylene
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl Chloride
QbD	Quality by Design
QTPP	Quality Target Product Profile
RH	Relative Humidity
RTRT	Real Time Release Testing
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet Spectroscopy

XRD	X-ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Global Research and Development Centre (Europe) Limited submitted on 30 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vipdomet, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 October 2011. During the procedure the applicant has changed to Takeda Pharma A/S.

The applicant applied for the following indication:

"Vipdomet is indicated in the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycaemic control in adult patients, inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin.
- in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.
- in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control."

The legal basis for this application refers to:

New active substance (Article 8(3) of Directive No 2001/83/EC). The applicant indicated that alogliptin was considered to be a new active substance.

The application submitted is a new fixed combination medicinal product composed of administrative information, complete quality data, a clinical bioequivalent study with the individual tablets, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/165/2011 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC)

No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 29 September 2009 and 16 December 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Vipdomet has been given a Marketing Authorisation in the US on 25 January 2013.

A new application was filed in the following countries: Australia, Brazil, Canada, and Switzerland.

1.2. Manufacturers

Manufacturer responsible for batch release

Takeda Ireland Ltd.
Bray Business Park
Kilruddery
Co. Wicklow
Ireland

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Kristina Dunder

CHMP Peer reviewer(s): Karsten Bruins Slot

- The application was received by the EMA on 30 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 24 September 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012.
- During the meeting on 18 October 2012, 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 18 October 2012. As a result of minor updates a final updated consolidated

List of Questions was sent to the applicant on 12 November 2012.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 December 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 January 2013.
- During the CHMP meeting on 21 February 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 April 2013.
- During the CHMP meeting on 25 April 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or oral explanation by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 23 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 July 2013.
- During the meeting on 25 July 2013, 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 Vipdomet.

2. Scientific discussion

2.1. Introduction

The prevalence of T2DM has increased dramatically throughout the world, and is expected to continue to raise from approximately 366 million adults in 2011 to 552 million adults by 2030. T2DM is a chronic illness associated with a number of long-term microvascular (ie, nephropathy, retinopathy, and neuropathy) and macrovascular (i.e. cardiovascular [CV] disease, stroke, and peripheral vascular disease) complications.

Current pharmacologic interventions for T2DM include a diverse range of antidiabetic medications with different mechanisms of action, developed to manage the 2 different aspects of the disease: reduced insulin secretion and peripheral insulin resistance. The main classes of oral agents include biguanides (e.g. MET), SUs (e.g. glipizide), TZDs (e.g. pioglitazone), and other DPP-4 inhibitors (e.g. sitagliptin). Insulin and glucagon like peptide-1 (GLP-1) analogs (e.g. exenatide and liraglutide) are also commercially available and are administered by injection. Many therapies have clinically important side effects, such as hypoglycaemia (SUs), weight gain, fluid retention and heart failure (TZDs), and gastrointestinal effects and lactic acidosis (MET).

The application concerns a FDC of alogliptin and metformin at a dose of alogliptin 12.5 mg in combination with metformin 850 mg or 1000 mg for twice daily (BID) dosing in adults with T2DM. Originally an application was submitted for four strengths: 6.25 mg+850 mg, 6.25 mg+1000 mg, 12.5 mg+850 mg, or 12.5 mg+1000 mg of the drug substances alogliptin (as benzoate) and metformin hydrochloride, respectively. During the procedure, the applicant withdrew its application for the 6.25 mg+850 mg, 6.25 mg+1000 mg strengths.

Metformin is approved for use in the treatment of T2DM in many countries including the European Union (EU), the US, and Japan, and is used as first-line treatment as monotherapy, and in combination with insulin, SUs, TZDs, and DPP-4 inhibitors.

Alogliptin belongs to a relatively new class of agents, DPP-4 inhibitors, which has emerged as a novel treatment to help manage T2DM. In patients with T2DM, actions of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are blunted, which contributes to hyperglycaemia. GLP-1 and GIP are released into the bloodstream in response to meals/glucose levels, but are quickly inactivated by DPP-4. Inhibition of DPP-4 increases circulating blood levels of GLP-1 and GIP, thereby increasing insulin levels and decreasing glucagon levels.

The aim of the clinical program was to investigate the therapeutic effect and safety profile in the target population of T2DM subjects. As such, phase III studies were designed to evaluate the efficacy, safety, and tolerability of alogliptin compared with placebo and active comparators when used in combination with widely used and effective antidiabetic agents, MET, SU, TZD, and insulin. The clinical program was also designed to support global registration of alogliptin as a monotherapy product and in combination with the approved oral antidiabetic medications pioglitazone and MET, as fixed-dose combination (FDC) tablets.

Alogliptin and the alogliptin/pioglitazone FDC were first approved in Japan in April 2010 and July 2011, respectively (25 mg with 12.5 and 6.25 mg for renally impaired patients and 25/15 mg and 25/30 mg alogliptin/pioglitazone).

For this MAA, key guidance documents considered in the design of the clinical development program included the Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (May 2002), and the program is also largely consistent with the later draft guidance (September 2011).

2.2. Quality aspects

2.2.1. Introduction

Vipdomet is a fixed-dose combination (FDC) product. The drug product is a film-coated immediate-release tablet containing alogliptin benzoate and metformin hydrochloride. Four strengths were originally proposed: alogliptin 6.25 mg (as benzoate) and metformin hydrochloride 850 mg; alogliptin 6.25 mg (as benzoate) and metformin hydrochloride 1000 mg; alogliptin 12.5 mg (as benzoate) and metformin hydrochloride 850 mg; alogliptin 12.5 mg (as benzoate) and metformin hydrochloride 1000 mg. All strengths are oblong bioconvex, and strength is distinguished by size, film colour, and debossed markings. The tablets are presented in PCTFE/PVC blisters with push through aluminium lidding foil.

2.2.2. Active Substance

The drug product contains two active substances: alogliptin benzoate (a DPP-4 inhibitor) and metformin hydrochloride (a biguanide). Metformin hydrochloride is a well-known active substance described in Ph. Eur. A valid certificate of suitability to the Ph. Eur. monographs (CEP) has been submitted by the single manufacturer described in this application. The information provided regarding the manufacturing process and control of metformin hydrochloride was assessed and approved by the European Directorate for the Quality of Medicines and satisfactory quality is ensured through the CEP.

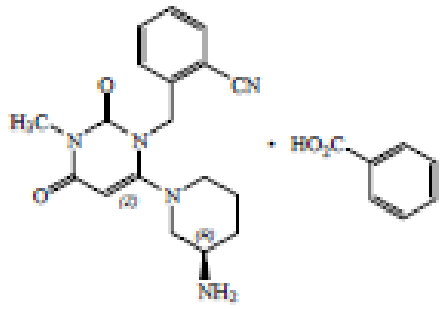
Alogliptin benzoate is a new active substance which is also the active ingredient of Vipidia (EMEA/H/C/2182 – a standalone therapy) and Incresync (EMEA/H/C/2178 – an FDC product with pioglitazone hydrochloride), marketing authorisations for which are sought in separate parallel marketing authorisation applications.

Alogliptin Benzoate

The active substance alogliptin benzoate (INN: alogliptin) is a white crystalline odourless powder, soluble in e.g. dimethylsulfoxide, sparingly soluble in methanol, slightly soluble in e.g. tetrahydrofuran, and practically insoluble in e.g. toluene and diethyl ether. The aqueous solubility is high and independent of pH between 3 and 11. The chemical name is 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)-benzonitrile monobenzoate, also known as 2-[[6-[(3R)-3-Amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2H)-pyrimidinyl]methyl]benzonitrile monobenzoate and has the structural formula C25H27N5O4. It is a 1:1 salt between alogliptin and benzoic acid.

The structure of alogliptin benzoate was unambiguously confirmed by NMR, UV, and IR spectroscopy, mass spectrometry, elemental analysis, and an X-ray crystal structural study. Physico-chemical properties such as crystalline form optical rotation and partition coefficients have been detailed. Although alogliptin exhibits polymorphism, a single stable polymorphic form is routinely delivered by the manufacturing process. The active substance is not hygroscopic. It has a single chiral centre and is manufactured as the R enantiomer.

The chemical structure of alogliptin benzoate is:



Manufacture

Alogliptin is synthesized in three steps from commercially available, well-defined starting materials. The active substance is then milled to attain the desired particle size. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates along with process development and validation has been provided.

The manufacturing process is adequately described. The full 3-step process can be carried out in its entirety at one manufacturer. Alternatively, step 1 is carried out at a different manufacturer.The synthetic scheme, including the raw materials suppliers and process descriptions is identical for all manufacturing sites although the scales differ.

The starting materials are well-defined, commercially available and purchased from vendors who have demonstrated the ability to supply materials that consistently meet the established acceptance criteria. Appropriate specifications have been adopted for the starting materials, taking into account their route of synthesis and impact on active substance quality. The applicant has discussed the formation and control of potential and actual impurities, including genotoxins, degradants, and residual solvents at each step of the synthesis. Critical process parameters were identified for each step and appropriate limits defined. All relevant impurities have been appropriately characterised and are well controlled by the process and intermediate specifications. Therefore, the manufacturer has good control over the manufacturing process and the described in-process controls and specifications are considered adequate to ensure the required quality of active substance.

Specification

The active substance specification includes the following parameters: appearance (visual and XRD), identification (UV, IR, HPLC), heavy metals (USP method), content of (S)-enantiomer (chiral HPLC), related substances (HPLC), residual solvents (GC), water (Ph. Eur. 2.5.12), residue on ignition (Ph. Eur. 2.4.14), assay (HPLC) and particle size (laser diffraction). The specifications have been adequately justified and are in compliance with the ICH guidelines including ICH Q3A(R2) and ICH Q3C for residual solvents. The potential effect of alogliptin benzoate particle size on the dissolution properties of Vipdomet tablets was investigated, and it was found to be negligible within the range evaluated.

The analytical results of 46 batches of alogliptin (manufactured and used in development, preclinical, clinical, stability studies as well as used for the purpose of validation and registration) have been provided. Results were found within the set specification. Analytical methods have been described and non-compendial methods validated in accordance with ICH guidelines.

Stability

Three pilot-scale batches of the active substance stored in the commercial packaging were put on stability studies under long-term (25 °C / 60% RH) for up to 60 months and accelerated (40 °C / 75% RH) for up to 6 months as per ICH guidelines. Additional stress studies (heat (50, 60 oC), humidity (93% RH) and photostability (white fluorescent and UV light) in line with ICH option 2) were performed on one batch for 3 months. The parameters tested in the stability studies were appearance, crystallinity, identification, (S)-enantiomer, related substances,

(R)-3-aminopiperidine, water content, assay and microbiological limit testing. The analytical procedures were detailed and validated. No significant changes were observed to any of the monitored parameters under any of the tested conditions. Furthermore, stability of the polymorphic form was demonstrated.

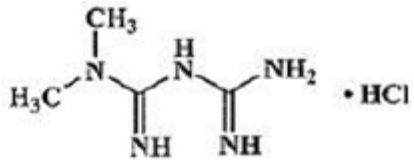
Forced degradation studies were also carried out and identified several degradation products formed under acidic, basic, and oxidative aqueous conditions. The drug substance was shown to be stable in neutral aqueous solution, even on exposure to light.

The stability studies indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Metformin Hydrochloride

Metformin hydrochloride is a 1:1 salt of hydrochloric acid and metformin which is achiral. Metformin hydrochloride is a white, almost odourless crystalline powder, which is freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and dichloromethane. Two polymorphic forms of metformin hydrochloride are described in the literature. The proposed supplier routinely manufactures polymorphic form I which is the most thermodynamically stable form at room temperature.

The chemical structure of metformin hydrochloride is:



The specification includes all of the controls specified in the monograph for metformin hydrochloride performed using the pharmacopoeial test methods indicated in the CEP, as well as additional specifications for particle size. The release specifications include tests for appearance (Ph. Eur.), identification (Ph. Eur.), appearance of solution (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), assay (Ph. Eur.), related substances and impurity A (Ph. Eur.), any other impurity (HPLC) and particle size (Ph. Eur. 2.9.38).

Qualification of all analytical methods has been performed by the applicant.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from the proposed manufacturer. The proposed particle size limits are comparable to those batches of metformin hydrochloride used in the manufacture of batches of Vipdomet used in clinical and bioequivalence studies.

According to literature data, metformin hydrochloride is very stable in the solid state. Degradation studies were carried out to confirm the literature data. Regular production batches of metformin hydrochloride packed in the intended commercial packaging were put on stability testing as per ICH conditions by the manufacturer: eight batches were stored under long term conditions (25 °C / 60% RH) for up to 60 months, and two were stored under accelerated conditions (40 °C / 75% RH) for up to 6 months. Stability was also tested under stressed conditions in the solid state (UV light (254

nm) and heat degradation (100 °C)) and in solution (50% aqueous solution, 100 °C / pH 2, 6, 12.3 or 100 °C / H_2O_2). The following parameters were tested: description; solubility; melting point; loss on drying; assay; related impurities (HPLC). Additionally, metformin hydrochloride is routinely tested against the specifications of the finished product manufacturer before use.

No significant changes were observed in any of the monitored parameters under long-term or accelerated storage conditions. The active substance is stable in the solid state at temperature and under UV irradiation, thus confirming the literature data. Metformin hydrochloride degrades in aqueous solution at all pHs and under oxidative conditions.

The stability studies indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical Development

The objective was to develop an immediate release orally available formulation containing a fixed dose combination of alogliptin benzoate and metformin hydrochloride. Good stability and dissolution characteristics were required for both active substances and the formulation needed to be adaptable to produce different strength doses with only minor adjustments to composition. A film coating was required to mask the bitter taste of both active substances.

Metformin hydrochloride (BCS class III) is freely soluble in aqueous media. Alogliptin benzoate (BCS class I) is sparingly soluble in water from pH 3-11 and particle size was demonstrated to have no effect on dissolution profile. Nonetheless, a specification for alogliptin benzoate is included to ensure the particle size distribution falls within a justified range. Excipients were chosen to maximise hardness, reduce friability, and maximise disintegration and dissolution time but also based on their compatibility with the active substances, which were also shown to be mutually stable.

Pharmaceutical development of the finished product contains QbD elements. The applicant has stated the quality target product profile (QTPP) based on the above requirements and justified the identified critical quality attributes (CQA) of the finished product. A failure mode effects analysis (FMEA) was undertaken to identify potential critical process parameters (CPP) of the tablet manufacturing process and these were investigated experimentally. Multi-variate analysis of the CPPs was undertaken using a design of experiments (DoE) approach on development scale, but none of the factors investigated were shown to be critical. The identified factors were further investigated on commercial scale and finished product of acceptable quality was produced when the process was operated within the claimed operating ranges. Furthermore, the applicant has demonstrated that the process operated within the claimed conditions is capable of delivering drug product of all strengths in acceptable quality. The applicant's proposed PARs for each of the drug product manufacturing steps are therefore acceptable.

Bioequivalence for all strengths of the fixed dose combination product was demonstrated in comparison to the standalone parent formulations in a pivotal clinical bioequivalence study.

All of the chosen excipients are compendial and widely used in film-coated tablets. The excipients include microcrystalline cellulose, mannitol, povidone, magnesium stearate, crospovidone, hypromellose 2910, talc, titanium dioxide, iron oxide red, and iron oxide yellow. All the excipients are controlled in accordance with Ph. Eur. except for iron oxide red which is in accordance with quality standard 95/45/EC (E172).

The film-coated tablets are packaged in blisters comprised of PCTFE/PVC clear film with an aluminium foil push-through lidding material to seal the film surface. The materials comply with Ph. Eur. and EU regulation requirements.

Adventitious agents

Magnesium stearate is the only excipient potentially of animal origin. The applicant certifies that only magnesium stearate of plant origin is used in the finished product manufacture.

Manufacture of the product

The manufacturing process for Vipdomet is considered to be non-standard as defined in the CHMP guideline on non-standard processes (CPMP/QWP/2054/03), since the alogliptin benzoate is as low as 0.5% of the tablet weight, and is equivalent for all strengths. The holding time for bulk tablets before packaging has been justified based on stability.

A disintegration test is used by the applicant as a real time release test (RTRT) for the tablet cores. This method is compendial (Ph. Eur. 2.9.1, apparatus A), the applicant has demonstrated its equivalence to a standard dissolution test for each individual active substance, and its use is therefore deemed acceptable. The manufacturing process has been validated on commercial scale and in commercial equipment.

Product Specification

The finished product specifications for release and shelf-life are appropriate for film-coated tablets and include tests for: appearance (visual description and tablet dimensions), identification (HPLC and UV), related substances (HPLC), content uniformity (HPLC), disintegration (Ph. Eur. 2.9.1), assay (HPLC) and microbiological examination.

Batch analysis data from eighteen commercial scale batches, including three of each proposed strength of drug product, (and a further three each of different strengths which won't be commercialised, as supporting evidence), confirm the consistency of the manufacturing process and its ability to consistently produce finished product within the intended specifications.

Stability of the product

For all proposed commercial strengths, stability data from three commercial scale batches, stored in the proposed commercial packaging under long-term conditions (25 ºC / 60% RH) for up to 36 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to ICH guidelines were provided. Additionally, supportive stability data from three commercial scale batches of further strengths (not planned for commercialization) stored in the proposed commercial

packaging under long-term conditions (25 ºC / 60% RH) for up to 36 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to ICH guidelines were provided. Samples were tested for appearance, assay, related substances, alogliptin (*S*)-isomer, dissolution, moisture content, hardness, and microbiological content. The analytical procedures used were stability indicating. The only observed trend was a slight decrease in alogliptin assay, and a concomitant increase in related substances after 36 months under long term conditions and 6 months under accelerated conditions. However, measured values remain well within the proposed specifications. A slight increase in moisture content was also noted over time under both storage conditions, but since this has no effect on tablet hardness, microbial content, or dissolution profile, this test is not included in the finished product specifications.

Photostability studies were also performed according to ICH Q1B guidelines and revealed no significant changes in any of the tested parameters. Bulk tablet stability was also investigated in the proposed intermediate packaging. The trends observed were analogous to those observed for tablets in the final commercial packaging and therefore, the proposed bulk storage shelf-life is acceptable.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable. In addition, future commercial lots will be placed on stability annually, and the applicant will continue on-going stability studies on registration batches for the duration of the proposed shelf-life.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory manner. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The alogliptin/metformin fixed-dose combination (FDC) tablet containing alogliptin and metformin hydrochloride is being developed by Takeda for the treatment of type 2 diabetes mellitus (T2DM).

Alogliptin is a potent and highly selective inhibitor of the dipeptidyl peptidase (DPP)-4 enzyme that is being developed as an antihyperglycemic agent. Metformin improves glucose tolerance in patients with T2DM by lowering both basal and postprandial plasma glucose; reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; improves peripheral glucose uptake and utilization in muscle by increasing insulin sensitivity; delays intestinal absorption of glucose; and stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of all types of membrane glucose transporters (GLUT).

Alogliptin has been characterized in a battery of in vitro and in vivo pharmacodynamic, pharmacokinetic, and toxicologic studies. Alogliptin, as synthesized, exists predominantly as the (R)-enantiomer (>99%). In vivo chiral conversion to (S)-alogliptin is minimal. Alogliptin is metabolized to 2 metabolites, an N-demethylated metabolite (M-I) and an N-acetylated metabolite (M-II). M-I has DPP-4 inhibitory activity that is similar to alogliptin, whereas the (S)-enantiomer has minimal DPP-4 inhibitory activity, and M-II does not inhibit DPP-4 in vitro.

Pivotal toxicity and safety pharmacology studies were conducted in compliance with the good laboratory practice (GLP).

The intended clinical route of administration is oral; therefore, with the exception of an IV single dose toxicity study in rats, IV and paravenous tolerance studies in rabbits, and an IP micronucleus study in mice, alogliptin was administered orally (gavage or capsule) in the in vivo toxicological evaluations.

Non-clinical studies assessing immunotoxicity, including in vitro assessments for immune function and immunophenotyping of leukocyte populations, were not conducted with alogliptin.

Metformin is a member of the biguanide class of compounds, which includes phenformin and buformin, and was introduced into clinical practice for the treatment of T2DM in 1957. The mode of action for metformin is not fully understood; however, it is considered to be multifactorial, potentiating insulin action mainly through a post receptor mechanism resulting in a reduction in insulin resistance. Metformin is considered an insulin sensitizer since it lowers glucose levels without increasing insulin secretion.

Metformin pharmacodynamic information presented in this document was obtained from published literature. No new nonclinical studies were conducted with metformin alone to support this FDC submission.

To support an FDC of alogliptin and metformin primary pharmacodynamic studies were conducted to evaluate the effects of concomitant treatment with alogliptin and metformin in diabetic rat models. Additionally, a pharmacodynamic drug interaction study evaluated the effects of treatment with alogliptin, pioglitazone, and metformin combined.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

Alogliptin

In vitro Pharmacodynamic assays

The primary pharmacological activity of alogliptin was determined in various enzyme assays. The target enzyme, dipeptidyl peptidase-4, was inhibited i*n vitro* by alogliptin with an IC_{50} (nM) ranging from 6 to 18 depending on source of enzyme. The assays demonstrated that alogliptin is a potent and specific inhibitor of rat, dog, and human DPP-4 activity. Similar to alogliptin, the M-I metabolite is equipotent and a selective inhibitor of DPP-4. No inhibitory activity was noted for M-II, while weak DPP-4 inhibition was noted for the (*S*)-enantiomer of alogliptin. The R-enantiomer is 1000-times more active than the (*S*)-enantiomer.

An assay comparing the potency and selectivity of alogliptin with other DPP-4 inhibitors (vildagliptin and sitagliptin) showed that alogliptin was more potent, and generally more selective; mean IC50 values for DPP-4 inhibition for alogliptin, vildagliptin, and sitagliptin were 6.9 nmol/L, 23.8 nmol/L, and 12.1 nmol/L, respectively.

In Vivo Primary Pharmacodynamic Assays

The effects of alogliptin on DPP-4 activity were assessed in normal, euglycemic animals and in various animal models of T2DM. These in vivo studies evaluated the effects of alogliptin on diabetic parameters such as GHb, glucose tolerance, and plasma glucose and insulin levels, as well as effects on endocrine pancreatic function and morphology. In vivo, alogliptin was pharmacologically active in normoglycemic mice, rats, dogs, and cynomolgus monkeys and in mouse and rat models of T2DM. Alogliptin improved glucose tolerance and increased plasma insulin levels in normal mice.

A single dose of alogliptin to wild-type C57BL/6 mice decreased the normalized plasma glucose area under the plasma concentration-time curve from time 0 to 90 minutes (AUC(0-90min)) to 75% of control values and increased plasma insulin levels to 146% of control values. When administered in the diet to diabetic *ob*/*ob* mice for 4 weeks, alogliptin decreased GHb and increased plasma insulin levels, plasma insulin/glucose ratio, and pancreatic insulin levels.

In established rat models of T2DM, female Wistar fatty rats and nonobese N-STZ-1.5 rats, alogliptin produced a dose-dependent improvement in glucose tolerance and a dose-dependent increase in plasma immunoreactive insulin (IRI) levels.

Oral administration of alogliptin to normal cynomolgus monkeys increased insulin and GLP-1 levels and decreased glucagon levels with no notable effect on plasma glucose.

Alogliptin increased pancreatic insulin content in ob/ob mice and male N-STZ-1.5 rats. Immunohistochemical analyses of pancreatic β-cell and α-cell morphology in the ob/ob mice following 4 weeks of daily exposure to alogliptin revealed increased staining of the β-cells for insulin-like immunoreactivity. Apparent changes in β-cell number and size in the islets could not be

detected, suggestive of a lack of β-cell proliferation or hypertrophy. There were no apparent changes in α-cell morphology.

Metformin

The regulatory effects of metformin on glucose involve suppression of hepatic glucose output, increased peripheral glucose utilization, reduced fatty acid utilization, and increased glucose turnover, particularly in the splanchnic bed. In addition, metformin alters glucose handling by erythrocytes and reduces hypertriglyceridemia. The primary route is via decreased hepatic glucose production (gluconeogenesis). Studies in isolated, perfused livers and hepatocytes from animals show that metformin acts directly in the liver to reduce gluconeogenesis from a range of substrates including lactate, pyruvate, alanine, glutamine, and glycerol. In addition to this effect, metformin also reduces hepatic glucose output by decreasing the overall rate of glycogenolysis; in diabetic mice, metformin increased glycogen synthase and glycogen phosphorylase in the liver indicating increased glycogen turnover. Both gluconeogenesis and glycogenolysis probably reflect, in part, a suppressive effect by metformin on hepatic glucagon activity.

Metformin increased insulin-stimulated glucose utilization, mainly in skeletal muscle, under conditions of hyperglycaemia and/or insulin resistance. Metformin is found in high concentrations in the wall of the small intestine and may decrease intestinal absorption, thereby affecting postprandial hyperglycaemia. Metformin reduces the rate of fatty acid oxidation which correlates approximately with suppression of hepatic glucose production; this suggests that reduced fatty acid oxidation contributes to reduce gluconeogenesis. Metformin also reduces circulating triglyceride levels in hypertriglyceridemic patients resulting in reductions in triglyceride levels reduce insulin resistance.

At the cellular level, metformin increases the functional activity of glucose transporters (GLUT-1 and GLUT-4) and influences membrane events affecting tyrosine kinase activity that leads to the augmentation of a range of insulin signals. The glucose lowering effect of metformin has been demonstrated in STZ-induced diabetic mice, normal and mildly hyperglycemic rats, insulin-resistant Zucker rats, and normal dogs.

2.3.2.2. Secondary pharmacodynamic studies

Alogliptin

Secondary activity of alogliptin at concentrations of 1 and 10 µmol/L was evaluated *in vitro* in receptor binding assays and enzyme activity screening. At the high concentration alogliptin caused a 50% inhibition of naloxane binding at the opioid receptor in the rat cerebral cortex. No activity equal to or exceeding 50% was evident on other receptors, ion channels or enzymes.

GLP-1 has been associated with decreased gastrointestinal (GI) motility and appetite. In vivo studies have shown that a single dose of alogliptin is effective in lowing plasma glucose levels, increasing plasma intact GLP-1 levels, and increasing plasma IRI levels in Wistar fatty rats. However, in this same strain (Wistar fatty rat), exposure to alogliptin for 8 consecutive weeks did not produce notable changes in body weight or in metabolic indices. Plasma total cholesterol (TC) was statistically decreased ($p \leq 0.025$) at the highest dose evaluated (10 mg/kg/day). Unlike the

DPP-4 inhibition that occurred in this model after a single dose of alogliptin, only minimal DPP-4 inhibition was observed after 8 consecutive weeks of treatment.

A study to investigate effect of alogliptin or metformin on xylose absorption in male Wistar fatty rats was conducted. Metformin or alogliptin (1 mg/kg) were administered 1 hour prior to xylose challenge. No effect of alogliptin on xylose absorption was noted while metformin dose-dependently inhibited xylose absorption.

Metformin

Cardiovascular pathology is the major determining factor of morbidity and mortality in type II diabetic patients. Metformin appears to possess potentially beneficial vascular properties, in addition to an effect on serum lipid profiles. In the United Kingdom Prospective Diabetes Study, metformin was found to be associated with reduced macrovascular complications and all-cause mortality in overweight type II diabetic patients. Studies in animal models of T2DM demonstrated the vasculoprotective effects of metformin. Anti-ischemic effects have been demonstrated in non-diabetic hamsters, rats, and humans. The beneficial effects in both diabetic and non-diabetic subjects indicate that the effect is independent of the antihyperglycemic activity of metformin. A model of ischemia in rabbit hearts showed that both metformin and pioglitazone have a cardioprotective effect mediated by nitric oxide (NO).

Regarding the antihypertensive effects of metformin, most studies in animals have been positive showing a reduction in various models of hypertension, but results in diabetic and non-diabetic human subjects have been less clear cut. A hypotensive response for metformin (administered IV) in hypertensive and normotensive rats, suggested withdrawal of sympathetic activity.

Metformin reduces triglyceride, total cholesterol, and free fatty acid levels in patients with type II diabetes. In animal models of atherosclerosis, metformin shows anti-atherogenic properties. Several mechanisms appear to be involved including a reduction in lipid accumulation in the arterial wall, and cellular events including inhibition of leukocyte-endothelial interaction, foam cell formation, smooth muscle proliferation, and platelet aggregation.

2.3.2.3. Safety pharmacology programme

Alogliptin

The potential of alogliptin to elicit unintended pharmacological activity in non-target systems has been investigated. With the exception of preliminary, investigative hERG assays with the HCl and TFA salts and the action potential duration assay; the core safety pharmacology studies were conducted in compliance with GLPs.

Central Nervous System

Alogliptin is unlikely to have untoward pharmacologic activity in the central nervous system (CNS). Although alogliptin inhibited naloxone binding at nonselective opioid receptors in vitro in the rat cerebral cortex, it did not show any binding affinity for human receptors typically associated with abuse potential (human recombinant μ, κ, δ opiate receptors). In vivo, no noteworthy

alogliptin-related effects on general behavior and activity were observed in rats at doses of up to 300 mg/kg/day for 4 consecutive weeks. The evaluations were performed at day -1, day 1 and day 25 and included open-field observations, forelimb and hindlimb grip strength, hindlimb splay and pain perception.

Respiratory and Cardiovascular Systems

Alogliptin is not expected to interfere with respiratory or cardiovascular function at the proposed clinical dosage of 25 mg/day. The IC50 value for the in vitro inhibition of human *ether a-go-go*-related gene (hERG) channel currents by alogliptin was >30 μmol/L. At concentrations up to 30 μmol/L, alogliptin did not delay action potential repolarization in isolated canine Purkinje fibers, and no alogliptin-related effects on resting membrane potential, action potential amplitude, or the maximum rate of depolarization were noted. The sensitivity of these in vitro assays was confirmed by the appropriate positive controls.

Alogliptin had no effect on body temperature, heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), or electrocardiogram (ECG) parameters (PR or RR intervals, QRS duration, QT interval or corrected QT interval [QTc] value) in telemetrized beagle dogs given oral gavage doses of up to 25 mg/kg. No alogliptin-related cardiovascular effects were noted in dogs in the repeat-dose toxicity studies at oral doses of up to 200 mg/kg/day for up to 39 weeks.

Alogliptin did not affect cardiac troponin (I or T isoform) concentrations in dogs. The 200 mg/kg/day dose to beagle dogs for 26 weeks provides an estimated exposure margin of alogliptin, based on area under the plasma concentration-time curve from time 0 to 24 hours (AUC(0-24)), of approximately 227-fold higher than the clinical dose of 25 mg/day.

Respiratory function of rats administered a single oral dose of 10 to 100 mg/kg alogliptin was unaffected.

Metformin

No formal safety pharmacology studies have been performed on metformin. No such studies are considered necessary in view of the extensive clinical experience accumulated over several decades of use. Lactic acidosis has been shown to be a risk with the biguanides, which may arise because of increased lactate production (hypoxia) or decreased elimination. However, among patients taking metformin, lactic acidosis is of very rare occurrence.

2.3.2.4. Pharmacodynamic drug interactions

Alogliptin

Because T2DM is a progressive disease, combination therapies are used to achieve better glycemic control. Combination treatment with alogliptin, which stimulates insulin secretion, and pioglitazone, which enhances insulin sensitivity or with alogliptin and glibenclamide, which enhances insulin secretion, could augment their effects on glycemic control. Similarly, combination treatment with alogliptin and metformin or alogliptin and voglibose, therapeutic agents that affect intestinal glucose absorption, may provide better efficacy than treatment with either agent alone.

Combined treatment with alogliptin and pioglitazone to db/db mice resulted in additive decreases in plasma GHb levels, plasma triglyceride (TG) levels, plasma nonesterified fatty acid (NEFA) levels, and plasma glucose area under the plasma concentration time curve (AUC) values, and an additive increase in the insulinogenic index. This treatment synergistically decreased plasma glucose and synergistically increased pancreatic insulin content and, immunohistochemical analyses of pancreatic tissues revealed intense expression of insulinlike immunoreactivity (IR), normal β-cell/α-cell distributions, and overall expression of insulin promoter transcription factor (pdx-1)-like IR. Combined treatment with alogliptin and pioglitazone in ob/ob mice additively decreased GHb, fed and fasting plasma glucose levels, and plasma NEFA and additively increased plasma insulin, fed and fasting plasma/insulin glucose ratios, and pancreatic insulin content. Additionally, treatment with alogliptin alone or in combination with pioglitazone decreased plasma glucagon levels.

Combination treatment with alogliptin and glibenclamide to N-STZ-1.5 rats additively decreased plasma glucose levels and additively increased plasma insulin levels.

Combined treatment with alogliptin and voglibose to db/db mice additively decreased plasma DPP-4 activity, synergistically increased plasma intact GLP-1 levels and pancreatic insulin content, and additively prevented deterioration of glycemic control while additively preserving plasma insulin levels. Immunohistochemical analyses of the pancreatic tissue from these mice showed that combination treatment with alogliptin and voglibose effectively preserved islet architecture and islet cell composition in db/db mice.

Metformin

Changes in mean arterial pressure (MAP) and heart rate (HR) occurred during IV metformin administration concomitant with administration of an α-adrenergic (phentolamine), β-adrenergic (propranolol), muscarinic (atropine), ganglionic (hexamethonium), NO synthase (NG-methyl-L-arginine acetate salt), or combination ganglionic plus α-adrenergic plus β-adrenergic blockade in spontaneously hypertensive rats. The hypotensive actions of metformin in spontaneously hypertensive rats were abolished and reversed into pressor responses by hexamethonium, phentolamine, or by combination ganglionic plus adrenergic blockade. Neither propranolol, nor atropine, nor NG-methyl-L-arginine acetate salt affected hypotensive responses to metformin. Acute IV metformin administration decreased MAP by causing withdrawal of sympathetic activity. The increase in MAP uncovered by hexamethonium and phentolamine suggested that the original depressor response to metformin is buffered by mechanisms unrelated to the autonomic nervous system.

Alogliptin combined with metformin

Combination treatment with alogliptin and metformin to Wistar fatty rats additively decreased plasma glucose, synergistically increased plasma active GLP-1 levels, and enhanced insulin secretion. In Wistar fatty rats, combination treatment with alogliptin and metformin or pre-treatment with pioglitazone followed by treatment with alogliptin or metformin decreased the plasma glucose AUC(0-120min) by 37% to 38% and, pre-treatment with pioglitazone followed by treatment with alogliptin and metformin combined, decreased the plasma glucose AUC(0-120min) by up to 55%.

2.3.3. Pharmacokinetics

2.3.3.1. Performed studies

Alogliptin

The pharmacokinetics of alogliptin were determined after oral or IV administration to rats, dogs and cynomolgus monkeys. The disposition of 14C-alogliptin was studied in rats and dogs. Plasma protein binding in mouse, rat, dog and human plasma was determined in vitro, and tissue distribution (including distribution to the eyeball and the placenta) of 14C-alogliptin was evaluated in rats. The absorption, distribution, metabolism, and excretion of alogliptin and its metabolites were studied in rats and dogs. The biotransformation of alogliptin was investigated extensively in vitro and in vivo in rats and dogs. A milk excretion study was also conducted in rats. Non-clinical pharmacokinetic and metabolism studies used formulations that were similar, or identical, to those used in toxicology and pharmacodynamic studies.

The kinetics of alogliptin were also investigated when co-administered with pioglitazone and metformin. The effect on the kinetics of the combination of alogliptin with sulphonylurea or triple therapies was not investigated in the pre-clinical species.

Validated LC-MS-MS methods having acceptable linear range, LLOQ, intra assay accuracy and precision were used to analyse Alogliptin, Alogliptin M-I and Alogliptin M-II in mouse plasma, rat plasma, rat fetal serum, rat milk, rabbit plasma, dog plasma or monkey plasma. Acceptable and validated methods were also developed for analysis of (S)-alogliptin in rat and dog plasma.

For LC/MS/MS assays, alogliptin-d4 TFA salt and M-I-d4 were used as the internal standards for quantitation of alogliptin and M-I.

For rat metabolism studies, a bioanalytical method based on HPLC with liquid scintillation detection and counting of radioactivity was used.

Metformin

Metformin has been approved in the European Union for over 50 years for the treatment of type 2 Diabetes Mellitus. Therefore, only few publications relating to the non-clinical pharmacokinetics of metformin have been found in literature searches. The pharmacokinetic properties from literature searches were presented and discussed. Analysis of metformin was performed using validated and acceptable analytical methods.

Alogliptin combined with metformin

No new non-clinical pharmacokinetic studies on the combination of alogliptin and metformin were conducted.

2.3.3.2. Absorption

Alogliptin

Caco-2 permeability

Alogliptin has low permeability as the apparent permeability (P_{app}) coefficients were comparable to those of mannitol, which is a reference compound for low permeable compounds. The P_{app} ratios were different at each time point (1 and 2 hours) and were relatively low compared with those of digoxin. Therefore, the involvement of P-glycoprotein in the transport of alogliptin was not clear in a Caco-2 assay but expected to be limited.

Single-dose pharmacokinetics

The single-dose pharmacokinetics of alogliptin was studied in rats, dogs, monkeys and humans via PO and IV routes of administration.

Alogliptin was absorbed in rats, dogs and monkeys following PO dose administration. The oral bioavailability of alogliptin in the non-clinical species evaluated differed across species 41-45% in rats, 69-85% in dogs and 72-88% in monkeys. Studies with radiolabeled alogliptin benzoate showed an oral absorption ratio of 61.1% in rats and 88.6% in dogs based on $AUC_{0\text{-}24hr}$ values. In rats, ~30% of the dose radioactivity was absorbed via the jejunal loop within 2 hours after administration of ^{14}C-alogliptin benzoate (3 mg freebase/kg) into the jejunal loop suggesting that the jejunum is one of the major absorption sites in rats.

Alogliptin was poorly absorbed (<0.1% at 24 hours post-dose) via the lymph after a single PO administration of 3 mg free base/kg radiolabeled alogliptin to rats.

The terminal elimination half-life (T½) of alogliptin after IV administration was a little bit shorter in rats and dogs (1.1-1.4 hours and 1.5-2.9 hours, respectively) when compared to monkeys (5.7 hours). In studies with PO (3 mg/kg) or IV (1 mg/kg) administered ^{14}C-alogliptin, the half-life of the measured radioactivity was found to be 4.9 and 3.4 hours after oral and IV dosing, respectively, in rats and 6.7 and 5.3 hours, respectively, in dogs. The volume of distribution of alogliptin after IV dosing was ~2.6 – 3.9 L/kg in all pre-clinical species used. Plasma clearance values were higher in rats (~3.0 – 3.3 L/kg/hr) and dogs (~1.3 – 2.4 L/kg/hr) than in monkeys (~0.5 L/kg/hr).

After a single PO administration of alogliptin benzoate in male rats and dogs, C_{max} and $AUC_{0\text{-}24hr}$ values increased dose-proportional between 0.3 to 3 mg/kg in dogs, and more than dose-proportional between 3 to 30 mg/kg in dogs and between 3 to 100 mg/kg in rats. T_{max} and T½ values were generally constant over the tested dose range, but in dogs T½ was lower (~2-fold) at 0.3 mg/kg and T_{max} higher (~3-fold) at 30 mg/kg compared to the other doses tested.

Among the several salts of alogliptin that were evaluated, the benzoate salt showed the best bioavailability in rats and dogs. Therefore, it was selected for toxicity studies.

Repeated-dose pharmacokinetics of alogliptin and its metabolites (M-I & M-II)

The repeated-dose pharmaco- and toxicokinetics of alogliptin were determined after repeated PO dosing in mice, rats, dogs and monkeys. Alogliptin was rapidly absorbed in all species studies.

In mice and monkeys, exposure to alogliptin was generally dose-proportional. For male mice, the exposure was higher than expected at the 200 mg/kg dose leading to dose non-proportionality on visual inspection, which was the result of the high, but largely variable plasma concentrations at 8 hours and 12 hours post-dose on Day 1 and Day 90, respectively. In rats and dogs, the increase in alogliptin exposure was more than dose-proportional. In addition, there was an increase in T½ at increasing dose in rats.

In general, no significant accumulation of alogliptin was observed in mice and monkeys after repeated dosing with alogliptin. In rats, accumulation of alogliptin was observed with accumulation ratios mostly in the range of 1.7-2.8. In dogs, a slight accumulation was seen for alogliptin after repeated dosing with accumulation ratios ranging between 1.1 and 1.7.

As only up to 1% of alogliptin will be present in vivo as [S]-alogliptin, its pharmaco- and toxicokinetics will not influence the pharmacological effects of alogliptin.

Less than ~3.2% of alogliptin was converted to M-I in mice at all dose levels when the AUC values were compared and decreased with increasing dosages. On the other hand, in rats, the metabolite-to-parent ratio (in %) was maximally 33.8% with lower contribution of the metabolite to total exposure at increasing dosage. The elimination of M-I in rats seemed to be saturable since its T½ increased with increasing dose. Following a low oral dose of 10 mg/kg alogliptin, the 24-hour total exposure to M-I was 76 and 85% of that to the parent drug in female and male dogs, respectively. With increasing dose, the contribution of the metabolite exposure decreased (to 20-40%). A saturable formation of the metabolite may be responsible for the decrease of M-I contribution with increasing dose. The 24-hour total exposure to M-I in monkeys was 11 and 12.6% of that to the parent drug for females and males, respectively, at the low dose and decreased to 2.5 and 1.6%, respectively, at the high dose suggesting saturation of metabolism.

No significant accumulation of M-I was observed in mice, rats, dogs and monkeys after oral repeated dosing with alogliptin.

In all species for which data on M-II was present, $AUC_{0\text{-}24hr}$ values showed that M-II was only formed to a small extent: 0.5% in monkeys and <3% in rats. In rats, slight accumulation occurred at all dose levels except at 400 mg/kg/day in male rats with accumulation ratios up to ~2.6. In monkey, no accumulation of M-II was observed.

Repeated-dose pharmacokinetics in pregnant animals

Pregnancy had an impact on total exposure of alogliptin in pregnant rats and rabbits leading to differences in exposure to alogliptin and alogliptin metabolites most likely due to increases in distribution volume and differences in elimination.

After oral dosing with 250, 500 and 1000 mg/kg in pregnant rats, T_{max} and systemic exposure of alogliptin were generally higher on gestation day (GD) 17 compared to GD6. Plasma half-life was generally ~2.2 to 4 hours, but was ~49 hours at the highest dose on GD6 and not determinable on GD17.

In pregnant rabbits, exposures were slightly lower on GD6 than on GD18 at doses of 100 and 200 mg/kg but comparable at higher doses of 500 and 700 mg/kg which may indicate less absorption at the late stage of gestation for higher doses.

Repeated-dose pharmacokinetics in juveniles

The toxicokinetic effects of alogliptin in juvenile rats were assessed in an oral 4-week and 8-week toxicity study with dose levels of 30, 100 and 300 mg/kg. $AUC_{0\text{-}24hr}$ values for alogliptin and M-II increased more than dose-proportional with increases in dose and $AUC_{0\text{-}24hr}$ values for M-I less than dose-proportional with dose, and tended to increase with repeated doses (up to max. ~3-fold).

Pharmacokinetics when concomitantly administered with metformin or pioglitazone

The combination treatment of alogliptin and metformin was investigated in one single-dose study and in two repeated-dose toxicity studies of 4 and 13 weeks, respectively. No effects on the toxicokinetics of metformin were observed when co-administered with alogliptin. The effects of concomitant treatment with alogliptin and pioglitazone on the toxicokinetic parameters of both compounds were assessed in a single-dose and two repeated-dose studies for 4 weeks and 13 Weeks, respectively. These studies showed no toxicokinetic interactions regarding the kinetic parameters of alogliptin.

Metformin

Uptake of metformin was facilitated by over-expression of hOCT1 and hOCT2 and showed saturable processes, indicating that metformin is a substrate of these transporters. The inhibitory effects on metformin uptake by OCT-inhibition were greater for hOCT2 than for hOCT1. In vivo, plasma concentrations of metformin were elevated only by the co-administration of tetraalkylammoniums with higher affinities for OCTs (Choi et al. 2007a).

The pharmacokinetics of metformin in rats after IV and oral administration were determined by Choi et al. (2006a). After oral administration, absorption of metformin from the gastro-intestinal (GI) tract was rapid with Tmax being 15-120 minutes. Absolute bioavailability values of metformin were low, ~30-34%, which was mainly due to considerable GI tract first-pass effects. The intestinal and gastric first-pass effects of metformin were ~32 and 24% of dose. AUC values of metformin were dose-proportional between among doses of 50 and 200 mg/kg independent of the route of administration. Total clearance and volume of distribution, determined after IV administration, were ~25 ml/min/kg and 0.6 L/kg, respectively.

After administration of oral and IV doses of metformin to alloxan-induced diabetic and normal male Wistar rats, the serum concentrations of metformin followed a 2-compartment open model of absorption for both IV and oral administration. Peak serum concentrations of metformin after oral doses of 100 and 200 mg/kg were of the order of 9 and 15 µg/mL, respectively in normal rats and 10 and 25 µg/mL, respectively in diabetic rats. Following oral administration, the extent of absorption ranged from 31 to 59% in alloxan rats and 14 to 19% in normal rats. The apparent volume of distribution was calculated to be in the region of 0.6 L/kg for both normal and diabetic rats (Kakemi et al., 1983).

In the study of Stepensky et al. (2002) intraduodenal administration produced larger response than intraportal metformin infusion, and the lowest response was observed following IV administration, despite the similarity in the concentration-time profiles obtained for different routes of metformin administration. This finding indicates that a significant first-pass effect, which occurs in the pre-systemic sites of action, contributes to the overall glucose-lowering response of metformin.

The study of Chou (2000) revealed that hepatic uptake is rate-limited by a permeability barrier and although metformin is accumulated in the liver, the organ does not extract it.

2.3.3.3. Distribution

Alogliptin

Protein binding

In vitro plasma protein binding of alogliptin was studied in mice, rats, dogs and humans. The results indicate that alogliptin has low protein binding (<60% in all species) and was concentration dependent. Plasma protein binding of M-I was also low (<40% in all species).

Red blood cell partitioning

Following PO administration of 3 mg free base/kg ^{14}C-alogliptin benzoate to rats, concentrations of radioactivity in red blood cells were 35% to 41% and were almost constant from 1 to 24 hours post-dose. In dogs, the distribution ratio of radioactivity into blood cells constantly decreased from 1 to 8 hours post-dose from 38% to 23% when dosed with 3 mg free base/kg ^{14}C-alogliptin.

Tissue distribution

Distribution was studied in rats following PO administration of a single dose of ^{14}C-alogliptin benzoate (3 mg freebase/kg) to male albino and male pigmented rats. Radioactivity was absorbed rapidly with most matrices reaching Cmax at 4 hours post dose. In albino rats, the tissues with the highest mean Cmax values at 4 hours, excluding the gastrointestinal (GI) tract tissues, were kidneys, liver, lungs, pituitary gland, and submaxillary glands. The tissues with the lowest Cmax values were brain and spinal cord. By 72 hours post dose, concentrations of radioactivity were low in all tissues except the kidneys.

In pigmented rats, the concentrations of radioactivity in the plasma showed a similar profile to that in albino rats. The concentrations of radioactivity in the eyes of pigmented rats, however, were much higher than those in the eyes of albino rats. These results suggest that alogliptin-related materials have an affinity to melanin and Alogliptin accounted for most of the residual radioactivity in sclera of pigmented rats after a single PO administration of ^{14}C-alogliptin benzoate.

Placental transfer

On gestation day (GD) 18, pregnant rats were administered ^{14}C-alogliptin benzoate (3 mg free base/kg) via PO (322-00246). Radioactivity was quickly absorbed and C_{max} was reached at 4 hours.

The C_{max} of total radioactivity in fetal tissues (136 ng equiv/g) was lower than the corresponding value in maternal plasma (191 ng equiv/g). The C_{max} of total radioactivity in placenta was higher (639 ng equiv/g) than that in maternal plasma.

Elimination of total radioactivity in fetal plasma, amniotic fluid, and fetal tissues was rapid (0.004, 0.002, 0.003 ng equiv/g at 24 hours post-dose, respectively). The concentration-time profiles of radioactivity in the fetuses and fetal plasma were parallel to those in the maternal plasma. The radioactivity in the placenta was higher than that in maternal plasma or in amniotic fluid. However, elimination of total radioactivity in placenta was also rapid. The concentrations of radioactivity in the fetuses and fetal plasma were lower than those in the maternal plasma at all the time points examined, suggesting that the transfer of radioactive compounds from the maternal side to the fetal side was quantitatively restricted by placental passage. Based on these results, it can be concluded that ^{14}C-alogliptin-derived radioactivity is able to cross the blood-placental barrier.

Metformin

Protein binding

The plasma protein binding of metformin was very low. In rat plasma, only about 15% was reported to be protein bound *in vitro* (Choi et al., 2006).

Red blood cell partitioning

In rat blood, metformin is slightly more distributed into plasma than into red blood cells. The equilibrium plasma-to-blood cells partition ratios of metformin were independent of initial blood metformin concentrations in the concentration range of 1 to 20 µg/mL (Choi et al., 2006).

Tissue distribution

Mehnert (1969) found that, in mice, the highest concentrations of metformin were observed in the liver, kidney, adrenals and pancreas. Metformin was not bound to serum protein in blood.

In the Wilcock and Bailey study (1994), tissue accumulation of metformin was examined after oral administration to normal and STZ diabetic mouse. Administration of 50 mg/kg radiolabeled metformin via intragastric gavage resulted in maximum plasma concentrations at 0.5 hours, which declined to <5% of maximum by 24 hours. The greatest accumulation of metformin occurred in tissues of the small intestine, where maximum concentrations were reached at 0.5 to 2 hours, but declined to <2% of maximum by 24 hours. High concentrations were also noted in stomach, colon, salivary gland, kidney and liver, which accumulated metformin more than 2-fold, and concentrations of the drug in heart and skeletal muscle were greater than plasma concentrations on some occasions up to 8 hours.

In a normal mouse IV study, IV bolus administration of 50 mg/kg metformin produced a maximum inferior vena cava plasma concentration at 0.5 hours, which declined rapidly at 4 hours. Metformin was selectively accumulated by tissues of the small intestine, with maximum values noted at 0.5 hours. Thus, retention of metformin by tissues of the small intestine may represent a deep compartment for the drug (Wilcock and Bailey, 1994).

Distribution into the liver

The subcellular localization of metformin in livers of 18 hour fasted rats treated orally with 50 mg/kg ^{14}C-metformin was studied by Wilcock (1991). Sequential determination of ^{14}C-radioactivity showed that maximum concentrations of metformin in plasma (15 µmol/L) and liver (50 µmol/kg) were achieved at 60 and 30 minutes, respectively, and approximately half-maximal concentrations were achieved at 4 hours. The higher concentration in liver compared with plasma suggests that metformin enters hepatocytes via a specific mechanism, and is distributed mainly within the cytosol.

2.3.3.4. Metabolism

Alogliptin

Alogliptin was stable in all metabolic systems investigated (human, rat, dog, and monkey cryopreserved hepatocytes and rat, dog, monkey, and human liver microsomes) with the exception of dog and rat hepatocytes (approximately 50% and 65% of the parent compound remained after 2-hour incubation with dog and rat hepatocytes, respectively).

Identification of the metabolites showed that alogliptin is considered to be biotransformed to M-I by N-demethylation, and to M-II by acetylation of the amino group. M-I is an N-demethylated metabolite and a pharmacologically active metabolite with a DPP-4 inhibitory activity similar to that of alogliptin (IC50: 14 and 10 nmol/L, respectively in human plasma). M-II is an N-acetylated metabolite and has no DPP-4 inhibitory activity and thus a pharmacologically inactive metabolite.

Both M-I and M-II are minor human metabolites with an exposure to these 2 identified minor metabolites in plasma, relative to unchanged drug, of <1% and <6%, respectively. All metabolites found in humans were also found in rats and dogs and there are thus no unique human metabolites of alogliptin.

When the exposure to M-I was compared following oral (gavage) administration of alogliptin to Sprague Dawley rats, beagle dogs and monkeys during a 28-day toxicity study Cmax levels of M-I were found to be much higher in dogs (day 26) as compared to rats (day 28) and monkeys (day 1).

The in vivo chiral conversion of [R]-alogliptin to [S]-alogliptin was negligible (<1%) in rats and dogs in both plasma and urine samples.

Metformin

Metformin was reported as not being metabolized in all species. However in a recent study of Choi et al. (2006b), it was shown that metformin is metabolized by CYP2C11, CYP2D1 and CYP3A1/2 in rats as demonstrated by concomitant administration with relevant CYP inhibitors and inducers.

2.3.3.5. Excretion

Alogliptin

Following PO administration of ^{14}C-alogliptin benzoate to rats and dogs, the major route of elimination of total radioactivity was via the feces in both species.

In rat alogliptin and M-I were the major components in the urine and feces, M-II was a minor component in feces. A study to evaluate the potential enterohepatic recirculation of alogliptin indicated that alogliptin-related radioactivity undergoes some enterohepatic recirculation in rats. In dogs alogliptin and M-I were the major components in urine and feces and M-II was not detected.

After PO administration of ^{14}C-alogliptin benzoate (3 mg freebase/kg) to lactating rats on Lactation Day (LD) 14, the concentrations of radioactivity in the plasma reached a maximum of 0.170 µg equiv/mL at 0.5 hours post dose and rapidly decreased to 0.006 µg equiv/mL at 24 hours post dose, followed by a gradual decrease to 0.003 µg equiv/mL 48 hours postdose. The concentrations of radioactivity in the milk reached a maximum of 0.316 µg equiv/mL at 0.5 hours postdose and rapidly decreased to 0.012 µg equiv/mL at 24 hours postdose, followed by a gradual decrease to 0.003 µg equiv/mL at 48 hours postdose. These results indicate that alogliptin and its related compounds were secreted into the milk of lactating rats after a single PO administration of ^{14}C-alogliptin benzoate.

Metformin

Twenty-four hours after oral administration of 100 mg/kg of labelled metformin to mice, about 75% of activity can be recovered in the urine and approximately 10% in the faeces. Rats excrete about 10% less in the urine and, therefore more in the faeces. Less than 1% of the radioactivity was found in the bile. Unchanged metformin was the only substance which appeared in the urine of rats and mice (Mehnert, 1969).

2.3.3.6. Pharmacokinetic drug interactions

Alogliptin

In vitro, alogliptin is a weak direct CYP2D6 inhibitor at concentrations ≥40 µM (=~14 µg/mL). Metabolism-dependent inhibition of CYP3A4/5 was observed for alogliptin with an IC_{50} value of 78 µM (=~26 µg/mL). These concentrations are however much higher than the human C_{max} of 0.483 µg/mL reached after a 100 mg dose, which is four times higher than the clinical recommended dose of 25 mg. Therefore, alogliptin is not expected to be an inhibitor of CYP2D6 and CYP3A4/5 *in vivo* in humans as is underlined by the results of the clinical drug-drug interaction study with midazolam (CYP3A4) and dextromorphan (CYP2D6). CYPs 1A2, 2C8, 2C9, 2C19 were not inhibited in vitro by alogliptin as is supported by the observation that alogliptin does not interact with rosiglitazone, glyburide or glipizide.

Induction of CYP enzymes by alogliptin was only observed for CYP3A4/5 at a concentration of 100 µM based on testosterone 6ß-hydroxylase activity, although this was not statistically significant. However, the induction potential was about a fourth of the effectiveness of the known inducer

rifampin, and no induction was observed clinically. Therefore, no CYP induction is expected in humans.

The applicant investigated if alogliptin is an in vitro inhibitor of OAT1, OAT3 and OCT2. The study included both control cells and cells transfected with the specific transporter of interest. Further, the used probe substrates (PAH, E3S and metformin) and positive control inhibitors (probenecid, probenecid and quinidine) are appropriate. No clinically relevant inhibition by alogliptin (based on its Cmax of 0.3 µM) was seen for any of the investigated transporters.

The inhibitory effect of alogliptin on BCRP was examined using BCRP expressed cells. After incubation of [3H]prazosin (0.01 µmol/L), a substrate for BCRP, at 37°C with alogliptin at concentrations of 0, 0.3, 1, 3, 10, 30, and 100 µmol/L, the Papp ratios of [3H]prazosin (0.01 µmol/L) were 12.5, 12.6, 11.2, 12.0, 10.6, 12.8, and 11.9×10−6 cm/sec across the BCRP-expressing cells, and were 1.3, 1.3, 1.2, 1.3, 1.2, 1.3, and 1.3×10−6 cm/sec across the control cells, respectively. The corrected Papp ratios were 9.6, 9.7, 9.3, 9.2, 8.8, 9.8, and 9.2, respectively. These results suggest that alogliptin had no inhibitory effect on BCRP-mediated efflux activity. Therefore, alogliptin is not an inhibitor of BCRP.

No in vitro studies were performed with MATE and OATP. A clinical study was performed to study the interaction potential between alogliptin and cyclosporine (inhibitor of OATP1B1/OATP1B3, BCRP and P-glycoprotein). Whether alogliptin is a substrate and/or an inhibitor of MATE1 and MATE2 was investigated in a clinical study in healthy volunteers with cimetidine and metformin. (Please see clinical pharmacology section for further details)

Metformin

Although metformin is mainly excreted unchanged via urine, limited metabolism by CYP2C11, 2D1 and 2A1/2 occurs in the rat. Several studies in rat have demonstrated that metformin kinetics may be altered in disease models, for example where hepatic expression levels of these CYPs are changed, e.g. streptozotocin induced diabetes in rats or challenge of E. coli LPS or with Klebsiella pneumoniae endotoxin in rats (Choi et al., 2007b; Cho et al., 2009; Choi et al., 2008), or where rats suffered from acute renal failure (Choi et al., 2010). Further, altered body functions due to lifestyle may affect the pharmacokinetics of metformin by increasing hepatic OCT1 expression in mice fed a high-fat diet (Jang et al., 2010) or by decreased urinary excretion due to dehydration in rats (Choi et al. 2007c). Another study showed that swimming before administration of metformin significantly improved insulin sensitivity and the rate of metformin absorption in insulin-resistent rats (Chien et al., 2008).

2.3.4. Toxicology

The safety of alogliptin has been investigated in a battery of nonclinical toxicity studies including single- and repeat-dose toxicity studies in mice, rats, and dogs, reproductive toxicity studies in rats and rabbits, and in vitro and in vivo genotoxicity studies. Two-year carcinogenicity studies were conducted in mice and rats. Repeat-dose toxicity studies were also conducted in juvenile rats (4 weeks of age at dose initiation), including one study specifically aimed at evaluating the possible toxicity on male reproductive organs. Local tolerance studies assessing the hemocompatibility of a parenteral formulation of alogliptin in human blood/plasma and the IV and paravenous tolerance of

alogliptin were performed in rabbits. Special toxicity studies (4- and 13-week) were conducted in monkeys to evaluate the potential dermal toxicity of alogliptin. The potential of alogliptin to induce phototoxicity was evaluated in a hairless mouse model.

In addition repeat-dose toxicity studies (4- and 13 week) in rats and an embryo-fetal development toxicity study in rats were conducted to assess the toxicity of combination treatments with alogliptin and pioglitazone and with alogliptin and metformin.

2.3.4.1. Single dose toxicity

Alogliptin

The lethal single oral and IV doses of alogliptin in rats were greater than 1471 mg/kg and 25 mg/kg, respectively. The lethal single oral dose in dogs was greater than 368 mg/kg. There were no sex-related differences in the single-dose toxicity of alogliptin. Clinical signs were observed in dogs only. Reddened skin around the ears and face were observed in males following oral doses of ≥ 92 mg/kg and in females at ≥ 221 mg/kg. Warm to touch and/or decreased activity were observed at doses of ≥ 221 mg/kg. A female dosed with 368 mg/kg also exhibited swelling around the face, skin cold to touch, salivation, and emesis; this female also lost weight during the 2-week post dose observation period.

Metformin

Toxicity was found to be very variable in the rat. The oral LD50 values in all species are high in relation to a human dose of 12 mg/kg, based on 850 mg dose and 70 kg body weight. Deaths occurring at massive doses generally resulted from hypoglycaemia.

Alogliptin combined with metformin

Sprague-Dawley rats (2/sex/group, 6 weeks of age) were administered oral gavage doses of 100, 300, or 1000 mg/kg metformin; 100 mg/kg alogliptin; or 100 mg/kg alogliptin with 1000 mg/kg metformin. This was an investigative, non-GLP study. Plasma levels of metformin were not affected by alogliptin exposure; however, alogliptin plasma levels were reduced following concomitant treatment with metformin.

2.3.4.2. Repeat dose toxicity

Alogliptin

Low toxicity was showed for mice, with a NOAEL of about 50 times the intended human exposure based on AUC. In mice, several deaths occurred in the repeat-dose toxicity studies. Although pathologic examinations could not confirm the exact cause of these deaths, the incidence increased dose dependently at doses of 400 mg/kg/day and higher. Alogliptin-related observations were noted in male mice and included yellow discoloured fur and unkempt appearance at 200 mg/kg/day

and higher, and swelling in the anogenital area at 400 mg/kg/day and higher. Decreased RBC, HCT, and HGB were also noted at 600 mg/kg/day.

Most important alogliptin-related histopathologic findings in rats were noted in the liver, kidneys, and urinary bladder. Increased ALP, increased liver weights, and centrilobular hepatocellular hypertrophy were noted in rats administered doses of ≥900 mg/kg/day. With the exception of increased liver weights, liver-related findings were fully reversible. Mortality was observed in rats administered repeat doses of ≥1000 mg/kg/day. The The clinical pathologic findings observed included increased WBC, LYM, RET, or MON and decreased RBC, HCT, and HGB at 900 mg/kg/day and higher, and increased phosphorus and cholesterol at 1000 mg/kg/day and higher. Decreased ALB and A/G (albumin/globulin) ratio were also observed at 1333 mg/kg/day and higher. NOAEL for 6 months exposure was 400 mg/kg/day, which is about 50 – 150 times the intended human exposure.

In the repeat-dose toxicity studies in dogs, occasional and transient occurrences of reddened ears and facial swelling without associated histopathologic changes were observed at doses of 30 mg/kg/day and higher. In the 39-week repeat-dose toxicity study, dogs administered 200 mg/kg/day (highest dose evaluated) lost weight during the first month of the treatment period; these losses resulted in a decrease in mean body weight during the treatment period. The overall NOAEL in dogs was 200 mg/kg/day; at this dose, the AUC(0-24) was 400 µg·hr/mL (combined sexes).

The effects of concomitant treatment with alogliptin and pioglitazone on the toxicokinetic parameters of both compounds were assessed in a single-dose and two repeated-dose studies for 4 weeks and 13 Weeks, respectively. These studies showed no toxicokinetic interactions regarding the kinetic parameters of alogliptin. In addition, the incidence and magnitude of the findings seen in rats administered alogliptin and pioglitazone in combination for 13 weeks were comparable to rats that received pioglitazone alone. Combination treatment with alogliptin and pioglitazone did not produce new toxicities, and did not exacerbate any pioglitazone-related findings.

Metformin

Literature reveals that repeated exposure to metformin for 13 weeks in rats resulted in decreased body weights in males at ≥600 mg/kg/day and mortality at ≥900 mg/kg/day. Increased serum lactate and β-hydroxybutyric acid and decreased serum bicarbonate and urine pH occurred at ≥600 mg/kg/day. Histopathologic findings included an increased incidence of minimal necrosis with minimal to slight inflammation of the parotid salivary gland in males at 1200 mg/kg/day. The NOAEL was 200 mg/kg/day. Toxicokinetic data showed no sex- or duration-related differences in metformin plasma levels.

No toxic effects were observed in the liver, kidneys, spleen, adrenal glands, or bone marrow after administration of metformin for 12 months or longer to rats (10 mg/kg/day orally), rabbits (10 to 50 mg/kg/day SC or up to 100 mg/kg/day orally), or dogs (50 mg/kg/day SC). No abnormalities were noted in dogs dosed at 50 mg/kg/day SC for 2 years.

Alogliptin combined with metformin

Repeat-dose toxicity studies with alogliptin and metformin in rats for up to 13-weeks slightly augmented metformin-related effects on plasma lactic acid levels and increased the incidence of metformin-related effects in the adrenal gland, liver, heart, and submandibular gland (males), although it did not affect the severity of the changes. These effects were shown only at the combination of alogliptin with the high dose of 1000 mg/kg metformin.

2.3.4.3. Genotoxicity

Alogliptin

Alogliptin was evaluated for its potential to induce reverse mutations in S typhimurium and E coli, its mutagenic potential in vitro in L5178Y/TK+/- mouse lymphoma cells, and its mutagenic potential in vivo in a mouse bone marrow micronucleus study. Where appropriate, positive controls were used to confirm the sensitivity of the assay. Based on the results of these studies, alogliptin does not pose a mutagenic or clastogenic risk to humans.

Metformin

According to literature, no evidence of genotoxicity was found in Ames test (S typhimurium), mammalian gene mutation assay in mouse lymphoma cells, chromosomal aberration test in human lymphocytes, or in a mouse bone marrow micronucleus test.

2.3.4.4. Carcinogenicity

Alogliptin

Alogliptin was shown to be not oncogenic or carcinogenic in mice, and the NOAEL of the 2-year carcinogenicity study was 300 mg/kg/day. Slightly, statistically non-significant, increased incidence in malignant lymphoma in female mice was observed at doses of 150 mg/kg/day when compared with historical control data.

In rats, a slight, statistical non-significant increase in the incidence of thyroid C-cell tumours was noted in males at ≥ 400 mg/kg/day. This was weakly supported by increments of adenomas and hyperplasia. However, the incidence of these findings in this study was within the variability suggested by the historical control. Moreover, a rodent-specific mechanism through increased calcitonin release has been suggested for increases in C-cell tumours seen for GLP1 analogues (Knudsen et.al. Endocrinology 151:1473-86). Therefore, a weak increase in C-cell tumours after alogliptin treatment could be explained by the indirect impact on GLP1 levels following the administration of this DPP4 inhibitor.

Minimal to mild simple transitional cell hyperplasia in the urinary bladder was noted in 2, 6, 10, and 14 males at 0, 75, 400, and 800 mg/kg/day, respectively. In the male historical control series, simple transitional cell hyperplasia in the urinary bladder was reported for several studies and was

seen in 6/60 males in one study. NOAEL for simple transitional cell hyperplasia in the urinary bladder was considered to be 75 mg (males) and 400 mg (females)/kg/day.

Also, alogliptin-related non-neoplastic histopathologic changes were seen in the liver, lung, and urinary bladder of males and females, and in the testes, epididymides, and prostate of males. The NOAEL for nonneoplastic changes was 75 mg/kg/day for males and 400 mg/kg/day for females. The safety factors based on AUC are about 25 and >200 respectively.

Metformin

Long-term carcinogenicity studies have been performed in rats (≤900 mg/kg/day for 104 weeks) and in mice (≤1500 mg/kg/day for 91 weeks). No evidence of carcinogenicity was found in male or female mice or in male rats. In female rats, there was an increased incidence of benign stromal uterine polyps at the highest dose.

2.3.4.5. Reproduction Toxicity

Alogliptin

In a rat fertility study with dose levels of 0, 100, 500, 1000 mg/kg bw/day, maternal toxicity was observed at 500-1000 mg/kg/day, and paternal toxicity at 100 – 1000 mg/kg/day. In male rats, dose related increase of absolute and relative cauda epididymis weight, relative epididymis weight, relative weight of seminal vesicle with coagulating glands and relative testes weight and an increased % of abnormal sperm were observed, however, without any effect on fertility. At the highest dose of 1000 mg/kg increased post implantation loss and decreased number of viable foetuses occurred.

Two embryo-foetal developmental reproduction toxicity studies were done, one in rats and one in rabbits. In rats, doses 250, 500, and 1000 mg/kg/day induced maternal toxicity and foetal toxicity. It is likely that the foetal toxicity (bent ribs, decreased ossification) was secondary to the maternal effects (decreased food consumption and gravid uterine weight change). In rabbits, high doses resulted in maternal deaths (highest doses) and toxicity signs (lower food consumption and body weight and body weight and gravid uterine weight). The only observed foetal effect was decreased number of viable foetuses in the only surviving doe at the highest dose level, which can be considered a consequence of maternal toxicity.

An embryo-foetal developmental toxicity study in rats was also done with the combination of alogliptin with pioglitazone. The combination only showed a slight potentiation of foetal growth inhibition.

A pre/postnatal developmental study in rats revealed maternal toxicity in the form of decreased gestation body weights, gestation body weight changes, lactation body weight, food consumption during lactation at doses of 500 – 1000 mg/kg/day. At 1000 mg/kg, developmental toxicity was found, consisting of increased stillborn index, decreased pup viability and effects on motor activity, learning, memory in F1 males. At 500-1000 mg/kg/day, decreased pup body weight was observed up to PND28 and through pre/post mating of F1.

Two rat juvenile toxicity studies were performed, one with a treatment duration of 4 weeks and one with a treatment duration of 8 weeks, both with the same dose levels of 30, 100 and 300 mg/kg/day. In the 4-week study some slight effects were found on haematological and blood/urinary chemistry and slight hepatocyte hypertrophy, but these changes were not considered toxicologically significant and were not replicated in the second longer study.

Metformin

The fertility of male and female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day.

Metformin was not teratogenic in rats and rabbits at daily doses up to 600 mg/kg/day.

In an early study Tuchmann-Duplessis and Mercier-Parot dosed rats orally from GD 1 to 12 at 500 or 1000 mg/kg/day. At 500 mg/kg/day, there was a 19% decrease in the average number of fetuses per litter; 2 fetuses from 60 dams had severe malformation. There were no adverse effects at 1000 mg/kg/day. In a recent report by Bedaiwy et al (2001), embryotoxicity was observed in vitro in a mouse embryo model at the highest concentration of 100 µg/mL but not at 25 and 5 µg/mL, the latter concentration being similar to a maximum clinical serum level.

No study of potential for peri- and post-natal toxicity appears to have been performed.

Alogliptin combined with metformin

Fertility and early embryonic development and pre- and postnatal development studies were conducted with alogliptin alone and fertility studies were conducted with metformin alone; no additional studies were conducted with alogliptin/metformin.

The range-finding embryo-fetal toxicity study was conducted in rats at doses of up to 100/2000 mg/kg/day (alogliptin/metformin). The 100/2000 mg/kg/day dose was lethal to all dams dosed and 1 of 6 dams administered 100/1000 mg/kg/day died. A decrease in the number of ossified sacro-caudal vertebrae were noted in fetuses from dams administered doses of 100/500 mg/kg/day and 100/1000 mg/kg/day.

Based on the range-finding study, the highest dose evaluated in the definitive embryo-fetal developmental toxicity study in rats was 100/500 mg/kg/day. In this study, 5 abnormal fetuses were observed from dams administered 100/500 mg/kg/day (alogliptin/metformin). Four of the fetuses were from a single litter: 3 of the 4 fetuses had microphthalmia and the 4th fetus had a misshapen tail and absent sacral vertebra. The fifth fetus, from a second litter, had multiple abnormalities (microphthalmia, cleft palate, microglossia, and mandibular micrognathia). No treatment-related fetal abnormalities occurred following concomitant treatment with 100/150 mg/kg/day alogliptin/metformin or when either alogliptin or metformin was administered alone.

2.3.4.6. Toxicokinetic data

Alogliptin

Systemic exposure and maximum plasma concentrations increased generally more than dose-proportional in rats and dogs, except at low doses (0.3 to 3 mg/kg) in dogs over which dose range the kinetics were linear. This was observed both after single and repeated dosing to which saturation of metabolic pathways may be contributing in these species. An increase in elimination half-life and the less-than-dose-proportional increase in the exposure to M-I (and M-II) with increasing alogliptin doses support the idea of saturable metabolism. In mice and monkeys, exposure to alogliptin was generally dose-proportional where exposure to M-I was less than dose-proportional.

The formation of the pharmacologically active metabolite M-I differed across the non-clinical species: total 24-hour exposure to M-I was <3.2%, <34%, <85% and 13% of respective of alogliptin exposure in mice, rats, dogs and monkeys, respectively, with decreasing M-I contribution to total exposure with increasing dose. The formation of M-I is thus saturable. However, as M-I is pharmacologically active with a similar mode of action as alogliptin, the systemic exposures of both compounds need to be added up in the pre-clinical species for determining the total exposure to active substance in vivo.

Metformin

Toxicokinetic data collected from a 13 weeks repeat dose toxicity study in rats showed no sex- or duration-related differences in metformin plasma levels.

Alogliptin combined with metformin

Repeated concomitant treatment with alogliptin and metformin in rats for up to 13-weeks showed that the toxicokinetics of neither compound was affected by combination treatment.

2.3.4.7. Local Tolerance

Alogliptin

A parenteral formulation of alogliptin in physiological saline was not hemolytic in human blood and did not cause any macroscopic flocculation, precipitation, or coagulation in human plasma. A 2.5 mg/mL solution of alogliptin in physiological saline was well tolerated following IV or paravenous injection to rabbits.

Metformin

No published data were available on the local tolerance of metformin. Given that metformin has been approved for >50 years as an oral drug, ensuring that its toxicity in the human population has been thoroughly characterized, and a nonclinical local tolerance study was considered not required.

2.3.4.8. Other toxicity studies

2.3.4.8.1. Immunotoxicity

Alogliptin

Non-clinical studies assessing immunotoxicity, including in vitro assessments for immune function and immunophenotyping of leukocyte populations, were not conducted with alogliptin. No evidence of drug-induced immunosuppression or enhancement was seen in the non-clinical toxicity studies with alogliptin.

2.3.4.8.2. Phototoxicity

Alogliptin

Although alogliptin has been shown to bind to melanin in the eyes of pigmented rats, it only has minor or negligibly low absorbance in the ultraviolet B (UVB) range of 290 to 320 nm and the ultraviolet A (UVA) range of 320 nm and longer, and single doses of up to 800 mg/kg (a dose that exceeded the maximum-tolerated dose [MTD]) did not produce cutaneous phototoxicity in hairless mice. The positive control (lomefloxacin HCl) produced the expected response (erythema, edema, and flaking).

2.3.4.8.3. Dermal toxicity

Alogliptin

Repeated doses of up to 30 mg/kg/day administered to cynomolgus monkeys for 4 and 13 consecutive weeks did not produce alogliptin-related dermal toxicity. No alogliptin-related lesions were seen histopathologically in sections of skin obtained from the thoracic region, tail, left fore- and hindlimbs, left auricle, nasal area, and scrotum. The NOAEL was the highest dose evaluated (30 mg/kg/day). In the 13-week study, the mean AUC(0-24) at the NOAEL was 47 µg·hr/mL. This plasma concentration provides an exposure margin of approximately 27-fold higher than the clinical dose of 25 mg/day.

2.3.4.8.4. Dependence

Alogliptin

Abuse liability studies were not conducted with alogliptin. Although alogliptin inhibited naloxone binding at nonselective opioid receptors in vitro in the rat cerebral cortex, it did not show any binding affinity for human receptors typically associated with abuse potential. Additionally, no noteworthy alogliptin-related effects on general behavior and activity were observed in rats at doses of up to 300 mg/kg/day for 4 consecutive weeks.

2.3.4.8.5. Metabolites

Alogliptin

When plasma profiles were evaluated, humans were primarily exposed to alogliptin and exposure to M-I was minimal. The plasma metabolic profiles of mice, rats, dogs, and monkeys were broadly similar to that of humans except that a very low level of M-II was found in dog plasma. Based on current guidelines, both M-I and M-II are classified as minor human metabolites, since they account for plasma levels of less than 10 percent of systemic exposure in humans. No extra toxicological studies on metabolites have been performed.

2.3.4.8.6. Studies on impurities

Alogliptin

Impurities measured in the alogliptin drug substance and drug product are below the Qualification Thresholds specified in ICH guidances Q3A and Q3B; therefore, toxicity studies with the individual impurities are not required . The impurity profiles of alogliptin drug substance used in the pivotal toxicity studies, and for alogliptin, pioglitazone, and metformin drug substances used in the pivotal combination toxicity studies were comparable to the impurity profiles for the drug substances used in the clinical formulations.

Metformin/Alogliptin in combination with metformin

The impurity profiles of alogliptin drug substance and metformin drug substance used in the pivotal combination toxicity studies were comparable to the impurity profiles for the drug substances used in the clinical formulations.

2.3.5. Ecotoxicity/environmental risk assessment

2.3.5.1. Phase I

The applicant has submitted an ERA for Vipdomet (alogliptin/ metformin fixed dose combination). Alogliptin is a dissociating molecule; the amine moiety is deprotonated at a pKa of 8.5. The molecule becomes predominantly neutral at pH values around 10 and higher. The pH metric method was used to determine the apparent log P vs. pH profile. Log P is 0.6 at pH 10, 11 and 12. Hence, log Kow of alogliptin is 0.6. This corresponds with a high water solubility (approx. 20 g/L) and a QSAR estimate for log Kow of 0.9 (Biobyte's ClogP).

Need for PBT-assessment

Parameter	Substance	Study ID/GLP	Protocol	Results	Criteria	Conclusion
Bioaccumulation	alogliptin	[1]/N	pH metric method	log K_{ow} 0.6	log K_{ow} > 4.5	not B
Bioaccumulation	metformin	[1]/N	pH metric method	log K_{ow} -2.6	log K_{ow} > 4.5	not B

Based on the above results neither alogliptin nor metformin meet the screening criterion for the bioaccumulation. It can be concluded that both alogliptin and metformin are not qualifying for PBT (persistence, bioaccumulation, and toxicity) assessment.

Calculation of $PEC_{surface\ water}$

$$PEC_{SW} = \frac{DOSEai \cdot F_{pen}}{WASTEWinhab \cdot DILUTION}$$

*DOSE*ai =	25	(mg alogliptin patient^{-1} d^{-1})
*DOSE*ai =	1560	(mg metformin patient^{-1} d^{-1})
F_{pen} =	0.01	(patient inh^{-1})
*WASTEW*inhab =	200	(L inh^{-1} d^{-1})
DILUTION =	10	(–)

Vipdomet is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus. The recommended dose of is 25 mg alogliptin / 1700 mg metformin per patient, to be taken daily.

The applicant has used the default F_{pen} of 0.01. The resulting PEC_{sw} is 0.125 µg/L and 7.8 µg metformin/L. Based on these results a Phase II assessment was considered appropriate for both compounds.

2.3.5.2. Phase II, Tier A

The applicant performed a phase II Tier A ERA for alogliptin. For metformin, no phase II ERA was performed. The applicant justified no further assessment of metformin by the absence of increased environmental exposure. Vipdomet is prescribed to patients already taking existing metformin products which no longer provide adequate glycaemic control.

Alogliptin

The results of the phase II Tier A ERA for alogliptin are summarized in the below table.

Summary of main study results

Substance (INN/Invented Name): alogliptin benzoate			
CAS-number (if available): 850649-62-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	pH metric method	0.6	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.6	not B
Persistence	ready biodegradability	not readily biodegradable	
	$DT50_{water}$ $DT50_{sediment}$ $DT50_{system}$	1.8 and 6.9 d at 20°C > 100 d at 20°C > 100 d at 20°C	P
Toxicity	NOEC algae NOEC Daphnia NOEC fish	56 mg/L ≥ 10 mg/L ≥ 10 mg/L	
	CMR	not CMR	not T

PBT-statement	The compound is considered not PBT, not vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.125	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)	not investigated				(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 25.2 and 18.7 L/kg			two sludges
	OECD 106	PM			
Ready Biodegradability Test	OECD 301	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 1.8 and 6.9 d $DT_{50, sediment}$ = >100 d $DT_{50, whole\ system}$ = >100 d % shifting to sediment = 84 and 86%			all values determined at 20°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *P. subcapitata*	OECD 201	NOEC EC10	56 67	mg/L mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 10	µg/L	survival, reproduction, growth
Fish, Early Life Stage Toxicity Test / *P. promelas*	OECD 210	NOEC	≥ 10	mg/L	egg survival, embryo development, hatching survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 73.5	mg/L	
Sediment dwelling organisms/ *Species*	OECD 218	PM	PM	PM	

Alogliptin has a Kow value below the trigger for an assessment of the potential for bioconcentration.

A risk assessment for the soil compartment was not triggered as Koc, sludge <10,000 L/kg.

Since >10% of alogliptin shifted to sediment in the water/sediment simulation study, a Phase IIB assessment was triggered. However, alogliptin is not very toxic to aquatic organisms and based on the PECsediment and PNECsediment values derived from the equilibrium partitioning method the PECsediment/PNECsediment ratio indicates alogliptin is unlikely to represent a risk to the sediment compartment.

In conclusion alogliptin poses an acceptable risk to sewage treatment facilities, all standard surface water species and groundwater.

Metformin

No increased environmental exposure of metformin hydrochloride is expected based on the use pattern of Vipdomet. Therefore, no toxicity data for metformin were provided. Metformin does not meet the bioaccumulation criterion and is neither PBT, nor vPvB.

2.3.6. Discussion on non-clinical aspects

2.3.6.1. Pharmacology

Alogliptin

The primary pharmacodynamics of alogliptin is well characterised. Alogliptin is shown to be a selective and potent DDP4-inhibitor, as compared to the first gliptins on the market, sitagliptin and vildagliptin. The R-isomer is the active one as the S-isomer is 1000-times less active. From the metabolites the M-I is also showing activity. From a pharmacodynamic point of view (DPP4 inhibition) the duration of action is relatively long, e.g. in monkeys is lasting at least 24 hours, which suggests that a once-day administration in humans might be sufficient.

Not only the primary effect DPP4 inhibition has been shown *in vivo*, but also the resulting physiological consequences such as enhancement of GLP-1, and increase of insulin, and the decrease of glucose after a glucose infusion, supporting the use of alogliptin as an antidiabetic drug. The nonclinical data do not suggest any clinically relevant effects of alogliptin on immunological parameters in healthy animals.

From a safety point of view there are no concerns about the secondary pharmacology or on the safety pharmacology. Over a wide range of receptors and enzymes alogliptin appears to be a specific DPP4 inhibitor.

Combination pharmacodynamic studies confirmed the additive and/or synergistic effects of concomitant treatment with alogliptin and pioglitazone, alogliptin and metformin, alogliptin and glibenclamide, and alogliptin and voglibose.

Metformin

Effects of metformin on glucose involve suppression of hepatic glucose output, increased peripheral glucose utilization, reduced fatty acid utilization, and increased glucose turnover. In addition, metformin alters glucose handling by erythrocytes and reduces hypertriglyceridemia. The primary route is via decreased hepatic glucose production (gluconeogenesis). Metformin increased insulin-stimulated glucose utilization, mainly in skeletal muscle, under conditions of hyperglycaemia and/or insulin resistance. Metformin reduces the rate of fatty acid oxidation which correlates approximately with suppression of hepatic glucose production; this suggests that reduced fatty acid oxidation contributes to reduce gluconeogenesis. At the cellular level, metformin increases the functional activity of glucose transporters (GLUT-1 and GLUT-4) and influences membrane events affecting tyrosine kinase activity that leads to the augmentation of a range of insulin signals. The glucose lowering effect of metformin has been demonstrated in STZ-induced diabetic mice, normal and mildly hyperglycaemic rats, insulin-resistant Zucker rats, and normal dogs. Metformin appears to possess potentially beneficial vascular properties, in addition to an effect on serum lipid profiles.

Alogliptin in combination with metformin

In combination with metformin, alogliptin has a superior, additive effect on glycaemic control compared to the respective monotherapies.

2.3.6.2. Pharmacokinetics

Alogliptin

Kinetics of alogliptin was well investigated by the applicant.

Alogliptin has two enantiomers of which the [R]-enantiomer is clinically relevant. Chiral conversion into the [S]-enantiomer hardly occurs.

Alogliptin was well absorbed, with the jejunal loop being one of the major absorption sites, in the non-clinical species following oral dosing. Absorption into the lymphatic circulation hardly occurs. Oral bioavailability was moderate to high and differed across species.

Kinetics of alogliptin was generally linear in mouse and monkeys and in dogs in the dose range 0.3 to 3 mg/kg. In rats and at higher doses in dogs, kinetics were more than dose-proportional caused by saturation of metabolic pathways. In line with this, exposure to M-I displayed less than dose-proportional kinetics and its formation decreased with increasing alogliptin doses in all species.

Alogliptin is moderately bound to plasma proteins (<60%) and widely distributed among tissues, including passage over the blood testes barrier and placenta, as is expected by a high volume of distribution.

Metabolism: Identification of the metabolites showed that alogliptin is considered to be biotransformed to M-I by N-demethylation, and to M-II by acetylation of the amino group. Alogliptin and M-I are the major circulating components in dog plasma at dosages of 10 mg/kg and higher.

Alogliptin is excreted in milk from lactating rats and mainly present as unchanged parent and M-I. Elimination of alogliptin in rats and dogs is both by hepatic clearance and renal clearance. Enterohepatic circulation is also possible.

Interactions: CYPs 2D6 and 3A4/5 were inhibited *in vitro* by alogliptin via direct inhibition and metabolism-dependent inhibition, respectively, but at concentrations much higher than the clinical C_{max}. CYP induction by alogliptin is not found *in vitro* or *in vivo*.

In humans, alogliptin is mainly eliminated by the kidneys with some evidence of activerenal secretion. Therefore, the main focus of the in vitro transporter studies was in the transporters associated with renal clearance.

The applicant investigated if alogliptin is an in vitro inhibitor of OAT1, OAT3 and OCT2. The study included both control cells and cells transfected with the specific transporter of interest. Further, the used probe substrates (PAH, E3S and metformin) and positive control inhibitors (probenecid, probenecid and quinidine) are appropriate. No clinically relevant inhibition by alogliptin (based on its Cmax of 0.3 µM) was seen for any of the investigated transporters.

Alogliptin was not an in vitro inhibitor of BCRP at clinically relevant concentrations 12 µM (= 50 × Cmax,unbound = 50 × 0.24 µM = 12 µM) and 29.5 µM (=0.1 × dose/250 mL = 0.1 × 25 mg/250 mL = 10 µg/mL = 29.5 µM) for liver and intestinal transporter concentrations, respectively. Therefore, clinically relevant interactions via BCRP inhibition by alogliptin are not expected.

No in vitro studies were performed with MATE and OATP. Additional clinical studies investigating the interaction potential of alogliptin have been performed and discussed in the clinical pharmacology section of this report.

Pregnancy may have an influence on alogliptin and M-I exposure as a result of saturated alogliptin and M-I absorption, an increase in distribution volume and/or differences in elimination. Toxicokinetics in juvenile rats were not different compared to kinetics in adult rats. However, using healthy juvenile rats may not be representative for the human situation as it may be expected that T2DM is mainly present in obese children.

Co-administration with pioglitazone or metformin did not result in significant or clinically relevant alterations in pharmacokinetics of alogliptin, pioglitazone or metformin. Combinations with sulphonylurea, insulin or triple therapies were not investigated in the non-clinical species.

Metformin

The pharmacokinetic properties of methformin hydrochloride are well known. As metformin hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is considered sufficient.

Alogliptin in combination with metformin

When alogliptin and metformin are administered concomitantly, there are no direct interactions expected on the distribution and metabolism level.

The effect of co-administration of alogliptin and metformin on the absorption kinetics of both compounds could not be assessed as limited information is present about the involvement of transporters in absorption, which is inevitable in this case as the rat model is not a good predictive model since the absorption and elimination kinetics are too different from those in humans. However, clinically there are no indications of interactions regarding absorption and bioavailability.

2.3.6.3. Toxicology

Alogliptin

Acute and repeat-dose toxicity studies showed a very low toxicity of alogliptin in mice, rats, dogs and monkeys, with very high safety margins of 50-200 fold. Alogliptin-related toxicity occurred in rats at doses of ≥ 900 mg/kg/day and the findings were generally limited to the physical appearance of the animals and were frequently associated with decreases in body weight. Alogliptin-related histopathologic findings were noted in the liver, kidneys, and urinary bladder. In dogs, occasional and transient occurrences of reddened ears and facial swelling, without

histopathologic changes, were observed at doses of 30 mg/kg/day and higher. Although these effects remain unexplained, and a treatment-related effect cannot be ruled out, the transient nature of these findings and the lack of adaptive changes in any organs, suggest this may be an allergic reaction. This is not likely to be relevant for humans. Decreased food consumption and body weight gain occurred at 200 mg/kg/day only in the early weeks of the 39-week study. However, these effects on body weight did not adversely affect clinical pathology, organ weights, or histopathologic results.

Combination treatment with alogliptin and pioglitazone for up to 13 consecutive weeks did not produce unanticipated toxicities, and did not exacerbate any pioglitazone-related findings. Repeat-dose toxicity studies with alogliptin and metformin in rats for up to 13-weeks slightly augmented metformin-related effects on plasma lactic acid levels and increased the incidence of metformin-related effects in the adrenal gland, liver, heart, and submandibular gland (males), although it did not affect the severity of the changes. Because these differences were shown only at the combination of alogliptin with the high dose of 1000 mg/kg metformin, this is probably not of clinical relevance.

Alogliptin is not genotoxic and not clearly carcinogenic in rodent models. The finding of a low magnitude of an increased incidence of malignant lymphoma in female mice, commonly found in mice, and the lack of a clear immunological effect at lower dose levels, is considered most likely not relevant for humans and the clinical situation. A low potency of alogliptin in inducing C-cell tumours seen in the rat carcinogenicity study is likely not clinically relevant. A minimal to mild simple transitional cell hyperplasia in the urinary bladder was noted in male rats at 27-fold higher than the intended human exposure. Since no threshold has been defined for the possible induction of cell hyperplasia in the urinary bladder by alogliptin and bladder cancer has been confirmed to be associated with pioglitazone, possibly via a similar non-genotoxic mechanism, an interaction between alogliptin and pioglitazone cannot be excluded.

In reproduction and developmental toxicity studies alogliptin showed at the highest tested dose an increase in abnormal sperm, but fertility was not affected. The major developmental toxicity seen was most likely secondary to maternal toxicity. In the pre-postnatal toxicity study, effects on body weight and neuro-behavioral development appeared to be long-lasting. Exposure at the NOAEL levels was sufficiently above the clinical exposure. No juvenile toxicity was seen in rats, however in these studies the highest dose was at the level of the NOEL in the other studies. Embryo-foetal developmental toxicity studies in rats were also done with the combination of alogliptin with pioglitazone and alogliptin with metformin. The combination with pioglitazone only showed a slight potentiation of foetal growth inhibition.

Based on the presented data the CHMP can conclude that alogliptin did not show any local tolerance effects, no phototoxicity, and in monkeys no dermal toxicity.

No dedicated studies to investigate the imunotoxicity or dependence of alogliptin have been performed. The CHMP considers that no such studies are warranted since no imunological signals have been revealed in the extended non-clinical program and alogliptin did not show any binding affinity for human receptors typically associated with abuse potential.

Metformin

The acute toxicity of metformin in mice, rats, rabbits, and guinea pigs is very low. Repeated exposure for 13 weeks in rats resulted in decreased body weights in males at ≥ 600 mg/kg/day and mortality at ≥ 900 mg/kg/day. Increased serum lactate and β-hydroxybutyric acid and decreased serum bicarbonate and urine pH occurred at ≥ 600 mg/kg/day. There was an increased incidence of minimal necrosis with minimal to slight inflammation of the parotid salivary gland in males at 1200 mg/kg/day. The NOAEL was 200 mg/kg/day. Toxicokinetic data showed no sex- or duration-related differences in metformin plasma levels.

No toxic effects were observed in the liver, kidneys, spleen, adrenal glands, or bone marrow after administration of metformin for 12 months or longer to rats (10 mg/kg/day orally), rabbits (10 to 50 mg/kg/day SC or up to 100 mg/kg/day orally), or dogs (50 mg/kg/day SC). No abnormalities were noted in dogs dosed at 50 mg/kg/day SC for 2 years.

Metformin showed no genotoxicity or carcinogenicity.

Metformin showed no effects on fertility in rats, and was not teratogenic in rats and rabbits at high dose. Embryotoxicity was observed *in vitro* in a mouse embryo model only at the highest concentration of 100 µg/mL.

Alogliptin in combination with metformin

Repeat-dose toxicity studies with alogliptin combined with metformin in rats for up to 13-weeks slightly augmented metformin-related effects on plasma lactic acid levels and increased the incidence of metformin-related effects in the adrenal gland, liver, heart, and submandibular gland (males), although it did not affect the severity of the changes. Because these differences were shown only at the combination of alogliptin with the high dose of 1000 mg/kg metformin, this is probably not of clinical relevance. The combination with metformin revealed teratogenic potential in small numbers of foetuses (microphthalmia, small eye bulge and cleft palate) at high doses.

2.3.6.4. Ecotoxicity/environmental risk assessment

Alogliptin

The alogliptin PEC_{sw} value of 0.125 µg/L warranted a Phase II ERA assessment.

A risk assessment for the soil compartment was not triggered as Koc, sludge <10,000 L/kg. However, the EMA guideline requests determination of adsorption constants in three soils and two sludges. The applicant submitted a study with adsorption data for two sludges only. Since a Phase IIB assessment is to be performed, adsorption data determined in soil (or sediment) should be investigated.

Since >10% of alogliptin shifted to sediment in the water/sediment simulation study, a Phase IIB assessment was triggered. The applicant has performed a Phase IIB assessment using the PNECsw. This is not in accordance with the EMA guidance. A toxicity study with a sediment dwelling organism should be performed.

In addition, the applicant only provided summarized log Kow data published in literature of low quality. The Q&A document (EMA/CHMP/SWP/44609/2010) states that the log Kow should be determined experimentally and that a calculated value is generally not acceptable. Therefore the applicant is recommended to perform and submit the results of a Kow study.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of alogliptin to the environment. The CHMP considers that the disposal instructions given in the PL and SmPC are appropriate.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following studies to be performed:

- an OECD 106 study determining the adsorption constants in three soils (or sediments)
- a toxicity study with a sediment dwelling organism (OECD 218). Although alogliptin has a relatively high water solubility, the applicant is recommended to perform an OECD 218 (sediment spiked) study. This study results in mg/kg concentrations, which are needed in the sediment risk assessment and moreover, the OECD 308 study demonstrated that shifting of alogliptin to sediment occurred both rapidly and in substantial amounts. The results of the effect study with the sediment dwelling organism should be compared to the $PEC_{sediment}$.
- a Kow study for alogliptin

Metformin

Metformin does not meet the bioaccumulation criterion and is neither PBT, nor vPvB. For metformin, no phase II ERA was performed. The applicant justified no further assessment of metformin by the absence of increased environmental exposure, justification that was considered acceptable by the CHMP. It can be concluded that no increased environmental exposure of metformin hydrochloride is expected based on the use pattern of Vipdomet.

2.3.7. Conclusion on the non-clinical aspects

The applicant has investigated the non-clinical properties of alogliptin and metformin sufficiently to support the indication applied for. From a non-clinical point of view the application is approvable.

The CHMP recommends the following studies to be performed in order to fully investigate the potential risk of alogliptin to the environment:

- an OECD 106 study determining the adsorption constants in three soils (or sediments)
- a toxicity study with a sediment dwelling organism (OECD 218). Although alogliptin has a relatively high water solubility, the applicant is recommended to perform an OECD 218 (sediment spiked) study. This study results in mg/kg concentrations, which are needed in the sediment risk assessment and moreover, the OECD 308 study demonstrated that shifting of alogliptin to sediment occurred both rapidly and in substantial amounts. The results of the effect study with the sediment dwelling organism should be compared to the $PEC_{sediment}$.
- a Kow study for aloglitin

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

The clinical pharmacology program for alogliptin consisted of 28 studies (Table 1).

Twenty-two of the 28 clinical pharmacology studies were conducted in the United States (US) only, and 6 were conducted in Japan. In addition, population pharmacokinetics was evaluated in a Phase III efficacy and safety study that was conducted in 15 countries including those in the European Union (EU).

Single oral doses from 6.25 to 800 mg and multiple oral doses from 25 to 400 mg were evaluated. All doses of study drug (active or placebo) were administered orally with the exception of an intravenous (IV) dose in the absolute bioavailability study. All subjects who participated in the clinical program were at least 18 years of age.

The clinical development program for alogliptin examined the use of alogliptin in monotherapy and in combination use with 4 major classes of antidiabetic agents: (1) MET (2) SU, (3) TZD, and (4) insulin. The efficacy of alogliptin has been evaluated in 15 studies: 1 phase 2 dose-ranging study, 7 main Phase III studies, and 7 supportive Phase III studies (Table 2).

Metformin is a well-established drug that has been used extensively in the EU for many years in the T2DM patient population. The lowest and highest metformin doses used in clinical trials were 500 and 1000 mg; however, based on European clinical practice, an FDC containing metformin 850 mg is proposed.

In clinical trials, alogliptin plus metformin has been evaluated as the alogliptin/metformin FDC tablet (phase I) or concomitantly as individual tablets (phase III).

The clinical pharmacology program for the FDC alogliptin/metformin comprises 2 new bioequivalence studies (322MET-101 and 322MET-103) and 1 new food-effect study (322MET-102). Furthermore, the program is supported by 1 drug interaction study with alogliptin and metformin (005), and 1 pharmacokinetic study that assessed once daily vs BID dosing (101) which were also included in the alogliptin program (Table 3).

Additionally, the applicant provided a literature based overview of the pharmacokinetics of metformin.

The clinical development program for alogliptin/metformin examined the use of alogliptin in combination with metformin, with insulin, and with metformin and TZD. The efficacy of the combination has been evaluated in 5 main Phase III studies and 2 supportive Phase III studies (Table 4).

- Tabular overview of clinical studies

Table 1 Overview of Alogliptin Phase 1 and 2 Clinical Pharmacology Studies

Study Number (Country)	Description (a)
Single-Dose Studies	
014 (US)	ADME (mass balance)
103 (US)	Absolute bioavailability
027 (US)	Bioequivalence of Phase III clinical supply and proposed commercial formulations
001 and 001 Addendum (US)	Ascending dose: pharmacokinetics and pharmacodynamics
CPH-001 (Japan)	Ascending dose: pharmacokinetics and pharmacodynamics
026 (US)	Food effect on pharmacokinetics
CPH-006 (Japan)	Food effect on pharmacokinetics
CPH-007 (Japan)	Food effect on pharmacokinetics and pharmacodynamics
Multiple-Dose Studies	
CPH-002 (Japan)	Ascending dose: pharmacokinetics and pharmacodynamics
004 (US)	QTc
019 (US)	QTc
101 (US)	Pharmacokinetics and pharmacodynamics of once daily vs BID dosing
002 (US)	Ascending dose: pharmacokinetics and pharmacodynamics in subjects with T2DM
Effects of Intrinsic Factors	
022 (US)	Effect of age, race, and sex on pharmacokinetics and pharmacodynamics
CPH-003 (Japan)	Effect of age on pharmacokinetics and pharmacodynamics
006 (US)	Effect of renal impairment on pharmacokinetics
023 (US)	Effect of hepatic impairment on pharmacokinetics
Effects of Extrinsic Factors (Drug-Interaction Studies)	
Effect of Other Drugs on Alogliptin	
016 (US)	Fluconazole, ketoconazole, gemfibrozil
020 (US)	Cyclosporine
CPH-004 (Japan)	Voglibose
Effect of Alogliptin on Other Drugs	
015 (US)	Caffeine, tolbutamide, dextromethorphan, midazolam, fexofenadine (drug cocktail)
018 (US)	Glyburide
021 (US)	Warfarin
024 (US)	Ethinyl estradiol and norethindrone
Effect of Other Drugs on Alogliptin and Effect of Alogliptin on Other Drugs	
005 (US)	Cimetidine and metformin (and food effect)
017 (US)	Pioglitazone
025 (US)	Atorvastatin
029 (US)	Digoxin
Population Pharmacokinetics	
008 Population PK Report (multinational)	Population pharmacokinetic analysis in an efficacy and safety study of alogliptin in subjects with T2DM (Phase III)

All subjects were healthy unless otherwise stated.

Table 2 Alogliptin Main and Supportive Phase III Studies by Indication

Indication	Main Studies	Supportive Studies
Add-on to MET	008, 305(a), 010	302, 322OPI-001

Add-on to SU	007, 010	
Add-on to TZD	009, 010	322OPI-002
Add-on to MET and TZD	009, 322OPI-004, 010	322OPI-001
Add-on to insulin (with or without MET)	011, 010	
Other supportive studies (eg, special populations)		
402, a CV outcomes study with high-risk CV subjects and varying degrees of renal impairment (a); 303, elderly subjects; 012, long-term OLE; and 301, postprandial lipids		

(a) Study is ongoing; interim results are presented in this document.

Table 3 Clinical Pharmacology Studies: Alogliptin/Metformin

Study Number (Country/Region) (a)	Description (b)
322MET-101	Bioequivalence of proposed commercial formulation and individual alogliptin and US-sourced metformin HCl tablets
322MET-102	Food-effect on pharmacokinetics
322MET-103 (Europe)	Bioequivalence of proposed commercial formulation and individual alogliptin and EU-marketed metformin HCl tablets
322-101	Pharmacokinetics and pharmacodynamics of BID vs once daily dosing of alogliptin
322-005	Drug-interaction between alogliptin and metformin

(a) All studies were conducted in the US unless otherwise stated.
(b) All subjects were healthy.

Table 4 Alogliptin/Metformin Main and Supportive Phase III Studies by Indication

Indication	Main Studies	Supportive Studies
Add-on to MET	008, 305 (a)	302, 322OPI-001
Add-on to MET and TZD	009, 322OPI-004	322OPI-001
Add-on to insulin (with or without MET)	011	

(a) Study is ongoing; interim results are presented in this document.

2.4.2. Pharmacokinetics

2.4.2.1. Pharmacokinetics of alogliptin

With regard to the commercial tablets, four tablet strengths of alogliptin were developed: 3.125, 6.25, 12.5, and 25 mg. While the 3.125 mg dose strength was developed for the purpose of dose reduction in patients with severe renal impairment, the 6.25 mg dose is being proposed for use in patients with severe renal impairment/ end-stage renal disease (ESRD); the 12.5 mg dose strength is for patients with moderate renal impairment; the registration of the 3.125 mg tablet strength is not being sought. During the procedure, the applicant withdrew its application for the 6.25 mg+850 mg, 6.25 mg+1000 mg strengths.

Four formulations of alogliptin were used in the clinical program. The formulation of the Phase III tablet that was used in the main studies and the proposed commercial tablet differed substantially. Bioequivalence between the alogliptin Phase III and proposed commercial tablets was established for both the 12.5 and 25 mg tablets (90% CI within the 80%-125% range). Additionally the lower commercial tablet strengths had the same dissolution profile as the 12.5 and 25 mg tablet strengths.

2.4.2.1.1. Absorption

Alogliptin is absorbed rapidly with median time to reach C_{max} (T_{max}) occurring approximately 1-2 hours after single and multiple dosing. Food does not alter the pharmacokinetics of alogliptin. The absolute bioavailability of alogliptin is close to 100%. Therefore, alogliptin is considered to be highly permeable. This is confirmed by the mass balance study in which at least 76% of the (radioactivity) is recovered in urine.

2.4.2.1.2. Distribution

Protein binding of alogliptin was approximately 20% and was unaffected by renal impairment. Protein binding of M-I ranges from 12-32%. The volume of distribution (Vz) of alogliptin following a 12.5 mg IV dose was 417 L. The Vz was greater than total body water (42 L), which indicates that alogliptin is well distributed into tissues. The apparent volume of distribution (Vz/F) at steady state was 300 L at a dose of 25 mg alogliptin administered once daily for 14 days in patients with T2DM.

2.4.2.1.3. Elimination

The overall mean recovery of radioactivity in urine + faeces was 88.5 %. Approximately 76% of orally administered radioactivity was excreted in urine. This confirms that the extent of oral absorption in humans is high (at least 76%), and that alogliptin is moderately to highly permeable. Metabolism represents only a small part of the elimination of alogliptin; 95% of the radioactivity recovered in urine and 88% of the radioactivity recovered in faeces was alogliptin. The clearance (CL) of alogliptin following the 12.5 mg IV dose was 14 L/hr. CL/F ranges between 15- 20 L/hr.

2.4.2.1.4. Metabolism

Alogliptin is metabolized into 2 identified minor metabolites: M-I, an N-demethylated metabolite via CYP2D6, and M-II, an N-acetylated metabolite. CYP3A4 may also be involved in the formation of other unidentified minor metabolites. Exposure to these 2 metabolites in plasma, relative to unchanged drug, are < 1% and < 6%, respectively. M-I has DPP-4 inhibitory activity similar to that of alogliptin; M-II has no DPP-4 inhibitory activity.

Alogliptin exists predominantly as the (R)-enantiomer (> 99%) and undergoes little or no enantiomeric conversion to the (S)-enantiomer in vivo. The (R)-enantiomer is the active moiety, and is > 150-fold more active against DPP-4 than the (S) enantiomer. Therefore, inter-conversion has no clinical implications.

2.4.2.1.5. Dose proportionality and time dependencies

Dose proportionality has been established across the dose range of 6.25 to 800 mg. Steady state is achieved after 7 days. Accumulation was ~1.4 fold.

The intersubject variability of alogliptin ranged for the C_{max} and AUC between 17-31%. The intrasubject variability was (<23% for C_{max} and AUC values).

Exposure to alogliptin is similar in subjects with T2DM and healthy subjects.

2.4.2.1.6. Special populations

Renal impairment

Exposure to alogliptin increased with increasing severity of renal impairment. Peak exposure (Cmax) to alogliptin was approximately 13%, 42%, 27%, and 32% greater in subjects with mild, moderate, and severe renal impairment, and subjects with ESRD, respectively, than in healthy

subjects. Total exposure (AUC(0-inf) to alogliptin in subjects with renal impairment increased with decreases in renal function, and was approximately 71%, 112%, 251%, and 377% greater in subjects with mild, moderate, and severe renal impairment, and ESRD, respectively, than in healthy subjects. No significant differences in Tmax for any of the renal impairment groups vs the healthy matched controls for each group were observed. Metabolic ratios of alogliptin to M-I in healthy subjects and in subjects with severe renal impairment or ESRD were similar.

Hepatic impairment

No clinical significant differences in AUC and peak Cmax exposure to alogliptin was observed in subjects with moderate hepatic impairment than in healthy subjects; therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment (Classes A and B). Subjects with severe hepatic impairment were not evaluated.

Gender and weight

No clinically meaningful changes in exposure related to gender, and weight were observed. Therefore, no dose adjustment is required.

Age and race

Small increases in exposure related to age and race were observed, the AUC was about 30% increased after multiple doses.

2.4.2.1.7. Pharmacokinetic interaction studies

In vitro results: Alogliptin did not induce CYP1A2, CYP2B6, CYP2C9, and CYP2C19 in vitro. Little or no direct inhibition was observed for CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5) in vitro.

Alogliptin was not an in vitro inhibitor of BCRP, OAT1, OAT3 and OCT2 at clinically relevant concentrations. Therefore, clinically relevant interactions via BCRP, OAT1, OAT3 and OCT2 inhibition by alogliptin are not expected.

Clinical results: Clinical alogliptin drug-drug interaction studies of digoxin (a substrate of P-glycoprotein [P-gp]) and cyclosporine (an inhibitor of P-gp) confirmed that alogliptin is neither a substrate of P-gp, nor an inhibitor of P-gp.

It can be concluded that at clinically relevant concentrations (Cmax = 0.3 µM), alogliptin is not a substrate or inhibitor of P glycoprotein, OAT1, OAT3, and OCT2.

A clinical study was performed to study the interaction potential between alogliptin and cyclosporine (inhibitor of OATP1B1/OATP1B3, BCRP and P-glycoprotein). No clinically relevant interactions were observed. In addition, OATP is involved in the transport from the systemic circulation to the liver based on the in vivo excretion pattern most likely not relevant. However, alogliptin is mainly

excreted as parent compound via urine and BCRP transporters are involved in the transport to urine. Based on the provided clinical data it cannot be concluded that alogliptin is not an inhibitor of BCRP. Since, the bioavailability of alogliptin is high, no clinically relevant changes in alogliptin exposure are expected if alogliptin was a substrate of BCRP and it was concomitantly administered with a drug that is an inhibitor of BCRP. In addition, since excretion via faeces is <15%, it will be unlikely that an inhibitor of BCRP could have an effect on the excretion of alogliptin if alogliptin would be a substrate of BCRP.

Whether alogliptin is a substrate and/or an inhibitor of OCT1, OCT2, MATE1 and MATE2 was investigated in a clinical study in healthy volunteers with cimetidine and metformin. Cimetidine is an inhibitor of OCT1, OCT2, MATE1 and MATE2. Metformin is a substrate of OCT1, OCT2, MATE1 and MATE 2. No clinically relevant effects were observed on the exposure of alogliptin, cimetidine and metformin. Therefore, no clinically relevant drug-drug interactions are expected for alogliptin as either a substrate or as an inhibitor of OCT1, OCT2, MATE1 and MATE2 at current exposure levels (dose up to 100 mg once daily).

Alogliptin and co-administrated drugs were dosed together in the studies. Based on the data presented there is no obvious effect of alogliptin on the tmax and subsequently on the gastric emptying of the drugs coadministrated with alogliptin.

No clinically meaningful changes in exposure to a number of drugs that are metabolized by CYP isozymes (pioglitazone [2C8]; glyburide, tolbutamide and (S)-warfarin [2C9]; midazolam, atorvastatin, ethinyl estradiol, and norethindrone [3A4]; caffeine and (R)-warfarin [1A2]; dextromethorphan [2D6]), transported by P-glycoprotein (Pgp) (fexofenadine and digoxin) or organic cation transporter 2 (OCT2) (MET), or drugs that are excreted unchanged in urine (MET, cimetidine [an OCT2 inhibitor], and digoxin) were observed when these drugs were administered with alogliptin.

In addition, no clinically meaningful changes in exposure to alogliptin were observed when it was administered with MET, cimetidine, or digoxin (drugs that are excreted renally), pioglitazone (a 2C8 substrate), or atorvastatin (a 3A4 substrate); with drugs that inhibit CYP isozymes (ketoconazole [3A4], fluconazole [2C9], and gemfibrozil [2C8/9]); with Pgp or OCT2 substrates (digoxin [Pgp], MET [OCT2]) or inhibitors (cyclosporine [Pgp], cimetidine [OCT2]); or with a drug that is excreted primarily in the feces (voglibose [an α-glucosidase inhibitor]). In general, alogliptin seems to have a low potential for interactions with co-administered medicinal products.

2.4.2.2. Pharmacokinetics of metformin

The applicant provided an overview of the pharmacokinetics of metformin based on literature data. A summary is provided below. The results are in line with the SmPC of metformin. This approach is acceptable as metformin is a well characterized drug that has been used extensively in the EU for many years.

2.4.2.2.1. Absorption

The Tmax of metformin is reached in approximately 2.5 hours after an oral dose of metformin HCl. Absolute bioavailability of a 500 or 850 mg metformin HCl tablet is approximately 50% to 60% in healthy subjects. The non-absorbed fraction recovered in feces after an oral dose was 20% to 30%.

Metformin absorption is saturable and incomplete after oral administration. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the usual metformin HCl doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally <1 µg/mL. Maximum metformin plasma levels (Cmax) did not exceed 4 µg/mL in controlled clinical trials, even at maximal doses.

Food decreases the extent and slightly delays the absorption of metformin. Cmax was 40% lower, AUC was 25% lower, and Tmax was prolonged by 35 minutes following oral administration of a metformin 850 mg tablet with food than without food. The clinical relevance of these findings is unknown. Nevertheless, to reduce undesirable gastrointestinal symptoms associated with metformin, it is common clinical practice for metformin HCl to be given with or just after food.

2.4.2.2.2. Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged from 63 to 276 L.

2.4.2.2.3. Elimination

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Renal clearance of metformin is > 400 mL/min, which is approximately 3 to 4 times greater than the creatinine GFR; this indicates that metformin is eliminated by glomerular filtration and active tubular secretion. The apparent T1/2 following an oral dose is approximately 6.5 hours. Renal clearance decreases in proportion to creatinine clearance when renal function is impaired, thus the T1/2 is prolonged, which leads to increased levels of metformin in plasma.

2.4.2.2.4. Special populations

Metformin is excreted by the kidney; therefore, serum creatinine levels should be determined before initiating treatment with metformin HCl and regularly thereafter. Metformin is contraindicated in patients with moderate to severe renal failure or renal dysfunction (e.g. serum creatinine levels >135 µmol/L in male patients and > 110 µmol/L in female patients) or in patients with acute conditions that may alter renal function (e.g. dehydration, severe infection, or shock) due to the risk of lactic acidosis.

Because of the potential for decreased renal function in elderly patients, metformin should be used in this population as described in the paragraph above. In addition, special caution should be exercised in situations where renal function may become impaired, such as when initiating antihypertensive, diuretic, or NSAID therapy.

Metformin is contraindicated in patients with hepatic insufficiency due to the increased risk of lactic acidosis.

2.4.2.2.5. Pharmacokinetic interaction studies

The SmPC for metformin HCl contains the following recommendations for administration of metformin HCl with alcohol, iodinated contrast agents, medicinal products with intrinsic hyperglycaemic activity, and ACE inhibitors:

The risk of lactic acidosis is increased in acute alcohol intoxication, and consumption of alcohol and alcohol-containing medications should be avoided.

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis; therefore, metformin therapy should be discontinued prior to, or at the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Glucocorticoids, β-2-agonists, and diuretics have intrinsic hyperglycemic activity; patients should be informed and blood glucose should be monitored more frequently, especially at the beginning of treatment and if necessary, the dose of metformin HCl should be adjusted during therapy with the other medicinal product and upon its discontinuation.

Angiotensin-converting enzyme (ACE) inhibitors may decrease blood glucose levels; if necessary, the dose of metformin HCl should be adjusted during therapy with the other drug and upon its discontinuation.

2.4.2.3. Pharmacokinetics of alogliptin/metformin combination

In this Marketing Authorisation Application (MAA), Takeda seeks registration of alogliptin/metformin at a dose of alogliptin 6.25 mg or 12.5 mg in combination with metformin 850 mg or 1000 mg for twice daily (BID) dosing in adults with T2DM.

The product is manufactured as immediate-release, oblong, biconvex, film-coated tablets for twice daily oral administration.

Six dosage strengths of alogliptin/metformin (A6.25+M500, A6.25+M850, A6.25+M1000, A12.5+M500, A12.5+M850, and A12.5+M1000) were developed. All 6 tablet strengths have a bilayer structure and contain the same ingredients. The alogliptin and metformin layer are each based on a dose proportional composition. Therefore the tablets are varying with size and weight as are the relative amounts of mannitol, microcrystalline cellulose, and povidone.

Four tablet strengths are proposed for commercial use containing 6.25mg+850mg, 6.25mg+1000mg, 12.5mg+850mg and 12.5mg+1000mg of alogliptin and metformin hydrochloride.

2.4.2.3.1. Bioequivalence studies

Six dosage strengths of alogliptin/metformin (A6.25+M500, A6.25+M850, A6.25+M1000, A12.5+M500, A12.5+M850, and A12.5+M1000) were developed. In agreement with CHMP scientific advice, a bracketing approach (evaluation of the highest and lowest dose strengths in humans in vivo) in conjunction with in vitro comparative dissolution analysis of all 6 dose strengths was used to evaluate the bioequivalence of the FDC tablets to individual alogliptin and EU-marketed metformin HCl tablets. This analysis is consistent with recommendations in the EMA Guideline on

the Investigation of Bioequivalence, January 2010. Two bioequivalence studies (322MET-101 and 322MET-103), were performed.

In study 322MET-103, the pivotal BE study, the developed combination tablets containing the lowest and highest amount of metformin (500 mg and 1000 respectively) and the tablets containing the lowest and highest amount of alogliptin (6.25 and 12.5 respectively) were compared with individual corresponding alogliptin and metformin tablets.

Bioequivalence between the combination A6.25+M500, A6.25+M1000, A12.5+M500, A12.5+M1000 combination tablets and corresponding individual tablets was shown (see tables 5, 6 and 7). In all cases the 90% CI of the AUC and C_{max} was within the 80%-125% range. Therefore, it can be considered that bioequivalence of the alogliptin/metformin 6.25 mg+1000 mg tablet and 12.5 mg+1000 mg tablet to individual alogliptin and metformin tablets were shown.

No identifiable effects on inter- or intra-subject variability in the pharmacokinetic parameters of alogliptin or metformin due to administration of individual or FDC tablets, to different tablet strengths, or to study design were observed.

A6.25+M500 tablet

The statistical analyses of the plasma pharmacokinetic parameters of alogliptin and metformin following administration of an A6.25+M500 tablet and individual alogliptin 6.25 mg and metformin HCl 500 mg tablets are presented in the table below.

Table 5. Statistical Comparison of the Plasma Pharmacokinetic Parameters of Alogliptin and Metformin Following Administration of an A6.25+M500 Tablet and Individual Alogliptin 6.25 mg and Metformin HCl 500 mg Tablets: Study 322MET-103

		Arithmetic Mean		
Analyte Parameter (units)	N	A6.25+M500 (T)	Alogliptin 6.25 mg + Metformin HCl 500 mg (R)	Point Estimate·100 (90% CI) (a)
Alogliptin				
AUC(0-tlqc) (ng·hr/mL)	33	452.23	452.06	100.06 (97.47, 102.72)
AUC(0-inf) (ng·hr/mL)	32	496.94	493.56	100.59 (98.22, 103.01)
Cmax (ng/mL)	33	28.86	30.75	94.74 (89.35, 100.46)
Tmax (hr) (b,c)	33	3.00	2.98	N/A
Metformin				
AUC(0-tlqc) (ng·hr/mL)	33	8608.38	8529.88	101.22 (95.93, 106.79)
AUC(0-inf) (ng·hr/mL)	29	8763.13	8607.40	102.27 (96.66, 108.20)
Cmax (ng/mL)	33	1137.21	1163.94	98.78 (92.57, 105.39)
Tmax (hr) (b,d)	33	2.98	2.98	N/A

N/A=not applicable, T=test treatment, R=reference treatment.
(a) Point estimates (differences between the LS mean values for the test treatment and the reference treatment) and CIs were calculated using natural log-transformed data and are presented as percentages.
(b) Tmax is presented as the median.
(c) p=0.332 for the mean Tmax values (original scale) for the test vs the reference treatment.
(d) p=0.723 for the mean Tmax values (original scale) for the test vs the reference treatment.

The 90% CIs for the point estimates of the ratios of the central values for the area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration ($AUC_{(0\ tlqc)}$), area under the plasma concentration-time curve from time 0 to infinity ($AUC_{(0\ inf)}$), and maximum observed plasma concentration (C_{max}) values of both alogliptin and metformin were within the 80% to 125% bioequivalence range. Therefore, the A6.25+M500 tablet met the standards for bioequivalence to the individual alogliptin 6.25 mg and metformin HCl 500 mg tablets.

No differences in the median T_{max} values for either alogliptin or metformin were observed between the A6.25+M500 tablet and the individual alogliptin 6.25 mg and metformin HCl 500 mg tablets.

A6.25+M1000 tablet

Table 6. Statistical Comparison of the Plasma Pharmacokinetic Parameters of Alogliptin and Metformin Following Administration of an A12.5+M500 Tablet and Individual Alogliptin 12.5 mg and Metformin HCl 500 mg Tablets: Study 322MET-103

		Arithmetic Mean		
Analyte Parameter (units)	**N**	**A12.5+M500 (T)**	**Alogliptin 12.5 mg + Metformin HCl 500 mg (R)**	**Point Estimate·100 (90% CI) (a)**
Alogliptin				
AUC(0-tlqc) (ng·hr/mL)	33	917.95	851.17	100.97 (99.15, 102.82)
AUC(0-inf) (ng·hr/mL)	33	860.75	907.98	100.97 (99.22, 102.75)
Cmax (ng/mL)	33	61.01	60.22	101.98 (95.69, 108.69)
Tmax (hr) (b,c)	33	3.98	2.98	N/A
Metformin				
AUC(0-tlqc) (ng·hr/mL)	33	8698.77	8491.37	102.46 (97.91, 107.23)
AUC(0-inf) (ng·hr/mL)	32	8885.81	8716.63	101.89 (97.65, 106.32)
Cmax (ng/mL)	33	1178.73	1136.58	103.07 (96.76, 109.79)
Tmax (hr) (b,d)	33	2.98	2.98	N/A

(a) Point estimates (differences between the LS mean values for the test treatment and the reference treatment) and CIs were calculated using natural log-transformed data and are presented as percentages.
(b) Tmax is presented as the median.
(c) p=0.022 for the mean Tmax values (original scale) for the test vs the reference treatment.
(d) p=0.512 for the mean Tmax values (original scale) for the test vs the reference treatment.

The 90% CIs for the point estimates of the ratios of the central values for the $AUC_{(0\text{-}tlqc)}$, $AUC_{(0\ inf)}$, and C_{max} values of both alogliptin and metformin were within the 80% to 125% bioequivalence range. Therefore, the A12.5+M500 tablet met the standards for bioequivalence to the individual alogliptin 12.5 mg and metformin HCl 500 mg tablets.

No differences in the median T_{max} values for either alogliptin or metformin were observed between the A12.5+M500 tablet and the individual alogliptin 12.5 mg and metformin HCl 500 mg tablets.

A12.5+M1000 tablet

The statistical analyses of the plasma pharmacokinetic parameters of alogliptin and metformin following administration of an A12.5+M1000 tablet and individual alogliptin 12.5 mg and metformin HCl 1000 mg tablets are presented in the table below.

Table 7. Statistical Comparison of the Plasma Pharmacokinetic Parameters of Alogliptin and Metformin Following Administration of an A12.5+M1000 Tablet and Individual Alogliptin 12.5 mg and Metformin HCl 1000 mg Tablets: Study 322MET-103

		Arithmetic Mean		
Analyte Parameter (units)	**N**	**A12.5+M1000 (T)**	**Alogliptin 12.5 mg + Metformin HCl 1000 mg (R)**	**Point Estimate·100 (90% CI) (a)**
Alogliptin				
AUC(0-tlqc) (ng·hr/mL)	34	835.37	824.02	101.31 (99.51, 103.15)
AUC(0-inf) (ng·hr/mL)	34	898.49	885.39	101.35 (99.61, 103.11)
Cmax (ng/mL)	34	57.99	59.12	98.62 (92.60, 105.04)
Tmax (hr) (b,c)	34	3.00	3.03	N/A
Metformin				
AUC(0-tlqc) (ng·hr/mL)	34	13503.52	13963.67	97.56 (93.27, 102.05)
AUC(0-inf) (ng·hr/mL)	30	13974.16	14418.12	98.77 (94.53, 103.21)
Cmax (ng/mL)	34	1754.41	1888.97	94.09 (88.39, 100.16)

Tmax (hr) (b,d)	34	3.00	3.00	N/A

(a) Point estimates (differences between the LS mean values for the test treatment and the reference treatment) and CIs were calculated using natural log-transformed data and are presented as percentages.
(b) Tmax is presented as the median.
(c) p=0.367 for the mean Tmax values (original scale) for the test vs the reference treatment.
(d) p=0.348 for the mean Tmax values (original scale) for the test vs the reference treatment.

The 90% CIs for the point estimates of the ratios of the central values for the $AUC_{(0\text{-}tlqc)}$, $AUC_{(0\ inf)}$, and C_{max} values of both alogliptin and metformin were within the 80% to 125% bioequivalence range. Therefore, the A12.5+M1000 tablet met the standards for bioequivalence to the individual alogliptin 12.5 mg and metformin HCl 1000 mg tablets.

No differences in the median time to reach C_{max} (T_{max}) values for either alogliptin or metformin were observed between the A12.5+M1000 tablet and the individual alogliptin 12.5 mg and metformin HCl 1000 mg tablets.

2.4.2.3.2. Food interaction

Food does not clinically significantly alter the pharmacokinetics of alogliptin. Food influenced the pharmacokinetics of metformin when given as a combination tablet with alogliptin. C_{max} was 28% lower, and T_{max} was prolonged by 1.5 hours following oral administration of a alogliptin/metformin 12.5/1000 mg tablet with food than without food (see table below). It is known for metformin that food decreases the extent and slightly delays the absorption of metformin. The clinical relevance of these findings is unknown. Nevertheless, to reduce undesirable gastrointestinal symptoms associated with metformin, it is common clinical practice for metformin HCl to be given with or just after food. Correspondingly, in the SmPC of Vipdomet it is stated that Vipdomet should be taken twice daily because of the pharmacokinetics of its metformin component. It should also be taken with meals to reduce the gastrointestinal undesirable effects associated with metformin.

Table 8. Plasma Pharmacokinetic Parameters of Alogliptin and Metformin Following Administration of an A12.5+M1000 Tablet Under Fed and Fasted Conditions: Study 322MET-102

			Geometric Means		
Analyte Parameter (units)	**N (T)**	**N (R)**	**A12.5+M1000 Fed (T)**	**A12.5+M1000 Fasted (R)**	**Ratio T/R·100 (90% CI) (a)**
Alogliptin					
AUC(0-tlqc) (ng·hr/mL)	24	24	810.49	832.32	97.38 (92.27, 102.77)
AUC(0-inf) (ng·hr/mL)	24	23	878.02	917.01	95.75 (91.52, 100.18)
Cmax (ng/mL)	24	24	56.16	64.67	86.85 (79.90, 94.39)
Tmax (hr) (b,c)	24	24	2.75	2.50	N/A
Metformin					
AUC(0-tlqc) (ng·hr/mL)	24	24	12573.39	13624.16	92.29 (85.64, 99.45)
AUC(0-inf) (ng·hr/mL)	22	23	12637.16	13798.21	91.59 (84.63, 99.12)
Cmax (ng/mL)	24	24	1509.23	2106.59	71.64 (66.53, 77.15)
Tmax (hr) (b,d)	24	24	4.00	2.50	N/A

(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as the median.
(c) p=0.263.
(d) p<0.001.

2.4.2.3.3. Posology - Once daily dosing vs twice daily dosing

Twice daily dosing compared with once daily dosing resulted in identical exposure (AUC) but resulted in lower C_{max} of approximately 35% (study 101). Clinical results indicate no difference in efficacy when alogliptin is administered once daily vs twice daily.

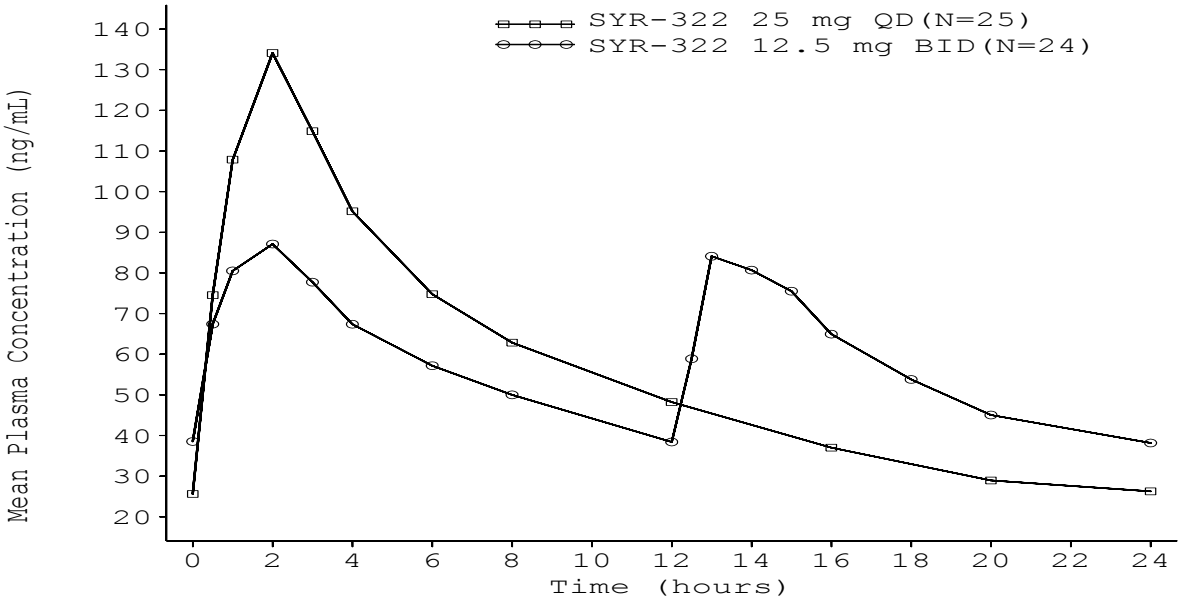
Mean plasma concentrations of alogliptin following administration of alogliptin 12.5 mg BID and 25 mg once daily for 7 days are presented in figure 1. For pharmacokinetic results (see table 9).

Table 9. Summary of Plasma and Urine Pharmacokinetic Parameters of Alogliptin 12.5 mg and Alogliptin 25 mg on Day 7

Analyte Parameter (units)	Arithmetic Mean (%CV)		LS Mean		
	Alogliptin 12.5 mg BID (T) n=24	Alogliptin 25 mg QD (R) n=25	Alogliptin 12.5 mg BID (T) n=24	Alogliptin 25 mg QD (R) n=25	Ratio (T/R)·100 (90% CI) (a)
Alogliptin Plasma					
AUC(0-24) (ng·hr/mL)	1383.58 (14.386)	1362.22 (17.877)	1378.53	1339.21	102.94 (97.57, 108.60)
AUC(0-12) AM	706.69 (15.364)	—	698.77	—	95.88 (93.39, 98.44) (b)
AUC(12-24) PM	676.89 (14.482)	—	670.01	—	(b)
Cmax (ng/mL)	92.65 (22.668)	144.26 (24.812)	91.02	139.23	65.38 (59.17, 72.24)
Cmin (ng/mL)	37.23 (17.577)	24.84 (21.977)	37.17	24.43	152.16 (145.27, 159.37)
Ctrough (ng/mL) (c)	38.62 (16.287)	24.59 (18.644)	—	—	—
Tmax (hr) (d,e,f)	1.98 (0.983, 3.017)	1.98 (0.517, 2.983)	1.98	1.98	—
Swing (%)	152.94 (37.830)	496.91 (34.473)	—	—	—
Fluctuation (%)	—	208.61 (20.585)	—	—	—
Fluctuation (0-12) (%)	92.29 (26.526)	—	—	—	—
Cavg (ng/mL)	—	56.80 (17.877)	—	—	—
Cavg (0-12) (ng/mL)	59.31 (15.370)	—	—	—	—
Cavg (12-24) (ng/mL)	56.14 (14.460)	—	—	—	—
Alogliptin Urine					
Ae(0-24) (mg)	16.36 (12.961)	16.03 (28.670)	16.25	14.85	109.41 (90.91, 131.68)
CLr(0-24) (L/hr)	12.03 (17.139)	11.97 (30.549)	11.82	11.09	106.61 (89.77, 126.60)
Fe(0-24) (%)	65.44 (12.961)	64.13 (28.670)	—	—	—

– =not applicable, %CV=percent coefficient of variation, T=test treatment (treatment B), R=reference treatment (treatment A).
(a) Ratios and CIs were presented as percentages.
(b) Value shown is the ratio of AUC(12-24) PM to AUC(0-12) AM.
(c) Alogliptin 25 mg QD N=75, alogliptin 12.5 mg BID N=74. Sample size for Ctrough is defined in the Statistical Analysis Plan as observed predose (trough) plasma concentration on Days 5, 6, and 7.
(d) Median (minimum, maximum) values are presented for Tmax.
(e) n=24 for alogliptin 25 mg QD Tmax LS Mean and AUC(0-tau).
(f) P=0.905.

Figure 1. Mean Plasma Concentrations of Alogliptin vs Time On Day 7 Following Administration of Alogliptin 12.5 mg BID and 25 mg Once Daily for 7 Days: Study 322-101



The 90% CI for AUC for the 12.5 mg BID dose to the 25 mg once daily dose was within the 80% to 125% range. Therefore, total exposure from time 0 to 24 hours was similar between the once daily and BID dosing regimens. The 90% CIs for the ratios of the C_{max} and C_{min} were not within the 80% to 125% range; this is expected for a drug with linear pharmacokinetics. According to the superposition principle, C_{max} will be lower with BID administration (every 12 hours) than with QD administration of the same total daily dose. No difference in the median T_{max} values of alogliptin was observed between the 25 mg once daily dose and the morning 12.5 mg BID dose (2 hours).

The renal excretion for alogliptin was similar when alogliptin was dosed as 25 mg once daily or 12.5 mg BID.

2.4.2.3.4. Interaction profile of alogliptin and metformin

No changes in exposure to alogliptin and no clinically meaningful changes in exposure metformin (an OCT2 substrate that is primarily excreted unchanged in the urine) were observed when alogliptin and metformin were coadministered (see table below).

Table 10 Effect of Alogliptin on Exposure to Metformin: Study 005

		LS Mean		
Parameter (unit)	**N**	**Alogliptin 100 mg QD + Metformin 1000 mg BID (T)**	**Metformin 1000 mg BID (R)**	**Ratio T/R·100 (90% CI) (a)**
AUC(0-12) (ng·hr/mL)	16	12022.75	10112.82	118.9 (109.5, 129.1)
Cmax (ng/mL)	16	1875.65	1867.75	100.4 (91.9, 109.7)
Tmax (hr) (b)	**16**	**2.00**	**1.03**	**N/A**

N/A=not applicable, R=reference treatment, T=test treatment.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as the median.

2.4.3. Pharmacodynamics

2.4.3.1. Alogliptin

Pharmacodynamics of alogliptin were investigated in 8 PK/PD studies, including healthy volunteers, Japanese healthy volunteers, and subjects with T2DM.

Study 001 was an ascending single dose study in healthy subjects, using doses from 25 mg -800 mg.

Study CHP-001 was a single dose study including lower dosages of alogliptin (6.25 mg to 200 mg) and was performed in healthy Japanese subjects.

Study 002 was a multiple dose study (25, 100 or 400 mg or placebo) in subjects with T2DM. Subjects received alogliptin or placebo once daily for 14 days.

Study CHP-002 was a multiple dose study in healthy male Japanese subjects, using doses of 25 or 50 mg alogliptin once daily for 7 days. After safety data were confirmed, subjects received alogliptin 100 mg once daily for 7 days.

Study 101 was a randomized, open-label, 2-sequence, 2-period crossover study in healthy adults to determine if alogliptin/metformin could be given twice daily as recommended for metformin.

Study 022 investigated effects of age, race and sex on single and multiple-dose pharmacodynamics of alogliptin.

Study 004 and study 019 were QT/QTc studies.

2.4.3.1.1. Mechanism of action

Alogliptin inhibits DPP-4. DPP-4 is the primary enzyme involved in the rapid degradation of the incretin hormones GLP-1 and GIP. GLP-1 augments glucose-induced insulin secretion, inhibits glucagon secretion and hepatic glucose production, and increases glucose disposal. Based on the mechanism of action, DPP-4 inhibition is expected to increase active GLP-1 levels in patients with T2DM.

Alogliptin and metformin have complementary mechanisms of action.

2.4.3.1.2. Primary and Secondary pharmacology

DPP-4 inhibition

Based on current literature, DPP-4 inhibition of $\geq$ 80% is necessary to achieve optimal glucose reduction. Following single-dose administration in healthy subjects, maximum inhibition (Emax) was > 93% for all dose groups (25, 50, 100, 200, 400, and 800 mg), with median time to Emax (Tmax) of 2 to 3 hours (study 001), and > 88% for all dose groups (6.25, 12.5, 25, 50, 100, and 200 mg), with median Tmax of 1.00 to 1.25 hours [CPH-001]. Emax and Tmax for the placebo group were 12.2% and 6 hours, respectively, in study 001, and 16.0% and 12.5 hours, respectively, in study CPH-001. Mean inhibition at 24 and 72 hours post dose (E24 and E72) ranged

from 74.3% and 47.5%, respectively, for the 25 mg group, to 97.0% and 83.0%, respectively, for the 800 mg group in study 001, and from 64.7% and 27.8%, respectively, for the 6.25 mg group, to 94.2% and 74.4%, respectively, for the 200 mg group in study CPH-001.

Following multiple-dose administration in healthy Japanese subjects [CPH-002], Emax was > 95% for all dose groups (25, 50, and 100 mg), with Tmax of 1 hour on both Day 1 and after 7 days of once-daily dosing (Day 7). Emax and Tmax for the placebo group were 3.8% and 15 hours, respectively, on Day 1, and 4.6% and 15 hours, respectively, on Day 7. E24 ranged from 79.7% for the 25 mg group to 89.8% for the 100 mg group on Day 1 and from 83.5% for the 25 mg group to 92.0% for the 100 mg group on Day 7.

Following multiple-dose administration in subjects with T2DM (study 002), Emax was >93% for all dose groups (25, 100, and 400 mg), with Tmax of approximately 1 hour on Day 1 and 1 to 2.5 hours after 14 days of once-daily dosing (Day 14). Emax and Tmax for the placebo group were 25.3% and 1.5 hours, respectively, on Day 1, and 20.8% and 6.5 hours, respectively, on Day 14. E24 ranged from 78.3% to 95.7% on Day 1 and from 81.8% to 96.7% on Day 14, and E72 ranged from 66.3% to 81.6% for the 3 alogliptin groups on Day 14.

The multiple-dose pharmacodynamics of alogliptin when dosed orally as alogliptin 12.5 mg BID and as alogliptin 25 mg once daily were compared in study 101. This study was relevant for the FDC alogliptin/metformin, since metformin is recommended to take 2-3 times daily. The DPP-4 inhibition with BID dosing of alogliptin was similar to that with once daily dosing. In this study, the DPP-4 inhibition at 24 hours post-dose, as measured by E24, was ≥ 80% during BID dosing (mean E24=84.74%) and during QD dosing (mean E24=80.30%).

NONMEM modeling that combined a 2-compartment, first order absorption pharmacokinetic model with an Emax pharmacodynamic model confirmed the potency of alogliptin as an inhibitor of DPP-4 activity with a predicted Emax value of 96.2% and a predicted EC50 value of 3.73 ng/mL in healthy subjects in study 001 and a predicted Emax of 98.9% and a predicted EC50 value of 6.55 ng/mL in subjects with T2DM in study 002. The EC80 in study 002 was around 30 ng/mL in T2DM patients. This concentration is in line with the 25 mg alogliptin dose.

The effects of age, race, and sex on the single- and multiple-dose pharmacodynamics of alogliptin alone was investigated in a randomized, single-blind, placebo-controlled, parallel-group study in healthy male and female subjects [study 022]. Peak levels of mean DPP-4 inhibition were at least 92% and were reached by 2 hours postdose. DPP-4 inhibition 24 hours after alogliptin administration was 76±4% vs 79±4% in young vs elderly, 77±4% vs 79±5% in men vs women, and 76±4% vs 80±4% in Black vs White. No relevant differences were observed between subgroups.

GLP-1 levels

The inhibition of DPP-4 activity by alogliptin elicited prominent increases in plasma active GLP-1 levels in healthy subjects (this parameter was not evaluated in subjects with T2DM in the phase 1 program), with mean changes from baseline in plasma active GLP-1 levels that were consistently greater in the alogliptin groups than in the placebo groups. Dose-related elevations in plasma levels of GLP-1 persisted through 72 hours after dosing, which is consistent with continuing DPP-4

inhibition. As expected, the effects of alogliptin were most evident after meals when GLP-1 levels increased.

Postprandial glucose concentrations

Following multiple-dose administration in subjects with T2DM (002), statistically significant decreases, compared with placebo, from baseline in 4-hour postprandial glucose concentrations were observed following each meal (breakfast, lunch, and dinner) as well as when averaged across all 3 meals.

Effects on QT time

The applicant performed one QT-study with alogliptin doses 50 mg and 400 mg. This study did not reveal effects of alogliptin on cardiac repolarization. Although, in the highest dose (400 mg alogliptin, which is 16 times the proposed dosage), the 2-sided 90% CI of the difference from placebo in LS mean change from baseline in QTcI interval was >10 msec at two time points (0.5 hours and 1 hour postdose) on Day 7, the difference from placebo at these time points for alogliptin 400 mg was 5.84 msec (90% CI, 1.44-10.24 msec) at 0.5 hour; and 6.60 msec (90% CI, 2.50-10.70 msec) at 1 hour postdose. All other measurements were within the boundary and no other signals on cardiac repolarization in clinical or non-clinical studies have been found, therefore alogliptin is not considered to have effects on cardiac repolarization in the proposed posology (25 mg).

2.4.3.2. Metformin

The pharmacodynamics of metformin was derived from the SmPC and scientific literature available for metformin, which was included in the submission package.

2.4.3.2.1. Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

2.4.3.2.2. Primary and Secondary pharmacology

Metformin improves glucose tolerance in patients with T2DM by lowering both basal and postprandial plasma glucose; reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; improves peripheral glucose uptake and utilization in muscle by increasing insulin sensitivity; delays intestinal absorption of glucose; and stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of all types of membrane glucose transporters (GLUT).

2.4.4. Discussion on clinical pharmacology

2.4.4.1. Alogliptin

Several studies were performed to characterize the PK and PD of alogliptin.

The Pharmacokinetics of alogliptin is fairly uncomplicated. It is absorbed fast and almost completely, the maximum plasma concentration is found after 1-2 hours after administration. Bioequivalence between the alogliptin Phase III and proposed commercial tablets was established for both the 12.5 and 25 mg tablets (90% CI within the 80%-125% range). Additionally the lower commercial tablet strengths had the same dissolution profile as the 12.5 and 25 mg tablet strengths. As all tablet strengths including the lower strengths were used in the pharmacokinetics studies and dose proportionality was sufficiently shown, it is agreed that the conclusion on bioequivalence can be extended to the lower 6.25 and 3.125 mg tablet.

Alogliptin is mainly excreted unchanged via the urine (75%), two minor metabolites were identified: M-I and M-II. The Exposure to these 2 metabolites are <1% and <6%. M-I has DPP-4 inhibitory activity similar to that of alogliptin; M-II has no DPP-4 inhibitory activity. Therefore, small to moderate changes in exposure to these metabolites are not considered to be clinically relevant. CYP2D6 is involved in the formation of these two metabolites and CYP3A4 may also be involved in the formation of other unidentified minor metabolites.

In the PD-studies, alogliptin showed a dose-dependent reduction in DPP-4 levels in both healthy and T2DM patients. Multiple-dose of 25 mg alogliptin treatment caused a≥ 80% reduction in DPP-4 levels, which is considered necessary to achieve optimal glucose reduction. However, it is not known if a lower dose of 12.5 mg could cause a comparable clinically effect. Therefore, both 12.5 mg and 25 mg dose have been used in the clinical trials.

The DPP-4 inhibition with BID dosing of alogliptin was similar to that of once daily dosing. The DPP-4 inhibition at 24 hours post-dose, as measured by E24, was ≥80% during BID dosing (mean E24=84.74%) and during QD dosing (mean E24=80.30%). This is relevant for the FDC alogliptin/metformin, since metformin is recommended to take 2-3 times daily.

The inhibition of DPP-4 activity by alogliptin elicited prominent increases in plasma active GLP-1 levels in healthy subjects, and significant decreases in 4-hour post prandial glucose concentrations in T2DM subjects.

Subjects with severe hepatic impairment were not evaluated; therefore alogliptin is not recommended for patients with severe hepatic impairment (Class C) as stated in section 4.4 of the SmPC.

Increased exposure to alogliptin is observed in patients with renal impairment. An approximate 1.7-fold increase in AUC for alogliptin was observed in patients with mild renal impairment. However, as the distribution of AUC values for alogliptin in these patients was within the same range as control subjects, no dose adjustment of alogliptin and Vipdomet for patients with mild renal impairment is necessary. Metformin is contraindicated for use in patients with moderate and severe renal impairment and end-stage renal disease (creatinine clearance < 60 mL/min) thefore Vipdomet is contraindicated in such patients..

The PK-study 022 showed that gender did not influence the AUC or other PK-parameters. Small increases in exposure related to age and race were observed, the AUC was about 30% increased after multiple doses of alogliptin. These changes were not considered clinically relevant since age or race had no effect on alogliptin inhibition of DPP-4 activity.

However the CHMP had concerns regarding the quality of the population PK analysis in order to be used for description of the effect of weight on alogliptin exposure, and requested during the procedure several updated data sets to assess the influence of body weight.

The applicant provided an updated POP-PK analysis which included pooled data from studies 002, 006, and 008 for a detailed evaluation of the effects of renal function (measured by creatinine clearance [CRCL]) and weight in kilograms [WTKG]) on the PK and exposure of alogliptin. The applicant provided numerical (Bootstrap) and visual (pcVPC) diagnostics thus allowing assessment of the updated model. The effect of body weight in the view of the CHMP was thus well estimated and the model now sufficiently robust with high convergence rate and precise parameter estimates. The conclusion regarding the clinically insignificant effect of body weight on exposure to alogliptin was therefore accepted and is reflected in the text regarding the influence of body weight in SmpC section 5.2.

The alogliptin potential for interactions appears to be low; it has been studied in vivo with all relevant antidiabetic drugs. Most possibly relevant CYP enzymes have been evaluated. The applicant investigated if alogliptin is an in vitro inhibitor of OAT1, OAT3 and OCT2. The study included both control cells and cells transfected with the specific transporter of interest. Further, the used probe substrates (PAH, E3S and metformin) and positive control inhibitors (probenecid, probenecid and quinidine) are appropriate. No clinically relevant inhibition by alogliptin (based on its Cmax of 0.3 µM) was seen for any of the investigated transporters. Alogliptin and co-administrated drugs were dosed together in the studies. Based on the data presented there is no obvious effect of alogliptin on the tmax and subsequently on the gastric emptying of the drugs coadministrated with alogliptin.

The ability of alogliptin to inhibit CYP2B6 (as measured by efavirenz 8-hydroxylation rates) was investigated with a pool of 16 individual human liver microsomal samples at concentrations ranging from 0.1 to 100 µmol/L. The study setup of the submitted study to investigate if alogliptin is an in vitro inhibitor of CYP2B6 is acceptable. The marker CYP2B6 reaction efavirenz 8-hydroxylation and the CYP2B6 positive control inhibitors orphenadrine (750 uM) and phencyclidine (30 uM) is appropriate. No inhibition of CYP2B6 activity by alogliptin was seen up to 100 µM and subsequently the risk for alogliptin inhibition of CYP2B6 at clinically relevant concentrations is unlikely. Information that alogliptin is not an inhibitor of CYP2B6 in vitro is now included in section 5.2 of the SmPC.

2.4.4.2. Metformin

Alogliptin and metformin have complementary mechanisms of action. The absolute bioavailability of metformin is approximately 50% to 60%. Metformin partitions into erythrocytes, which most likely represent a secondary compartment of distribution. Metformin is well-distributed into tissues. Protein binding of metformin is negligible.

Metformin is eliminated by glomerular filtration and active tubular secretion. The plasma T1/2 of alogliptin is 21 hours. The apparent T1/2 of metformin is approximately 6.5 hours.

2.4.4.3. Alogliptin/Metformin combination tablets

In study 322MET-103, the pivotal BE study, the developed combination tablets containing the lowest and highest amount of metformin (500 mg and 1000, respectively) and the tablets containing the lowest and highest amount of alogliptin (6.25 and 12.5, respectively) were compared with individual corresponding alogliptin and metformin tablets.

Bioequivalence between the combination A6.25+M500, A6.25+M1000, A12.5+M500, A12.5+M1000 combination tablets and corresponding individual tablets was sufficiently shown. In all cases the 90% CI of the AUC and C_{max} was within the 80%-125% range. Therefore, the CHMP considers that the bioequivalence of the alogliptin/metformin 6.25 mg + 1000 mg tablet and 12.5 mg+1000 mg tablet to individual alogliptin and metformin tablets was demonstrated.

The applicant used a bracketing approach by making only an evaluation of the highest and lowest dose strengths in humans *in vivo*, as was previously advised by the CHMP scientific advice. Therefore, a bio-waiver for alogliptin/metformin 6.25 mg+850 mg tablet and 12.5 mg+850 mg tablet can be granted.

Both alogliptin and metformin are absorbed rapidly. Food does not affect exposure to alogliptin, but decreases exposure to metformin; however, it will be recommended that alogliptin/metformin be taken with food to decrease the risk of gastrointestinal symptoms. (SmPC section 4.2)

Alogliptin and metformin are eliminated primarily by the kidneys as unchanged drug. Results indicate that alogliptin undergoes some active tubular secretion. Additionally, metformin is eliminated by glomerular filtration and active tubular secretion. Alogliptin can be administered to patients with mild renal impairment without dose adjustments. Metformin is contraindicated in patients with moderate to severe renal dysfunction because of the risk of lactic acidosis. Although the applicant is of the opinion that there has been growing evidence that metformin is both efficacious and safe in patients with greater degrees of renal impairment, the CHMP considers that the new evidence is not strong enough in order to change metformin contraindication in patients with severe renal dysfunction. Based on the above considerations the CHMP agreed with the applicant proposal to contraindicate alogliptin/metformin combination in patients with moderate-to-severe renal impairment or ESRD. (SmPC sections 4.3 and 4.4)

2.4.5. Conclusions on clinical pharmacology

The applicant performed several clinical pharmacology studies and literature studies to show the pharmacokinetics and pharmacodynamics of alogliptin and metformin administered alone or in combination. Additionally specific studies with the combination products were performed including bioequivalence studies and a food-effect study.

The CHMP considers that the clinical pharmacokinetics and pharmacodynamics of alogliptin/metformin fixed combination were appropriately investigated.

2.5. Clinical efficacy

In support of this FDC application, seven phase III studies have been submitted (see table 11): study 008, 009, 011, 305 and study 322OPI-004 were main studies; 322OPI-001 and 302 were submitted as supportive trials; study 010 is included to show the efficacy and safety of alogliptin as monotherapy.

The main studies in the clinical development program relevant to the evaluation of efficacy comprise of four completed and one on-going phase III studies. Of these, there were three main phase III, 26-week, placebo-controlled studies that included adult subjects diagnosed with T2DM who failed to achieve adequate glycaemic control on background antidiabetic medication (i.e. metformin, TZD, or insulin). Additionally, there were 2 main long-term, active-comparator studies that included adult subjects diagnosed with T2DM with inadequate glycaemic control on metformin (study 305) or metformin and pioglitazone (or another antidiabetic agent) (study 322OPI-004).

The total clinical development program for alogliptin examined the use of alogliptin in monotherapy and in combination use with 4 major classes of antidiabetic agents: (1) MET, (2) SU, (3) TZD, and (4) insulin. The efficacy of alogliptin has been evaluated in 15 studies: 1 phase 2 dose-ranging study, 7 main phase III studies, and 7 supportive Phase III studies. (see table 12 for other trials performed with alogliptin and not included among the relevant ones for the FDC)

Table 11 Overview Studies relevant for Alogliptin/Metformin FDC

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
Phase II Study			
003 Dose-ranging	12-week, multicenter, randomized, double-blind, placebo-controlled study in T2DM subjects on diet and exercise alone, or monotherapy with SU/MET, or a combination of SU and MET. Age: 18 to 75 years; HbA1c: 6.8% to 11.0%. Change from baseline in HbA1c at Week 12.	265	A6.25, A12.5, A25, A50, A100 or Placebo once daily Randomization ratio: 1:1:1:1:1:1
Main Phase III, 26-Week, Placebo-Controlled Studies			
008 Add-on to MET	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on MET monotherapy (≥1500 mg or MTD). Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from baseline in HbA1c at Week 26.	527	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
009 Add-on to TZD, with or without MET or SU	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on TZD (pioglitazone or rosiglitazone), with or without MET or SU. Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from baseline in HbA1c at Week 26.	493 (b)	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
011 Add-on to insulin, with or without MET	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on insulin with or without MET. Age: 18 to 80 years; HbA1c: ≥8.0%. Change from baseline in HbA1c at Week 26.	390	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 1:1:1
Main Phase III, Long-Term, Active-Comparator Studies			
305 (a) Add-on to MET	2-year, multicenter, randomized, double-blind, active comparator (alogliptin vs SU) study in T2DM subjects on MET ≥1500 mg (or MTD) alone. Age: 18 to 80 years; HbA1c: 7.0% to 9.0%. Change from baseline in HbA1c at Weeks 52 and 104.	2638	A12.5 once daily or A25 once daily or Glipizide 5–20 mg (titrated) Randomization ratio: 1:1:1
322OPI-004 Add-on to PIO/MET	52-week, multicenter, randomized, double-blind, active-comparator (A25 vs titrating pioglitazone from 30 to 45 mg) study in T2DM subjects on combination pioglitazone	803	A25+P30 once daily or P45 once daily (titrated from P30)

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
	30 mg and MET ≥1500 mg (or MTD). Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from baseline in HbA1c at Weeks 26 and 52.		Randomization ratio: 1:1
Supportive Phase III Studies			
302 Initial combination ALO/MET	26-week, multicenter, randomized, double-blind, placebo-controlled, 7-arm, factorial study evaluating alogliptin alone, MET alone or alogliptin/MET in combination, in T2DM subjects on diet and exercise alone. Age: 18 to 80 years; HbA1c: 7.5% to 10.0%. Change from baseline in HbA1c at Week 26.	784	Placebo BID or A25 once daily or A12.5 BID or M500 BID or M1000 BID or A12.5+MET500, BID or A12.5+MET1000 mg, BID Randomization ratio: 1:1:1:1:1:1:1
322OPI-001 Combination ALO/PIO add-on to MET	26-week, multicenter, randomized, double-blind, placebo-controlled, 12-arm, factorial study evaluating alogliptin alone, pioglitazone alone and alogliptin/pioglitazone in combination, in T2DM subjects on MET monotherapy ≥1500 mg (or MTD). Age: 18 to 80 years, HbA1c: 7.5% to 10.0%. Change from baseline in HbA1c at Week 26.	1554	Placebo+placebo once daily or A12.5+placebo once daily or A25+placebo once daily or P15+placebo once daily or P30+placebo once daily or P45+placebo once daily or A12.5+P15 once daily or A12.5+P30 once daily or A12.5+P45 once daily or A25+P15 once daily or A25+P30 once daily or A25+P45 once daily Randomization ratio: 1:1:1:1:1:1:1:1:1:1:1:1

A/ALO=alogliptin, BID=twice daily, M/MET=metformin, MTD=maximum tolerated dose, N=randomized set, P/PIO=pioglitazone.
(a) Ongoing studies with interim results (as of 10 November 2011 for 305 and as of 29 April 2011 for 402) presented herein.
(b) 493 subjects were randomized and 1 additional subject was treated with double-blind study drug during stabilization but was not randomized.

Table 12 Overview other phase III alogliptin studies

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
Main Phase III, 26-Week, Placebo-Controlled Studies			
010 Monotherapy	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on diet and exercise alone. Age: 18 to 80 years; HbA1c 7.0% to 10.0%. Change from baseline in HbA1c at Week 26.	329	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
007 Add-on to SU	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in T2DM subjects on SU monotherapy (≥10 mg or maximum tolerated dose [MTD] of glyburide). Age: 18 to 80 years; HbA1c: 7.0% to 10.0%. Change from baseline in HbA1c at Week 26.	500	A12.5 once daily or A25 once daily or Placebo once daily Randomization ratio: 2:2:1
Supportive Phase III Studies			
322OPI-002 Initial combination ALO/PIO	26-week, multicenter, randomized, double-blind, placebo-controlled, 4-arm, study evaluating alogliptin alone, pioglitazone alone and alogliptin/pioglitazone in combination, in T2DM subjects on diet and exercise alone. Age: 18 to 80 years; HbA1c: 7.5% to 11.0%. Change from baseline in HbA1c at Week 26.	655	A12.5+P30 once daily or A25+P30 once daily or A25+placebo once daily or P30+placebo once daily Randomization ratio: 1:1:1:1
Other Supportive Phase III Studies			
303 Elderly	52-week, multicenter, randomized, double-blind, active-comparator (alogliptin vs SU) study in elderly T2DM subjects. Age: 65 to 90 years. HbA1c: 6.5% to 9.0% if on diet and	441	A25 once daily or Glipizide 5 mg once daily (titrated to 10 mg for inadequate control)

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
	exercise Alone; 6.5% to 8.0% if on oral monotherapy. Change from baseline in HbA1c at Week 52.		Randomization ratio: 1:1
402 (a) CV outcomes	~4.75-year, multicenter, randomized, double-blind, placebo-controlled, CV outcomes study in subjects with T2DM and recent ACS (within 15–90 days). Age: ≥18 years of age; HbA1c: 6.5% to 11.0% if antidiabetic regimen includes oral monotherapy or oral combination therapy; 7.0% to 11.0% if antidiabetic regimen includes insulin. MACE composite (CV death, nonfatal MI, nonfatal stroke).	2134 (interim) ~5400 (planned)	In addition to Standard of Care antidiabetic medications: A25 once daily (6.25 and 12.5 mg dose available for severe and moderate renal impairment) or Placebo once daily Randomization ratio: 1:1
012 Open-label extension	4-year, multicenter, open-label extension study. Subjects rolled over from Studies 010, 007, 008, 009, 011, 322OPI-001, and 322OPI-002. Safety.	3323	A12.5 once daily or A25 once daily Randomization ratio: 1:1
301 Postprandial lipids	16-week, multicenter, randomized, double-blind, active- and placebo-controlled study in T2DM subjects on diet and exercise or treatment with MET, SU, nateglinide, or repaglinide. Age: 18 to 70 years; HbA1c: 6.5% to 9.0%. Change from baseline in postprandial incremental area under the plasma concentration-time curve changes for triglycerides at Week 16.	71	A25 once daily A25+P30 once daily Placebo once daily Randomization ratio: 1:1:1

2.5.1. Dose response studies

No separate dose response studies were performed with the FDC. Dose selection for the FDC was based on alogliptin dose-range studies and approved dosing recommendations for metformin.

2.5.1.1. Alogliptin

Results from the phase I studies suggested a dose range between 6.25 and 100 mg should be tested to determine optimal dosage in confirmatory clinical studies. Hence, that dose range was used in the phase 2 dose-ranging study (study 003). Study 003 assessed the efficacy, safety, and tolerability of alogliptin 6.25, 12.5, 25, 50, and 100 mg over 12 weeks compared with placebo in 265 subjects with T2DM, 26 to 75 years of age, inclusive, who were either receiving no treatment (i.e. either newly diagnosed or experiencing inadequate glycaemic control with diet and exercise alone) or were being treated with an SU, MET, or a combination of SU and MET, but were experiencing inadequate glycaemic control.

Statistically significant and clinically relevant reductions in HbA1c were observed at alogliptin doses of ≥12.5 mg and in fasting plasma glucose (FPG) at doses of ≥25 mg, with no additional HbA1c benefit seen at doses >25 mg (see table 13). HbA1c levels were not significantly reduced with alogliptin 6.25 mg, which is likely due to lack of optimal DPP-4 inhibition.

Table 13 Change From baseline in HbA1c (%) and FPG (mmol/L) Levels on Day 85 (ITT, LOCF) (003)

	Placebo (N=41)	A6.25 (N=42)	A12.5 (N=42)	A25 (N=45)	A50 (N=43)	A100 (N=44)
baseline HbA1c						
Mean (SD)	8.24 (1.034)	7.99 (1.006)	7.87 (0.905)	8.02 (0.978)	8.11 (1.037)	8.00 (0.988)
LS Mean Change from baseline at Day 85 (SE) (a)	-0.01 (0.123)	-0.19 (0.121)	-0.54* (0.122)	-0.56* (0.117)	-0.44* (0.124)	-0.51* (0.119)
baseline FPG						
Mean (SD)	10.5 (2.80)	10.6 (2.73)	9.6 (2.27)	10.6 (3.47)	10.1 (2.89)	10.5 (3.14)
LS Mean Change from baseline at Day 85 (SE) (a)	-1.3 (0.39)	-0.9 (0.50)	-0.8 (0.50)	-2.0* (0.49)	-1.4* (0.51)	-1.6* (0.49)

ITT=intent to treat.
*p<0.05 vs placebo.
(a) LS mean from an analysis of covariance (ANCOVA) with effects for baseline value, treatment, BMI, T2DM duration (years), and prior antidiabetic treatment (yes/no) (Model 1).

These HbA1c and FPG results were the basis for selecting alogliptin 12.5 and 25 mg for evaluation in the Phase III clinical programs. Both doses were chosen for further evaluation because, at that point in time, only limited comparative safety data were available.

Total exposure to alogliptin in subjects with moderate and severe renal impairment/ESRD increased approximately 2- and 4-fold, respectively, compared with healthy matched control subjects. Dose reductions proportional to the increases in exposure seen in study 006 were used in study 402, in which a dose of alogliptin 25 mg was assigned to T2DM subjects with normal renal function and those with mild renal impairment, alogliptin 12.5 mg to T2DM subjects with moderate renal impairment, and alogliptin 6.25 mg to T2DM subjects with severe renal impairment/ESRD.

2.5.1.2. Metformin

For the FDC alogliptin/metformin, no separate dose response studies were performed with either the fixed dose combination or metformin alone.

The strengths of the metformin component are based on the approved dose of metformin in Europe (up to 3 mg daily taken as 3 divided doses). Although the recommended maximum daily dose is 3000 mg, most patients do not tolerate such high doses due to side effects, particularly gastrointestinal effects. In the UKPDS, for example, more than three-quarters of patients received >1700 mg metformin.

This is acceptable, since the proposed dose of the metformin component for the FDC alogliptin/metformin is in line with the SmPC of metformin and with clinical practice.

2.5.2. Main studies

2.5.2.1. Methods, study designs and statistical methods

The main studies relevant for the FDC comprised 4 completed and 1 on-going phase III studies. Of these, there were three main phase III, 26 week, placebo-controlled studies that included adult

subjects diagnosed with T2DM who failed to achieve adequate glycaemic control on background antidiabetic medication (i.e. metformin, TZD, or insulin).

In the three 26-week placebo-controlled main studies, the primary analysis was performed for the full analysis set (FAS) using an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) values. The primary model included in all studies, study treatment and geographic region as class variables and baseline HbA1c as covariate. Additional study-specific covariates or factors were included in the primary analysis model. For the primary analysis, the alogliptin 25 dose was compared with placebo at the 2 sided 0.05 significance level using a contrast derived from the primary model. Only if this test was statistically significant, the alogliptin 12.5 dose was to be evaluated in a similar fashion.

Furthermore, two active-comparator studies were included. Study 305 was, at the time of evaluation of this application, an on-going, 2-year, active-comparator study. For this study, a baseline HbA1c of between 7.0% and 9.0% was required for inclusion. All subjects are to be receiving MET at a dose of ≥ 1500 mg (or MTD). Subjects will be treated for a period of 2 years to assess maintenance of efficacy. An interim study report with data from a pre-planned, 1-year interim analysis was provided (study 305). At the time of the CHMP opinion for this procedure, the applicant has already made available a summary of the results and confirmed that the results are in line with the interim data formally assessed in this report. However, a full assessment can only occur once the final study report is submitted.

The primary analysis in the two main active-comparator studies was a non-inferiority assessment of change from baseline in HbA1c. In study 305, the primary efficacy endpoint evaluated glycaemic control through HbA1c changes from baseline to Week 52 or Week 104. The primary efficacy endpoint for the interim analysis was change from baseline in HbA1c at Week 52 (or at time of discontinuation of double-blind study medication or hyperglycaemic rescue) using the per protocol set (PPS) and ANCOVA models with change from baseline (LOCF) in HbA1c as the response variable, treatment, geographic region, and study schedule as fixed class effects and baseline MET dose and baseline HbA1c as continuous covariates. The A25 group was compared with the glipizide group at the 1 sided 0.0125 level using a non-inferiority margin of 0.3%. If A25 was non-inferior to glipizide, then the A12.5 group was compared with the glipizide group in a step-down fashion using the same significance level and non-inferiority margin. If both alogliptin groups were non-inferior to glipizide, then additional tests for statistical superiority of the alogliptin groups to the glipizide group were conducted in a step-down fashion in the same order at the 1 sided 0.0125 level.

Study 322OPI-004 was a 52 week active controlled study designed to evaluate the efficacy of alogliptin 25 mg as triple therapy (add-on to pioglitazone 30 mg and MET), in which efficacy was compared with up-titration of pioglitazone, in subjects on pioglitazone 30 mg and MET. Adult subjects with T2DM were included who failed (HbA1c between 7.0% and 10.0%) to achieve adequate glycaemic control on background antidiabetic medication consisting of pioglitazone 30 mg with metformin (≥ 1500 mg (or MTD). The primary efficacy variable was change from baseline in HbA1c at Weeks 26 and 52 in the PPS using the LOCF method for subjects who were rescued or who prematurely discontinued from the study. The primary model included study treatment, study schedule, and geographic region as class variables, and baseline MET dose and baseline HbA1c as covariates. The primary analysis was a non-inferiority assessment (non-inferiority margin of 0.3%) at Week 26 followed by an assessment at Week 52. Both analyses (at Weeks 26 and 52) were

performed at the 1-sided 0.025 significance level. The Week 26 analysis was a pre-planned interim analysis; the Week 52 analysis was considered the primary endpoint.

Study 010 was an alogliptin monotherapy trial. It was a 26-week, multicenter, randomized, double-blind placebo controlled study in T2DM patients were included who failed treatment with diet and exercise (HbA1c 7-10%).

2.5.2.2. Study Participants

Main Phase III, Placebo-Controlled Studies

A total of 1410 subjects were randomized into studies 008, 009, and 011 and received at least 1 dose of study drug. No meaningful differences across treatment groups were observed for any demographic or baseline characteristic with respect, specifically, to sex, age, race, and body mass index (BMI)(see Table 14). Mean age across studies was 55 years (min-max, 22-80 years). In these studies, 240 (17%) randomized subjects were elderly (≥65 years), with 33 subjects (2%) at least 75 years of age. The majority (73%) of all randomized subjects were White. Mean BMI for all randomized subjects ranged from 32 to 33. The duration of T2DM differed among studies and, as expected, subjects in study 011 (insulin add-on) had a longer mean duration of T2DM (12.56 years) compared with the other studies (study 008, 6.11 years; study 009, 7.58 years).

Study 010 included a total of 329 subjects were randomised. Overall, 53.2% of subjects were men. Mean age for all randomized subjects was 53.4 years. The majority of subjects were < 65 years of age (83.3%) and White (66.9%). Mean BMI for all randomized subjects was 32.02 and mean duration of T2DM was 3.22 years. Mean HbA1c values at baseline were similar among the placebo, A12.5, and A25 groups (8.03%, 7.91%, and 7.91%, respectively). Overall, no meaningful differences were observed among the treatment groups for any subject demographic or baseline characteristic.

Table 14 Subject Demographics and baseline Characteristics (studies 010, 008, 009, 011)

	Study 010 Monotherapy			Study 008 Add-on to MET			Study 009 Add-on to TZD, with or without MET or SU			Study 011 Add-on to insulin, with or without MET		
Category	**Placebo N=65**	**A12.5 N=133**	**A25 N=131**	**Placebo N=104**	**A12.5 N=213**	**A25 N=210**	**Placebo N=97**	**A12.5 N=197**	**A25 N=199**	**Placebo N=130**	**A12.5 N=131**	**A25 N=129**
Sex, n (%)												
Men	33 (50.8)	65 (48.9)	77 (58.8)	50 (48.1)	101 (47.4)	114 (54.3)	53 (54.6)	109 (55.3)	125 (62.8)	62 (47.7)	55 (42.0)	44 (34.1)
Women	32 (49.2)	68 (51.1)	54 (41.2)	54 (51.9)	112 (52.6)	96 (45.7)	44 (45.4)	88 (44.7)	74 (37.2)	68 (52.3)	76 (58.0)	85 (65.9)
Age (years)												
Mean (SD)	53.8 (10.99)	52.6 (12.01)	54.2 (10.16)	56.0 (10.58)	55.2 (10.58)	53.6 (10.45)	55.2 (10.82)	55.5 (9.37)	55.4 (10.16)	55.0 (10.57)	55.4 (9.79)	55.9 (10.18)
Min, Max	35, 80	24, 77	31, 80	27, 78	26, 80	22, 77	24, 80	36, 78	25, 80	27, 80	24, 78	23, 79
BMI												
Mean (SD)	32.17 (5.748)	31.82 (5.166)	32.16 (5.915)	32.39 (5.763)	31.59 (5.208)	31.80 (5.302)	33.23 (6.192)	32.34 (5.698)	33.06 (5.379)	32.42 (5.621)	32.66 (5.546)	32.28 (5.594)
HbA1c												
Mean	8.03	7.91	7.91	8.01	7.89	7.93	7.97	8.08	8.01	9.28	9.29	9.27

(SD)	(0.910)	(0.810)	(0.788)	(0.872)	(0.740)	(0.799)	(0.818)	(0.910)	(0.837)	(1.127)	(1.056)	(1.127)
Duration of T2DM (years)												
Mean	4.32	3.09	2.82	6.28	6.21	5.94	7.76	7.68	7.38	12.18	12.10	13.42
(SD)	(5.286)	(3.825)	(3.016)	(5.405)	(5.091)	(4.306)	(6.667)	(5.585)	(5.350)	(7.067)	(7.161)	(6.308)
Median	2.67	1.92	1.67	4.67	5.25	5.00	6.50	6.33	6.17	10.96	11.17	13.08

Main Phase III, Long-Term, Active-Comparator Studies

A total of 3441 subjects were randomized into the 2 studies. Of the 2638 subjects randomized into **study 305**, a total of 1900 subjects were on-going at the time of the interim data cut; and 526 subjects completed **study 322OPI-004**. A total of 1015 subjects discontinued from the studies, including 413 subjects who were rescued. In study 305, more subjects receiving MET+glipizide required hyperglycaemic rescue compared with those receiving MET+A12.5 or MET+A25. More subjects in the MET+A25+P30 group completed study 322OPI-004, primarily due to more subjects requiring hyperglycaemic rescue on MET+P45. The primary causes of discontinuation excluding hyperglycaemic rescue were AEs, major protocol deviations and voluntary withdrawals. No meaningful differences across treatment groups were observed for any demographic or baseline characteristic with respect to sex, age, race, and BMI (see table 15). Mean age across the studies ranged from 54 to 56 years. In these 2 studies, 615 subjects (18%) were elderly (≥ 65 years), with 57 subjects (2%) at least 75 years. The majority of all randomized subjects were White (59.9 to 64.2%). Mean BMI for all randomized subjects ranged from 31 to 32. Mean duration of T2DM was 5.51 years in study 305 and 7.16 years in study 322OPI-004.

Table 15 Subject Demographics and baseline Characteristics (studies 305 and 322OPI-004)

	Study 305 Add-on to MET (Ongoing)				**Study 322OPI-004 Add-on to PIO/MET**		
Characteristic	**MET+A12.5 N=880**	**MET+A25 N=885**	**MET+Glipizide N=873**	**Total N=2638**	**MET+A25+P30 N=404**	**MET+P45 N=399**	**Total N=803**
Sex, n (%)							
Men	419 (47.6)	452 (51.1)	441 (50.5)	1312 (49.7)	210 (52.0)	204 (51.1)	414 (51.6)
Women	461 (52.4)	433 (48.9)	432 (49.5)	1326 (50.3)	194 (48.0)	195 (48.9)	389 (48.4)
Age							
Mean (SD), yr	55.2 (9.60)	55.5 (9.81)	55.4 (9.59)	55.4 (9.66)	54.3 (9.86)	55.9 (9.94)	55.1 (9.93)
<65 years, n (%)	734 (83.4)	710 (80.2)	723 (82.8)	2167 (82.1)	339 (83.9)	320 (80.2)	659 (82.1)
≥65 years, n (%)	146 (16.6)	175 (19.8)	150 (17.2)	471 (17.9)	65 (16.1)	79 (19.8)	144 (17.9)
≥75 years, n (%)	13 (1.5)	17 (1.9)	15 (1.7)	45 (1.7)	5 (1.2)	7 (1.8)	12 (1.5)
BMI	n=879	n=885	n=872	n=2636			
Mean (SD)	31.27 (5.417)	31.27 (5.341)	31.11 (5.320)	31.22 (5.358)	31.52 (5.243)	31.58 (5.177)	31.55 (5.210)
HbA1c	n=876	n=883	n=871	n=2630	n=303 (a)	n=306 (a)	-
Mean (SD)	7.59 (0.599)	7.61 (0.606)	7.60 (0.617)	7.60 (0.607)	8.25 (0.820)	8.13 (0.832)	-
T2DM duration, yr							
Mean (SD)	5.65 (5.323)	5.42 (4.729)	5.48 (4.887)	5.51 (4.985)	7.47 (5.248)	6.85 (4.611)	7.16 (4.946)
MET dose (mg)							
Mean (SD)	1824.7	1835.3	1823.5	1827.9	1867.9 (476.71)	1847.6	1857.8

	(405.69)	(373.76)	(390.83)	(390.17)		(494.12)	(485.24)
Median (range)	-	-	-	-	1700 (500-3400)	1700 (500-3000)	1700 (500-3400)

-=Not applicable.
(a) PPS data are presented per the primary analysis.
Note: This table includes all randomized subjects.

2.5.2.3. Treatments

In studies 008 (add-on to metformin), 009 (add-on to TZD, with or without metformin) and 010 (monotheraphy) doses of 12.5 or 25 mg alogliptin were administered once daily vs placebo in a randomization ratio of 2:2:1. An HbA1c concentration between 7.0% and 10.0%, inclusive, was used as an inclusion criterion. In study 011 (add-on to insulin, with or without metformin), doses of alogliptin 12.5 or 25 mg or placebo were administered once daily in a randomization ratio of 1:1:1, and a higher baseline minimum HbA1c concentration of 8.0% was used as an inclusion criterion.

Subjects were treated with antidiabetic agents at a stable dose, consistent with clinical practice and international treatment guidelines. In the add-on studies, subjects underwent a 4-week Run in/Stabilization Phase during which they were stabilized on a dose of ≥ 1500 mg metformin (or MTD), 30 or 45 mg pioglitazone (or MTD), or insulin (≥ 15 and ≤ 100 units), according to protocol requirements.

In study 305 (add-on to MET) the subjects were randomized to receive either alogliptin 12.5 or 25 mg or glipizide (5-20 mg) in a 1:1:1 ratio.

In Study 322OPI-004, a 52-week, active-comparator study in subjects receiving metformin (≥ 1500 mg or MTD), a combination of alogliptin 25 mg and pioglitazone 30 mg once daily was compared with pioglitazone 45 mg once daily (randomization ratio 1:1).

Across these studies, the actual mean doses of background metformin or TZD medication were maximized (or optimized for insulin), in accordance with treatment paradigms. Subjects were instructed on proper nutrition and exercise and how to recognize signs and symptoms of hypoglycaemia in accordance with each study center's standard of care guidelines for subjects with T2DM.

2.5.2.4. Outcomes/endpoints

The primary efficacy endpoint for Studies 008, 009, 010 and 011 was the change from baseline in HbA1c at Week 26. The primary efficacy endpoint for Studies 305 and 322OPI-004 was change from baseline in HbA1c at Week 52 with statistical testing for non-inferiority and superiority against the active comparator.

Secondary endpoints include changes in other measures of glycaemic control, including clinical response rates, FPG, the incidence of marked hyperglycaemia, and the incidence of hyperglycaemic rescue.

2.5.2.5. Results

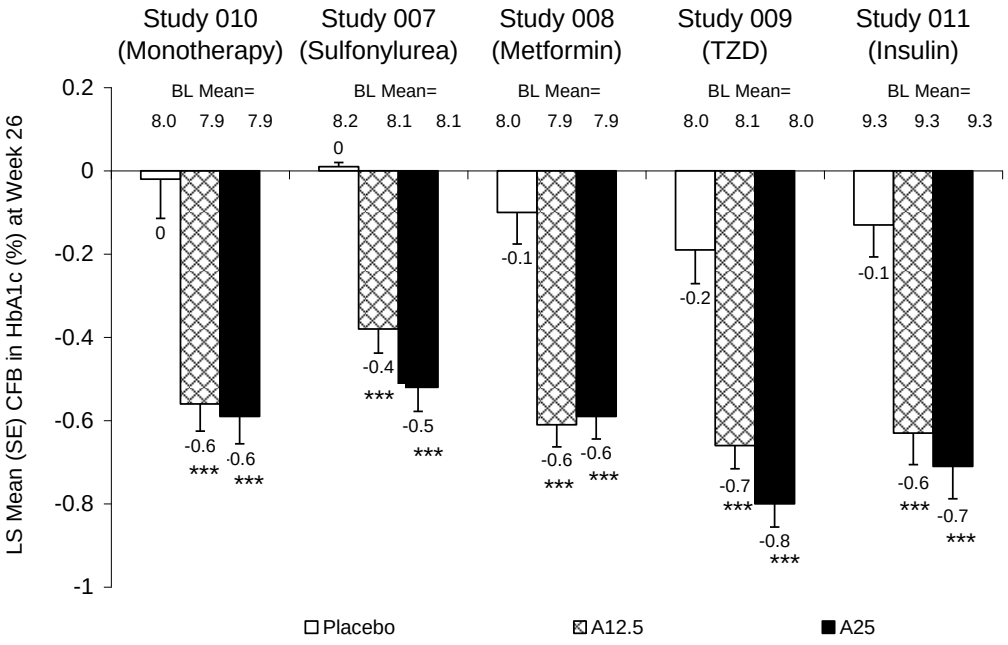
2.5.2.5.1. Outcomes and estimation

- **Primary Efficacy Results (HbA1c)**

Main Phase III, Placebo-Controlled Studies

Across the program, alogliptin efficacy results have shown reductions in HbA1c, as summarized in the figure below for the 4 main phase III placebo-controlled studies.

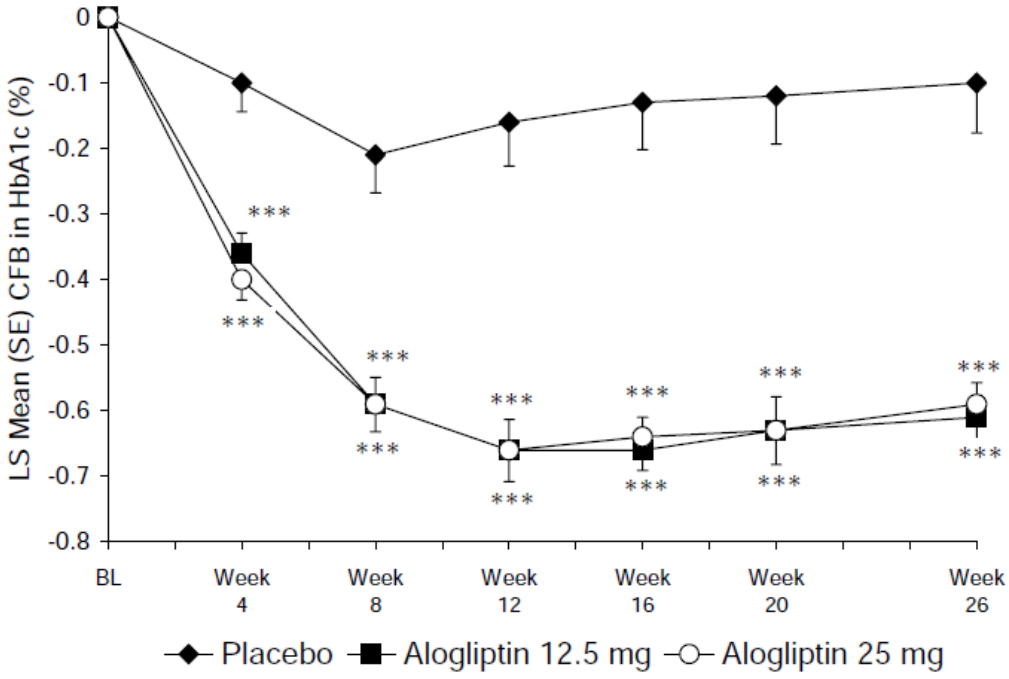
Figure 2. Change from baseline in HbA1c (%) (LOCF, FAS) at Week 26 (studies 010, 007, 008, 009, and 011)



BL=baseline. CFB=change from baseline.
***p<0.001 vs placebo.

All treated subjects in **study 008** received MET at baseline (mean dose of 1846.7 mg). Compared with placebo, subjects in both the alogliptin 12.5 and 25 mg groups achieved statistically significant, placebo-corrected LS mean reductions in HbA1c at Week 26. As in study 007, this effect was observed as early as Week 4 and continued throughout the 26-week treatment period. There was no differentiation in terms of HbA1c reduction between both alogliptin doses (see figure 3).

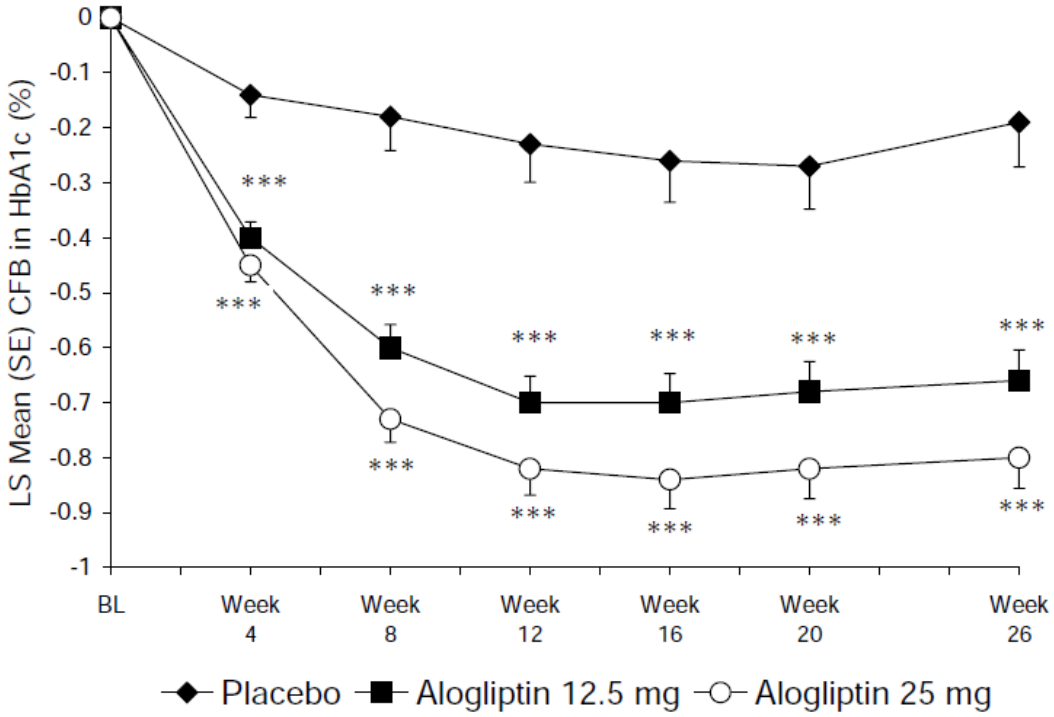
Figure 3. Study 008 (add-on to MET): Change from baseline in LS Mean of HbA1c (%) by Visit—Full Analysis Set



Source: Figure 15.2.1.13.
BL=Baseline
***P<0.001

In **study 009**, subjects received alogliptin or placebo as add-on therapy to TZD with or without MET or SU. Statistically significant LS mean differences from placebo were seen for both the alogliptin 12.5 mg and 25 mg groups (see figure 4). Reductions (compared with placebo) were seen regardless of pioglitazone dose or whether the subject was receiving pioglitazone with or without SU or MET. Of the 493 subjects randomized in the study, 112 (23%) received alogliptin (89 subjects) or placebo (23 subjects) as add-on therapy to pioglitazone alone. Although the number of subjects receiving add-on therapy to TZD alone is somewhat limited in this study, the overall response is clinically relevant. In the supportive initial combination study 322OPI-002, the combination of alogliptin 25 mg+pioglitazone 30 mg showed a decrease in HbA1c of 1.71%. In study 009, 277 subjects (56%) received alogliptin (221 subjects) or placebo (56 subjects) as add-on therapy to TZD plus MET.

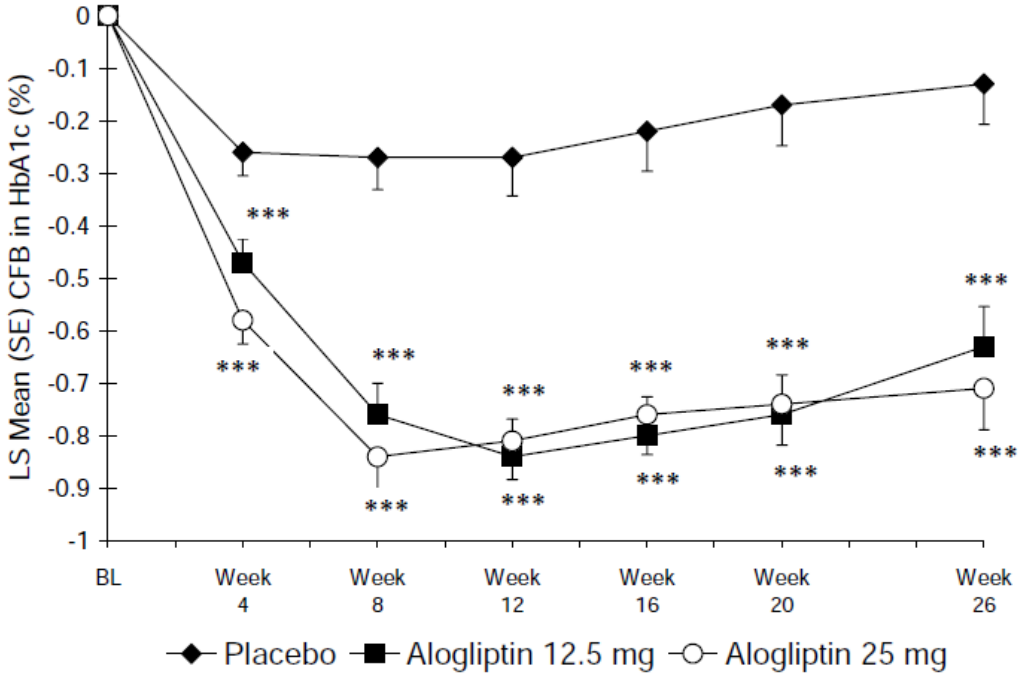
Figure 4. Study 009 (add-on to TZD): Change from baseline in LS Mean of HbA1c (%) by Visit—Full Analysis Set



Source: Figure 15.2.1.13.
BL=Baseline, CFB=change from Baseline.
***P<0.001.

In **study 011**, 390 subjects received alogliptin or placebo as add-on therapy to insulin with MET (228 subjects, 58%) or without MET (162 subjects, 42%). Over a 4-week Run-in Period, subjects were optimized (or stabilized) on insulin, but mean baseline Hb1Ac was higher in this study (9.27%-9.29% across treatment groups) compared with the other 4 studies. Mean baseline MET dose for subjects who received insulin with MET (58%) in this study was 1732.7 mg, a maximized dose. Mean insulin dose, which may have been adjusted for events of hypoglycaemia, was consistent throughout the study (approximately 56.5 and 56.7 IU at baseline and at Week 26, respectively). The observed reduction in HbA1c seen in the study overall was clinically and statistically significant (0.71% alogliptin 25 mg vs 0.13% placebo) (see figure 5). Because there was a higher baseline HbA1c in this study, a preplanned analysis with subcategories of baseline HbA1c (≤8.5%, ≥8.5%, and ≥9.0%, according to the broader inclusion criterion) confirmed that, irrespective of baseline HbA1c, subjects in the groups receiving alogliptin had clinically and statistically significant decreases from baseline in HbA1c levels at Week 26 (-0.62%, -0.72%, and -0.82% for alogliptin 25 mg, respectively) compared with subjects receiving placebo (0.06%, -0.22%, and -0.30%, respectively; p<0.002). In the subgroups of subjects taking insulin with or without MET, change from baseline HbA1c was clinically relevant (-0.77% and -0.66%, respectively, alogliptin 25 mg).

Figure 5. Study 011 (add-on to insulin): Change from baseline in LS Mean of HbA1c (%) by Visit—Full Analysis Set



Source: Figure 15.2.1.13.
BL=Baseline.
***P<0.001.

In **study 010**, at Week 26, the LS mean changes from baseline in HbA1c were -0.02%, -0.56%, and -0.59% for the placebo, A12.5, and A25 groups, respectively. LS mean differences from placebo were -0.54% ($p<0.001$) and -0.57% ($p<0.001$) for the A12.5 and A25 groups, respectively. Results for the primary efficacy endpoint are presented in the table below. Subjects in both alogliptin dose groups (A12.5 and A25) achieved statistically significant mean decreases in HbA1c levels compared with the placebo group at every time point.

Table 16 Change From baseline in HbA1c (%) (LOCF, FAS) (study 010)

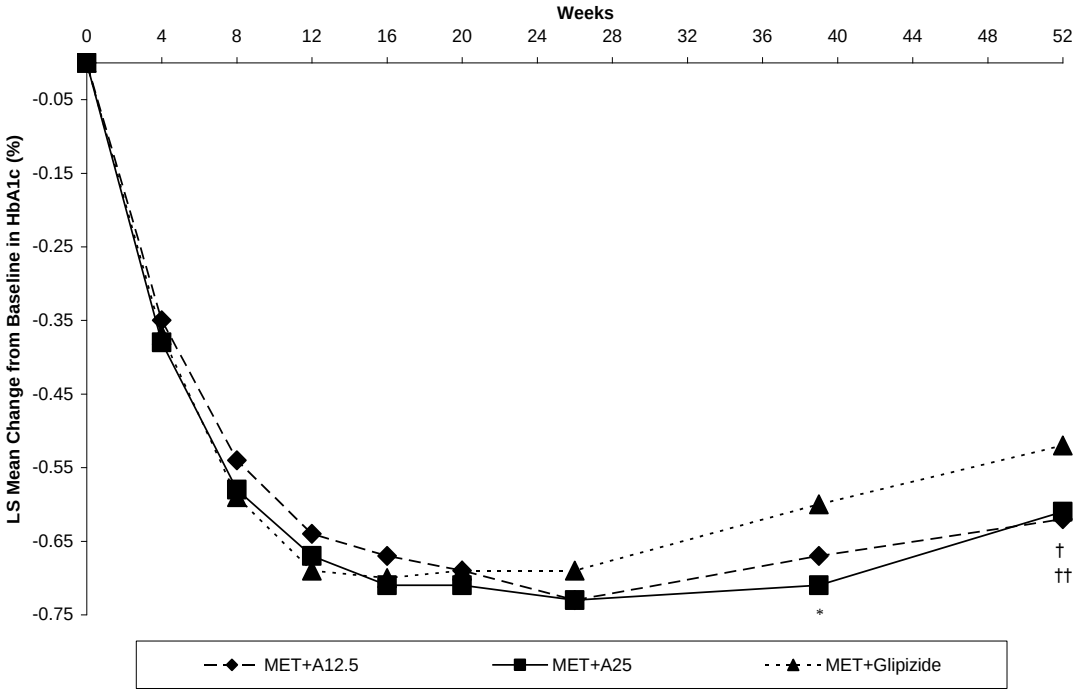
	Placebo N=64	A12.5 N=133	A25 N=131
N	63	131	128
baseline HbA1c (%)			
Mean (SD)	8.03 (0.910)	7.91 (0.810)	7.91 (0.788)
Median (range)	7.90 (6.7-10.0)	7.70 (6.6-10.2)	7.75 (6.4-10.3)
Week 26 CFB			
LS mean (SE)	-0.02 (0.094)	-0.56 (0.065)	-0.59 (0.066)
LS mean difference (95% CI)		-0.54 (-0.76, -0.31)	-0.57 (-0.80, -0.35)
p-value: treatment vs placebo		<0.001	<0.001

Reductions in HbA1c were seen regardless of sex, age, race, or baseline BMI. Subjects in the alogliptin 25 mg group achieved greater LS mean reductions in HbA1c than subjects in the alogliptin 12.5 mg group in 4 of the 5 studies. The difference in effect with alogliptin 25 mg group compared with the alogliptin 12.5 mg group is more apparent in subjects with higher baseline HbA1c levels.

Main Phase III, Long-Term, Active-Comparator Studies

In both long-term, active-controlled studies (305 and 322OPI-004), greater LS mean reductions from baseline in HbA1c were observed in the alogliptin groups than in the comparator groups at Weeks 26 and 52, and alogliptin efficacy was shown to be sustained for up to 52 weeks. In **study 305**, statistical non-inferiority of MET+alogliptin 25 mg and MET+alogliptin 12.5 mg was demonstrated vs MET+glipizide (see figure 6). Mean final glipizide dose of 5.2 mg in the MET+glipizide group was lower than expected. The low mean glipizide dose may be a reflection of the relatively low baseline HbA1c (mean, 7.60%) and FPG (mean, 8.19 mmol/L). This resulted in a low incidence of hyperglycaemic rescue in all treatment groups (9.1% MET+alogliptin 25 mg vs 12.0% MET+glipizide) requiring conservative dose titration. Due to the low baseline HbA1c and the low glipizide dose in the comparator group, a formal claim of non-inferiority would not be acceptable. However, despite the low mean glipizide dose, the incidence of hypoglycaemic events was greater in the MET+glipizide group (23.8%) compared with the MET+alogliptin 12.5 mg and MET+alogliptin 25 mg groups (2.5% and 1.4%, respectively).

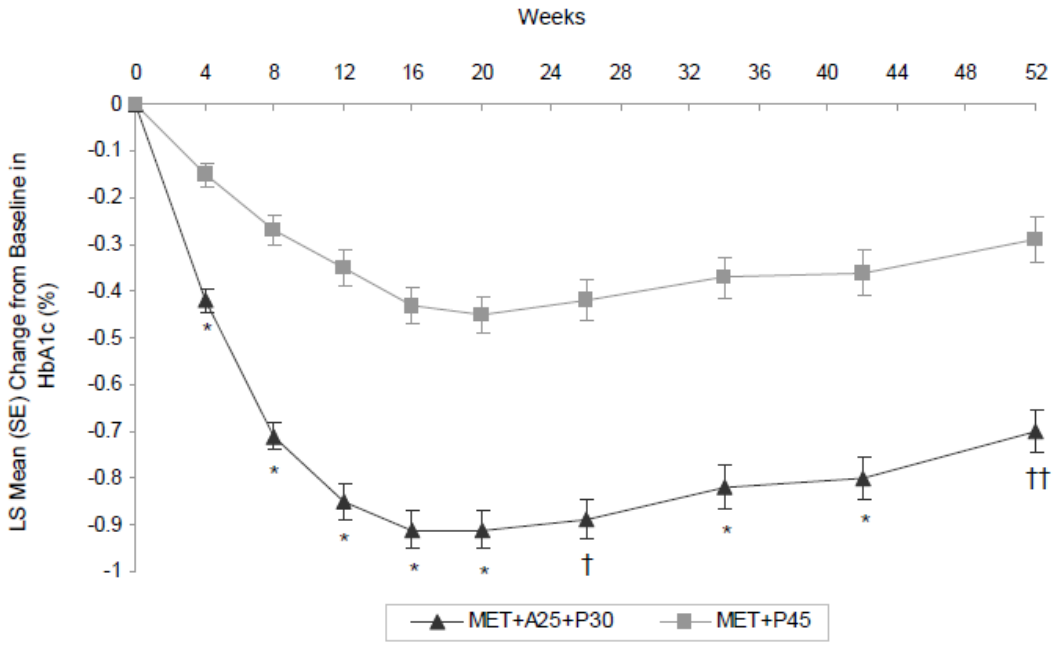
Figure 6. LS Mean Changes From baseline in HbA1c (%) (LOCF, PPS)



*p<0.010 vs MET+glipizide.
†LS mean difference (1-sided 98.75% CI) = -0.09 (-infinity, 0.004), indicating the average change from baseline in the MET+A25 group was non-inferior to that in the MET+glipizide group.
††LS mean difference (1-sided 98.75% CI) = -0.10 (-infinity, -0.002), indicating the average change from baseline in the MET+A12.5 group was non-inferior to that in the MET+glipizide group.

In **study 322OPI-004**, non-inferiority and superiority of alogliptin 25 mg was demonstrated vs titration of pioglitazone from 30 to 45 mg in subjects on a background treatment of MET and pioglitazone 30 mg (see figure 7).

Figure 7. LS Mean (SE) Changes From baseline in HbA1c (%) (LOCF, PPS)Secondary Efficacy Results



Source: Table 15.2.1.1.1a and Figure 15.2.1.12.
*P<0.001 versus MET+P45.
†LS mean difference (1-sided 97.5% CI) = -0.47 (-infinity, -0.35), indicating the average change from Baseline in the MET+A25+P30 group was non-inferior to that in the MET+P45 group .
††LS mean difference (1-sided 97.5% CI) = -0.42 (-infinity, -0.28), indicating the average change from Baseline in the MET+A25+P30 group was non-inferior and superior to that in the MET+P45 group.

- **Secondary Efficacy Results**

Secondary endpoints include clinical response, FPG, body weight and lipid parameters.

Clinical Response

Clinical response was evaluated by assessing the percentage of subjects who achieved HbA1c levels of ≤7.0% at Week 26, following treatment in the respective study. In all four phase III placebo-controlled studies, a higher percentage of subjects in both alogliptin groups achieved these clinical response endpoints at Week 26 than in the placebo group (see table 17). Except in isolated incidences, differences from the placebo group were statistically significant across studies. With the exception of study 011, which had a higher baseline HbA1c, similar percentages of subjects in the alogliptin 12.5 and 25 mg groups achieved HbA1c levels of ≤7.0% at Week 26.

Table 17 Percentage of Subjects Who Achieved a Clinical Response of HbA1c ≤7.0% (LOCF, FAS) (studies 010, 008, 009 and 011)

Study	Placebo	A12.5	A25
Study 010 (monotherapy)	23.4%	47.4%**	44.3%**
Study 008 (add-on to MET)	18.3%	51.6%***	44.4%***
Study 009 (add-on to a TZD)	34.0%	44.2%*	49.2%**
Study 011 (add-on to insulin)	0.8%	8.4%*	7.8%

*p<0.05, **p<0.01, ***p<0.001 compared with placebo.

In **study 010** the percentage of subjects who achieved an HbA1c level of ≤7.0% by Week 26 was also statistically significantly higher in the A12.5 and A25 groups (47.4% [p=0.001] and 44.3% [p=0.008], respectively) than in the placebo group (23.4%).

Overall, higher percentages of subjects in the alogliptin groups achieved the ≤7.0% clinical response endpoint at Week 52 than in the comparator groups in both Studies 305 and 322OPI-004. In **study 305**, significantly higher percentages of subjects in the MET+alogliptin 25 mg group (55.3%) achieved the HbA1c clinical response endpoint at Week 52 compared with the MET+glipizide group (47.4%; p<0.001). In **study 322OPI-004**, significantly higher percentages of subjects in the MET+A25+P30 group (33.2%) achieved the HbA1c clinical response endpoint at Week 52 compared with the MET+P45 group (21.3%; p<0.001).

Change from baseline in fasting plasma glucose (FPG)

Across the four main placebo-controlled studies, LS mean decreases in FPG observed in alogliptin-treated subjects were statistically significant compared with the placebo group for the alogliptin 25 mg group in all studies, and for the alogliptin 12.5 mg group for all studies except study 011 (add-on to insulin) (see table 18). Additionally, in 3 of the 4 studies, subjects in the alogliptin 25 mg group achieved greater LS mean reductions in FPG than subjects in the alogliptin 12.5 mg group.

Table 18. Change From baseline in FPG (mmol/L) (LOCF, FAS) (010, 008, 009 and 011)

	Placebo	A12.5	A25
Study 010 (monotherapy)	**N=64**	**N=133**	**N=131**
seline FPG (mmol/L)	9.62	9.63	9.55
S Mean Change at Week 26	0.63	-0.57***	-0.91***
Study 008 (add-on to MET)	**N=104**	**N=213**	**N=207**
seline FPG (mmol/L)	9.97	9.34	9.54
S Mean Change at Week 26	0.00	-1.04***	-0.96***
Study 009 (add-on to TZD)	**N=97**	**N=197**	**N=199**
seline FPG (mmol/L)	9.53	9.63	9.41
S Mean Change at Week 26	-0.32	-1.09**	-1.10**
Study 011 (add-on to Insulin)	**N=129**	**N=131**	**N=129**
seline FPG (mmol/L)	10.88	10.54	10.34
S Mean Change at Week 26	0.32	0.13	-0.65*

*p<0.05, **p<0.01, ***p<0.001 compared with placebo.
Note: Results from ANCOVA models with effects for treatment, geographic region, and baseline FPG. Additional factors and covariates are included as specified in the individual study tables.

In both long-term, active-comparator studies (305 and 322OPI-004), greater LS mean reductions from baseline in FPG were observed in the alogliptin groups than in the comparator groups at Weeks 26 and 52.

In **study 305**, the LS mean changes from baseline in FPG at Week 52 were -0.40, -0.28, and 0.05 mmol/L for the MET+alogliptin 25 mg, MET+alogliptin 12.5 mg, and MET+glipizide groups, respectively (p<0.001). In general, greater reductions were observed in the MET+alogliptin 25 mg group than in the MET+alogliptin 12.5 mg group. Additionally, LS mean decreases from baseline in FPG were apparent from the first assessment (Week 2) and continued throughout the majority of time points during the study.

In **study 322OPI-004**, the LS mean changes from baseline at Week 52 were -0.81 and -0.21 mmol/L in the MET+A25+P30 and MET+P45 groups, respectively (p<0.001).

Additionally, LS mean decreases from baseline in FPG were statistically significant for the MET+A25+P30 group at all time-points through Week 52 compared with the MET+P45 group ($p<0.01$).

Body weight and serum lipids

Across **Studies 008, 009**, and **011**, there were no meaningful differences between placebo and subjects receiving alogliptin in LS mean changes from baseline in body weight at Week 26. LS mean changes from baseline ranged from decreases of -0.4 to -0.7 kg in study 008 to increases of 1.0 to 1.5 kg in study 009.

Also in **study 010**, there were no meaningful differences in LS mean changes in body weight between the placebo group (0.18 kg) and A12.5 and A25 groups (-0.09 and 0.22 kg, respectively).

In **study 305**, statistically significant ($p<0.001$) LS mean decreases in body weight were observed at Week 52 in the MET+alogliptin 12.5 mg and MET+alogliptin 25 mg groups (-0.64 and -0.91 kg, respectively) compared with an increase in weight in the MET+glipizide group (0.89 kg). However, in **study 322OPI-004**, mean changes in body weight were consistent with the concomitant medication (i.e. pioglitazone) administered. At Week 52, LS mean increases in body weight were observed in both treatment groups (1.10 kg and 1.60 kg in the MET+A25+P30 and MET+P45 groups, respectively). These increases were not considered clinically meaningful and there was no statistically significant difference between treatment groups.

Overall, changes from baseline in lipid parameters were similar in the alogliptin and placebo groups suggesting that treatment with alogliptin has a neutral effect on lipid parameters, regardless of administration as a monotherapy or as an add-on to established concomitant antidiabetic medications.

2.5.2.5.2. Summary of main studies

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

Table 19 Summary of Efficacy - Study 010

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) Compared with Placebo in Subjects with Type 2 Diabetes		
Study identifier	SYR-322-PLC-010 (also referred to as Study 010)	
Design	Phase III, randomized, double-blind, placebo-controlled, parallel-group	
	Duration of Main phase:	26 weeks
	Duration of Run-in phase:	4 weeks (single-blind placebo)
	Duration of Extension phase:	4 years via Study SYR-322-OLE-012 (eligible subjects only)
Hypothesis	Superiority analysis of alogliptin treatment compared with placebo as measured by glycosylated hemoglobin (HbA1c) change from baseline (Day 1) to Week 26	
Treatment groups	Placebo	26-week treatment with placebo once daily (QD), 65 subjects randomized
	Alogliptin 12.5 mg (A12.5)	26-week treatment with A12.5 QD, 133 subjects randomized

	Alogliptin 25 mg (A25)	26-week treatment with A25 QD, 131 subjects randomized	
Endpoints and definitions	Primary endpoint	Confirmatory	HbA1c change from baseline to Week 26
	Key secondary endpoint	Exploratory	Fasting plasma glucose (FPG) change from baseline to Week 26
	Other endpoint	Exploratory	Body weight change from baseline to Week 26
Database lock	26 July 2007		

Results and Analysis				
Analysis description	**Primary Endpoint Analysis:** An analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) values was performed, with study treatment and geographic region as class variables and duration of T2DM and baseline HbA1c as continuous covariates. The A25 dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test result was statistically significant, the A12.5 dose was evaluated in a similar fashion.			
Analysis population and time point description	Full analysis set (FAS), which was defined as all randomized subjects who received at least 1 dose of double-blind study drug, had a baseline value, and had at least one post baseline value.			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	63	131	128
	LS mean change	-0.02	-0.56	-0.59
	SE	0.094	0.065	0.066
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.54	-0.57
		95% CI	-0.76, -0.31	-0.80, -0.35
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Key Secondary Endpoint Analysis:** Same as primary model except with baseline FPG value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	64	132	129
	LS mean change	0.628	-0.571	-0.913
	SE	0.2910	0.2010	0.2038
Effect estimate per comparison	Secondary endpoint: FPG (mmol/L)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-1.199	-1.541
		95% CI	-1.896, -0.503	-2.243, -0.839
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Other Endpoint Analysis:** Same as primary model except with baseline body weight value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			

Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	63	126	125
	LS mean change	0.18	-0.09	-0.22
	SE	0.368	0.258	0.259
Effect estimate per comparison	Other endpoint: body weight (kg)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.28	-0.40
		95% CI	-1.16, 0.61	-1.29, 0.49
		p-value	0.539	0.379
Notes	None.			

Table 20.Summary of Efficacy - Study 008

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Metformin in Subjects with Type 2 Diabetes				
Study identifier	SYR-322-MET-008 (also referred to as Study 008)			
Design	Phase III, randomized, double-blind, placebo-controlled, parallel-group			
	Duration of Main phase:	26 weeks		
	Duration of Run-in phase:	4 weeks (single-blind placebo and open-label metformin 1500 mg or MTD)		
	Duration of Extension phase:	4 years via Study SYR-322-OLE-012 (eligible subjects only)		
Hypothesis	Superiority analysis of alogliptin combination treatment with metformin compared with metformin alone as measured by HbA1c change from baseline to Week 26			
Treatment groups	Placebo	26-week treatment with placebo QD as add-on to metformin 1500 mg or MTD, 104 subjects randomized		
	Alogliptin 12.5 mg (A12.5)	26-week treatment with A12.5 QD as add-on to metformin 1500 mg or MTD, 213 subjects randomized		
	Alogliptin 25 mg (A25)	26-week treatment with A25 QD as add-on to metformin 1500 mg or MTD, 210 subjects randomized		
Endpoints and definitions	Primary endpoint	Confirmatory	HbA1c change from baseline to Week 26	
	Key secondary endpoint	Exploratory	FPG change from baseline to Week 26	
	Other endpoint	Exploratory	Body weight change from baseline to Week 26	
Database lock	05 July 2007			
Results and Analysis				
Analysis description	**Primary Endpoint Analysis:** An ANCOVA model using LOCF values was performed, with study treatment and geographic region as class variables and baseline metformin dose and baseline HbA1c as continuous covariates. The A25 dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test result was statistically significant, the A12.5 dose was evaluated in a similar fashion.			
Analysis population and time point description	FAS, which was defined as all randomized subjects who received at least 1 dose of double-blind study drug, had a baseline value, and had at least one post baseline value.			
Descriptive statistics	Treatment group	Placebo	A12.5	A25

and estimate variability	Number of subjects	103	210	203
	LS mean change	-0.10	-0.61	-0.59
	SE	0.076	0.053	0.054
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.50	-0.48
		95% CI	-0.68, -0.32	-0.67, -0.30
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Key Secondary Endpoint Analysis:** Same as primary model except with baseline FPG value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	104	211	204
	LS mean change	0.001	-1.039	-0.963
	SE	0.1971	0.1382	0.1403
Effect estimate per comparison	Secondary endpoint: FPG (mmol/L)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-1.040	-0.964
		95% CI	-1.514, -0.567	-1.439, -0.488
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Other Endpoint Analysis:** Same as primary model except with baseline body weight value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	103	206	198
	LS mean change	-0.39	-0.39	-0.67
	SE	0.274	0.194	0.198
Effect estimate per comparison	Other endpoint: body weight (kg)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	0.00	-0.28
		95% CI	-0.66, 0.66	-0.94, 0.38
		p-value	0.996	0.407
Notes	None.			

Table 21.Summary of Efficacy - tudy 009

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Pioglitazone in Subjects with Type 2 Diabetes

Study identifier	SYR-322-TZD-009 (also referred to as Study 009)			
Design	Phase III, randomized, double-blind, placebo-controlled, parallel-group			
	Duration of Main phase:	26 weeks		
	Duration of Run-in phase:	4 weeks (single-blind placebo and open-label pioglitazone 30 mg or MTD [converted from comparable rosiglitazone dose, as applicable])		
	Duration of Extension phase:	4 years via Study SYR-322-OLE-012 (eligible subjects only)		
Hypothesis	Superiority analysis of alogliptin combination treatment with pioglitazone (with or without metformin or a sulfonylurea) compared with pioglitazone alone (with or without metformin or a sulfonylurea) as measured by HbA1c change from baseline to Week 26			
Treatment groups	Placebo	26-week treatment with placebo QD as add-on to pioglitazone 30 mg or MTD (with or without metformin or a sulfonylurea), 97 subjects randomized		
	Alogliptin 12.5 mg (A12.5)	26-week treatment with A12.5 QD as add-on to pioglitazone 30 mg or MTD (with or without metformin or a sulfonylurea), 197 subjects randomized		
	Alogliptin 25 mg (A25)	26-week treatment with A25 QD as add-on to pioglitazone 30 mg or MTD (with or without metformin or a sulfonylurea), 199 subjects randomized		
Endpoints and definitions	Primary endpoint	Confirmatory	HbA1c change from baseline to Week 26	
	Key secondary endpoint	Exploratory	FPG change from baseline to Week 26	
	Other endpoint	Exploratory	Body weight change from baseline to Week 26	
Database lock	17 August 2007			
Results and Analysis				
Analysis description	**Primary Endpoint Analysis:** An ANCOVA model using LOCF values was performed, with study treatment, geographic region, and baseline treatment regimen as class variables and baseline pioglitazone dose and baseline HbA1c as continuous covariates. The A25 dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test result was statistically significant, the A12.5 dose was evaluated in a similar fashion.			
Analysis population and time point description	FAS, which was defined as all randomized subjects who received at least 1 dose of double-blind study drug, had a baseline value, and had at least one post baseline value.			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	95	196	195
	LS mean change	-0.19	-0.66	-0.80
	SE	0.081	0.056	0.056
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.47	-0.61
		95% CI	-0.67, -0.28	-0.80, -0.41
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Key Secondary Endpoint Analysis:** Same as primary model except with baseline FPG value in place of HbA1c as covariate.			

Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	97	196	197
	LS mean change	-0.318	-1.092	-1.103
	SE	0.2117	0.1490	0.1484
Effect estimate per comparison	Secondary endpoint: FPG (mmol/L)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.775	-0.785
		95% CI	-1.285, -0.265	-1.293, -0.277
		p-value	0.003	0.003
Notes	None.			
Analysis description	**Other Endpoint Analysis:** Same as primary model except with baseline body weight value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	94	193	189
	LS mean change	1.04	1.46	1.09
	SE	0.329	0.230	0.232
Effect estimate per comparison	Other endpoint: body weight (kg)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	0.42	0.05
		95% CI	-0.37, 1.22	-0.74, 0.84
		p-value	0.294	0.900
Notes	None.			

Table 22. Summary of Efficacy - Sudy 011

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Insulin in Subjects with Type 2 Diabetes		
Study identifier	SYR-322-INS-011 (also referred to as Study 011)	
Design	Phase III, randomized, double-blind, placebo-controlled, parallel-group	
	Duration of Main phase:	26 weeks
	Duration of Run-in phase:	4 weeks (single-blind placebo with subject's usual insulin with or without metformin)
	Duration of Extension phase:	4 years via Study SYR-322-OLE-012 (eligible subjects only)
Hypothesis	Superiority analysis of alogliptin combination treatment with insulin (with or without metformin) compared with insulin alone (with or without metformin) as measured by HbA1c change from baseline to Week 26	
Treatment groups	Placebo	26-week treatment with placebo QD as add-on to insulin (with or without metformin), 130 subjects randomized

	Alogliptin 12.5 mg (A12.5)	26-week treatment with placebo QD as add-on to insulin (with or without metformin), 131 subjects randomized	
	Alogliptin 25 mg (A25)	26-week treatment with placebo QD as add-on to insulin (with or without metformin), 129 subjects randomized	
Endpoints and definitions	Primary endpoint	Confirmatory	HbA1c change from baseline to Week 26
	Key secondary endpoint	Exploratory	FPG change from baseline to Week 26
	Other endpoint	Exploratory	Body weight change from baseline to Week 26
Database lock	21 June 2007		

Results and Analysis				
Analysis description	**Primary Endpoint Analysis:** An ANCOVA model using LOCF values was performed, with study treatment, geographic region, and baseline treatment regimen as class variables and baseline daily insulin dose and baseline HbA1c as continuous covariates. The A25 dose was compared with placebo at the 2-sided 0.05 significance level using a contrast derived from the primary model. If this test result was statistically significant, the A12.5 dose was evaluated in a similar fashion.			
Analysis population and time point description	FAS, which was defined as all randomized subjects who received at least 1 dose of double-blind study drug, had a baseline value, and had at least one post baseline value.			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	126	130	126
	LS mean change	-0.13	-0.63	-0.71
	SE	0.077	0.076	0.078
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.51	-0.59
		95% CI	-0.72, -0.30	-0.80, -0.37
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Key Secondary Endpoint Analysis:** Same as primary model except with baseline FPG value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	127	131	128
	LS mean change	0.324	0.130	-0.651
	SE	0.3156	0.3103	0.3156
Effect estimate per comparison	Secondary endpoint: FPG (mmol/L)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	-0.194	-0.975
		95% CI	-1.064, 0.677	-1.854, -0.096
		p-value	0.662	0.030
Notes	None.			

Analysis description	**Other Endpoint Analysis:** Same as primary model except with baseline body weight value in place of HbA1c as covariate.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	A12.5	A25
	Number of subjects	121	127	124
	LS mean change	0.63	0.68	0.60
	SE	0.244	0.237	0.241
Effect estimate per comparison	Other endpoint: body weight (kg)	Comparison group	A12.5 vs Placebo	A25 vs Placebo
		LS mean difference	0.05	-0.02
		95% CI	-0.62, 0.72	-0.70, 0.65
		p-value	0.874	0.948
Notes	None.			

Table 23. Summary of Efficacy - Study 305 (on-going study)

Title: A Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Durability of the Efficacy and Safety of Alogliptin Compared to Glipizide When Used in Combination with Metformin in Subjects with T2DM			
Study identifier	SYR-322_305 (also referred to as Study 305)		
Design	Phase III, randomized, double-blind, active-controlled, parallel-group		
	Duration of Main phase:	2 years	
	Duration of Run-in phase:	4 weeks (single-blind placebo and open-label metformin 1500 mg or MTD)	
	Duration of Extension phase:	Not applicable	
Hypothesis	Noninferiority analysis of alogliptin combination treatment with metformin compared with glipizide combination treatment with metformin as measured by HbA1c change from baseline to Week 52 (at interim cut) and Week 104 (at study conclusion)		
Treatment groups	Alogliptin 12.5 mg (A12.5)	2-year treatment with A12.5 QD as add-on to metformin 1500 mg or MTD, 880 subjects randomized	
	Alogliptin 25 mg (A25)	2-year treatment with A25 QD as add-on to metformin 1500 mg or MTD, 885 subjects randomized	
	Glipizide 5-20 mg*	2-year treatment with glipizide 5-20 mg* QD as add-on to metformin 1500 mg or MTD, 873 subjects randomized	
	*titrated between Weeks 3 and 20, at 5-mg increments in 4-week intervals, for subjects with persistent hyperglycaemia		
Endpoints and definitions	Primary endpoint	Noninferiority	HbA1c change from baseline to Weeks 52 and 104
	Key secondary endpoint	Exploratory	FPG change from baseline to Week 52
	Other endpoint	Exploratory	Body weight change from baseline to Week 52
Database lock	10 November 2011 (52-week interim data cut date)		
Results and Analysis			

Analysis description	**Primary Endpoint Analysis:** An ANCOVA model using LOCF values was performed, with study treatment, geographic region, and study schedule (see notes below) as class variables and baseline metformin dose and baseline HbA1c as continuous covariates. The A25 dose was compared with placebo at the 1-sided 0.0125 significance level using a noninferiority margin of 0.3%. If this test result was statistically significant, the A12.5 dose was evaluated in a similar fashion.			
Analysis population and time point description	Per protocol set, which was defined as all FAS subjects (ie, those randomized who received at least 1 dose of double-blind study drug, had a baseline value, and had at least one post baseline value) who had no major protocol violations.			
Descriptive statistics and estimate variability	Treatment group	A12.5	A25	Glipizide
	Number of subjects	542	537	509
	LS mean change	-0.62	-0.61	-0.52
	SE	0.029	0.030	0.030
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison group	A12.5 vs Glipizide	A25 vs Glipizide
		LS mean difference	-0.10	-0.09
		98.75% CI	-infinity, -0.002	-infinity, 0.004
		p-value	N/A	N/A
Notes	Subjects entered the Screening Period via 1 of 2 study schedules: - Schedule A for subjects with HbA1c of 7.0% to 9.0% while on metformin ≥1500 mg or MTD. These subjects directly entered the run-in phase. - Schedule B for subjects with HbA1c of 7.5% to 10.0% while on metformin <1500 mg with no MTD documentation. These subjects had to achieve HbA1c of 7.0% to 9.0% while on metformin ≥1500 mg or MTD before entering the run-in phase.			
Analysis description	**Key Secondary Endpoint Analysis:** Same as primary model except with baseline FPG value in place of HbA1c as covariate and at the 0.05 2-sided significance level for statistical difference rather than for non-inferiority.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	A12.5	A25	Glipizide
	Number of subjects	867	867	858
	LS mean change	-0.277	-0.399	0.049
	SE	0.0678	0.0678	0.0681
Effect estimate per comparison	Secondary endpoint: FPG (mmol/L)	Comparison group	A12.5 vs Glipizide	A25 vs Glipizide
		LS mean difference	-0.326	-0.448
		95% CI	-0.5147, -0.1378	-0.6368, -0.2597
		p-value	<0.001	<0.001
Notes	None.			
Analysis description	**Other Endpoint Analysis:** Same as primary model except with baseline body weight value in place of HbA1c as covariate and at the 0.05 2-sided significance level for statistical difference rather than for non-inferiority.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	A12.5	A25	Glipizide
	Number of subjects	867	868	862
	LS mean change	-0.64	-0.91	0.89

	SE	0.117	0.117	0.117
Effect estimate per comparison	Secondary endpoint: body weight (kg)	Comparison group	A12.5 vs Glipizide	A25 vs Glipizide
		LS mean difference	-1.52	-1.80
		95% CI	-1.846, -1.198	-2.122, -1.473
		p-value	<0.001	<0.001
Notes	None.			

Table 24. Summary of Efficacy - Study 322OPI-004

Title: A Multicenter, Randomized, Double-Blind Study to Determine the Efficacy and Safety of the Addition of SYR-322 25 mg versus Dose Titration from 30 mg to 45 mg of ACTOS® Pioglitazone HCl in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Control on a Combination of Metformin and 30 mg of Pioglitazone HCl Therapy				
Study identifier	01-06-TL-322OPI-004 (also referred to as Study 322OPI-004)			
Design	Phase III, randomized, double-blind, parallel-group			
	Duration of Main phase:	52 weeks		
	Duration of Run-in phase:	4 weeks (open-label pioglitazone 30 mg with metformin 1500 mg or MTD)		
	Duration of Extension phase:	Not applicable		
Hypothesis	Noninferiority analysis of alogliptin combination treatment with pioglitazone (plus background metformin) compared with pioglitazone titration (plus background metformin) as measured by HbA1c change from baseline to Weeks 26 and 52			
Treatment groups	Alogliptin 25 mg (A25)	52-week treatment with A25 QD as add-on to pioglitazone 30 mg (P30) and metformin 1500 mg or MTD, 404 subjects randomized		
	Pioglitazone 45 mg (P45)	52-week treatment with P45 QD as add-on to metformin 1500 mg or MTD, 399 subjects randomized		
Endpoints and definitions	Primary endpoint	Noninferiority	HbA1c change from baseline to Weeks 26 and 52	
	Key secondary endpoint	Exploratory	FPG change from baseline to Weeks 26 and 52	
	Other endpoint	Exploratory	Body weight change from baseline to Weeks 26 and 52	
Database lock	09 July 2009			
Results and Analysis				
Analysis description	**Primary Endpoint Analysis:** An ANCOVA model using LOCF values was performed, with study treatment, geographic region, and study schedule (see notes below) as class variables and baseline metformin dose and baseline HbA1c as continuous covariates. At Week 26, the A25+P30 dose was compared with P45 at the 1-sided 0.025 significance level using a non-inferiority margin of 0.3%. If this test result was statistically significant, Week 52 was evaluated in a similar fashion.			
Analysis population and time point description	Per protocol set, which was defined as all FAS subjects (ie, those randomized who received at least 1 dose of double-blind study drug, had a baseline value, and had at least one post baseline value) who had no major protocol violations.			
Descriptive statistics and estimate variability	Week 52	Treatment group	A25+P30	P45
		Number of subjects	303	306
		LS mean change	-0.70	-0.29

		SE	0.048	0.048
Effect estimate per comparison	Week 52	Primary endpoint: HbA1c (%)	Comparison group	A25+P30 vs P45
			LS mean difference	-0.42
			97.5% CI	-infinity, -0.28
			p-value	N/A
Notes	Subjects entered the Screening Period via 1 of 2 study schedules: - Schedule A for subjects with HbA1c of 7.0% to 10.0% while on a stable (2 months) regimen of pioglitazone 30 mg with metformin ≥1500 mg or MTD. These subjects directly entered the run-in phase. - Schedule B for subjects with HbA1c ≥7.5% while on metformin with other oral antidiabetic agent. These subjects entered a 12-week switching period, discontinued their antidiabetic treatment, were switched to pioglitazone 30 mg with metformin ≥1500 mg or MTD, and had to achieve HbA1c of 7.0% to 10.0% before entering the run-in phase.			
Analysis description	**Key Secondary Endpoint Analysis:** Same as primary model except with baseline FPG value in place of HbA1c as covariate and at the 0.05 2-sided significance level for statistical difference rather than for non-inferiority.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Week 52	Treatment group	A25+P30	P45
		Number of subjects	399	396
		LS mean change	-0.813	-0.207
		SE	0.1048	0.1051
Effect estimate per comparison	Week 52	Secondary endpoint: FPG (mmol/L)	Comparison group	A25+P30 vs P45
			LS mean difference	-0.606
			95% CI	-0.897, -0.315
			p-value	<0.001
Notes	None.			
Analysis description	**Other Endpoint Analysis:** Same as primary model except with baseline body weight value in place of HbA1c as covariate and at the 0.05 2-sided significance level for statistical difference rather than for non-inferiority.			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Week 52	Treatment group	A25+P30	P45
		Number of subjects	395	394
		LS mean change	1.10	1.60
		SE	0.194	0.194
Effect estimate per comparison	Week 52	Other endpoint: body weight (kg)	Comparison group	A25+P30 vs P45
			LS mean difference	-0.50
			95% CI	-1.03, 0.04
			p-value	0.071
Notes	None.			

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

2.5.3.1. Longer term studies

The persistence of efficacy of combination treatment including alogliptin has been demonstrated for up to 52 weeks in Studies 305 and 322OPI-004, showing the durability of the glucose-lowering effect as assessed by HbA1c reduction (see above).

In study 305, at each of the post-baseline study visits, decreases in HbA1c were generally similar among the treatment groups, and MET+alogliptin 25 mg was found to be non-inferior to MET+glipizide.

In study 322OPI-004, significantly greater decreases in HbA1c were observed in the MET+A25+P30 treatment group vs the MET+P45 treatment group ($p<0.001$ at all time-points). At Week 52, the LS mean difference between treatment groups indicated non-inferiority of MET+A25+P30 to MET+P45. Furthermore, results at Week 52 also indicated statistical superiority of the MET+A25+P30 group to the MET+P45 group.

2.5.3.2. Dose Response

In pharmacodynamic studies, the alogliptin 25 mg dose achieved optimal DPP-4 inhibition and increases in active GLP-1 compared with the 12.5 mg dose. For doses greater than 25 mg, no additional benefit in DPP-4 inhibition or GLP-1 levels was observed, indicating that the 25 mg dose is the optimal dose to achieve therapeutic effect. In the phase 2 dose-ranging study (003), LS mean differences from placebo at Day 85 were statistically significant for alogliptin doses ≥ 12.5 mg for HbA1c and ≥ 25 mg for FPG, with no additional HbA1c reduction seen at doses greater than 25 mg.

Across the 5 main phase III, 26-week placebo-controlled studies, alogliptin 25 mg generally provided more substantial HbA1c reductions compared with alogliptin 12.5 mg.

The differences in efficacy were consistently more apparent in the 3 studies with the relatively higher baseline HbA1c (i.e. Studies 007, 009, and 011).

In the 2 main studies evaluating alogliptin add-on to MET (008 and 305), differentiation in terms of HbA1c reduction between both alogliptin doses was less apparent, likely related to the lower mean baseline HbA1c (7.9% and 7.6%, respectively). In contrast, a good dose response for alogliptin add-on to MET was evident in 2 relevant treatment arms in supportive study 322OPI-001, in which alogliptin 25 mg showed greater reductions in HbA1c compared with alogliptin 12.5 mg (-0.90% vs -0.64%), in a setting with a higher mean baseline HbA1c (8.5%).

Across the clinical program, alogliptin 25 mg generally showed a greater response in secondary endpoints (analysis of HbA1c by baseline HbA1c values, clinical response, change from baseline in FPG, and hyperglycaemia) compared with alogliptin 12.5 mg.

To evaluate the consistency of HbA1c reduction across multiple subpopulations, efficacy was assessed for subgroups of subjects defined by various baseline demographic factors. In consideration of limited sample sizes of some of these subgroups in individual studies, pooled analyses were conducted to supplement those completed in the individual studies for sex, age, race, BMI, baseline HbA1c, and renal function categories.

For the pooled analyses, data were integrated from 4 of the main studies (010, 007, 008, and 009). Study 011 was excluded from the pooled analysis because of differences in the study design (different randomization ratio) and in the study population (mean baseline HbA1c, mean disease duration). A total of 1845 subjects are included in these post hoc pooled analyses.

Results indicate that the placebo-adjusted treatment difference in HbA1c is independent of sex and BMI. No clinically meaningful differences were observed between race categories. A tendency for greater efficacy in elderly subjects is observed. In addition greater efficacy observed in the alogliptin 25 mg group.

2.5.4. Clinical studies in special populations

No specific subpopulation investigations have been conducted with alogliptin/metformin; however, this FDC product is expected to have a similar efficacy profile as the individual components, in view of the evidence provided in the bioequivalence study with the FDC and the pharmacokinetic and pharmacodynamic studies with the individual components.

2.5.4.1. Elderly

A total of 239 subjects ≥65 years were treated in the placebo-controlled 3 Studies 008, 009, and 011. Of these, 32 subjects were ≥75 years. A total of 184 subjects ≥65 years, 23 subjects ≥75 years were treated with alogliptin specifically (see table 23).

Table 25 Change From baseline in Mean HbA1c (%) at Week 26 by Demographic Subgroup Age (LOCF, FAS) (008, 009, 011)

	Study 008 Add-on to MET			Study 009 Add-on to TZD, With or Without MET or SU			Study 011 Add-on to Insulin, With or Without MET		
ıbgroup	**Placebo N=104**	**A12.5 N=213**	**A25 N=207**	**Placebo N=97**	**A12.5 N=197**	**A25 N=199**	**Placebo N=129**	**A12.5 N=131**	**A25 N=129**
Age									
<65 years	-0.10 (n=82)	-0.62 (n=170)	-0.60 (n=172)	-0.22 (n=81)	-0.66 (n=164)	-0.80 (n=156)	-0.08 (n=106)	-0.62 (n=111)	-0.73 (n=103)
≥65 years	-0.22 (n=21)	-0.51 (n=40)	-0.52 (n=31)	0.11 (n=14)	-0.71 (n=32)	-0.78 (n=39)	-0.36 (n=20)	-0.71 (n=19)	-0.68 (n=23)
≥75 years	-1.03 (n=3)	-0.24 (n=7)	-0.35 (n=2)	0.03 (n=4)	-0.90 (n=3)	-1.34 (n=5)	-0.60 (n=2)	-0.60 (n=3)	-0.33 (n=3)

In the pooled analysis for alogliptin clinically relevant placebo-adjusted HbA1c mean changes from baseline were observed for both alogliptin doses (0.44% and -0.59% for 12.5 mg; -0.51% and 0.67% for 25 mg) in both age categories (<65 and ≥ 65 years, respectively), with no clinically meaningful differences observed. There was a relatively small number of patients aged ≥ 75 years. Nevertheless, in these patients, placebo-adjusted HbA1c changes were -0.418 % for alogliptin 12.5 mg (n=26) and -0.484% for alogliptin 25 mg (n=20). Overall, these results are supportive of the findings of the primary analyses from each of the individual main phase III studies.

In the long-term **Studies 305** and **322OPI-004**, clinically relevant HbA1c reductions were observed at Week 52 for elderly subjects (≥65 years) who received alogliptin 25 mg, in keeping with the results of the pooled analysis (-0.58% in Study 305 [n=173] and -0.97% in

study 322OPI-004 [n=50]). These reductions were greater than in the younger population (<65 years) (-0.44% in study 305 [n=693] and -0.68% in study 322OPI-004 [n=253]).

2.5.4.2. Subjects with impaired renal function

Dose recommendations for the FDC alogliptin/metformin in patients with *renal impairment* are based on monotherapy alogliptin and metformin data. Pharmacokinetic data generated in subjects with T2DM demonstrated increased systemic exposure of **alogliptin** with decreasing renal function (see pharmacokinetic section). These results confirm the pharmacokinetic profile observed in phase I study subjects with mild or moderate renal impairment. A dose reduction is therefore recommended for patients with moderate impairment so that exposure to alogliptin in these patients is similar to that of patients with normal renal function. No dose reduction needed in patients with mild renal impairment.

Metformin is contraindicated in patients with renal failure or dysfunction (creatinine clearance < 60 ml/min) or in patients with acute conditions that may alter renal function (e.g. dehydration, severe infection or shock) because of the risk of lactic acidosis. Therefore, because of the metformin HCl component, the FDC alogliptin/metformin should not be administered to patients with moderate or severe renal impairment (creatinine clearance < 60 ml/min).

In patients with mild renal impairment, no dose adjustment of the FDC 12.5 mg/ 850 mg BID or 12.5 mg/ 1000 mg BID is needed or recommended.

2.5.4.3. Subjects with hepatic impairment

Dose recommendations for patients with *hepatic impairment* are based on monotherapy alogliptin and metformin data: as a precautionary measure consistent with the metformin label, the administration of alogliptin/metformin is contraindicated (SmPC section 4.3) in patients with hepatic impairment.

2.5.5. Supportive studies

Supportive **studies 302** and **322OPI-001** were 26-week factorial studies that examined alogliptin alone or in combination with MET vs MET alone in subjects on diet and exercise alone (study 302) or alogliptin alone or in combination with pioglitazone vs pioglitazone alone in subjects receiving MET monotherapy (≥1500 mg or MTD) (study 322OPI-001).

In **study 302**, LS mean reductions in HbA1c from baseline at Week 26 were significantly greater ($p<0.001$) with both coadministration therapy regimens (-1.22% and -1.55% with A12.5+M500 BID and A12.5+M1000 BID, respectively) when compared with either of their individual component regimens, alogliptin alone (-0.56% with A12.5 BID) or MET alone (-0.65% and -1.11% with M500 and M1000 BID respectively).

Study 322OPI-001 evaluated 12 treatment groups (in addition to background MET) over a 26 week period: placebo+placebo, or pioglitazone 15 mg, 30 mg, or 45 mg once daily; alogliptin 12.5 mg+placebo or pioglitazone 15 mg, 30 mg, or 45 mg once daily; alogliptin 25 mg+placebo or pioglitazone 15 mg, 30 mg, or 45 mg once daily. A total of 1554 subjects were randomized to receive treatment. In subjects who were experiencing inadequate glycaemic control with MET alone

(mean baseline HbA1c values of approximately 8.5%), there were statistically significant ($p \leq 0.001$) decreases from baseline in the LS mean HbA1c levels at Week 26 in subjects treated in the alogliptin 12.5 mg+pioglitazone and alogliptin 25 mg+pioglitazone groups compared with pioglitazone alone (LS mean changes from baseline in HbA1c were 0.89%, 1.43%, and -1.42% in the pioglitazone alone, alogliptin 12.5 mg+pioglitazone, and alogliptin 25 mg+pioglitazone groups, respectively).

A dose response for alogliptin add-on to MET was evident, in which alogliptin 25 mg showed a greater reduction in HbA1c compared with alogliptin 12.5 mg (-0.90% vs -0.64%), in a setting with a higher mean baseline HbA1c.

Another supportive study is **Study 402**, which at the time of the evaluation of this application was on-going, a long-term CV outcomes study in subjects with T2DM and recent (within 15 to 90 days) acute coronary syndrome (ACS). Subjects were included with varying degrees of renal impairment. The primary endpoint in this study is the major adverse CV event (MACE) composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. At the time of the CHMP opinion for this procedure, the clinical phase of this study has been already completed as the calculated number of events had been reached; a final study report is expected to be made available during the first quarter of 2014.

Study 012 was a long-term (4 years), open-label extension study of alogliptin (12.5 or 25 mg) once daily in subjects enrolled in 7 of the controlled phase III studies.

2.5.6. Discussion on clinical efficacy

2.5.6.1. Design and conduct of clinical studies

An extensive number of randomized trials have been performed, including trials with placebo and active comparators, and in combination with several other antidiabetic agents. For this FDC five main studies, two supportive studies and the monotherapy trial 010 were considered relevant by the CHMP.

Analysis of change from baseline in HbA1c (primary endpoint) was based on full analyses set (FAS) for placebo-controlled studies or per protocol set (PPS) in active-comparator studies using the last observation carried forward (LOCF) as imputation method for missing data. This approach was considered acceptable by the CHMP.

More subjects in the placebo group than in the treatment group discontinued the studies, particularly due to need of hyperglycaemic rescue treatment. This was according to the protocol, and not considered a protocol deviation (i.e. these patients would still be included in the PPS). This could lead to an overestimation of the treatment effect. As expected, subjects in the placebo group who completed the studies had a larger reduction in HbA1c compared to placebo subjects in the FAS. Therefore, the differences between alogliptin and placebo were less pronounced when the analyses were performed on the FAS population. However, it is noted that the differences were still statistically significant.

2.5.6.2. Efficacy data and additional analyses

Dose selection

In dose finding studies, no additional efficacy was observed at doses greater than 12.5 mg. However, the inclusion of alogliptin 12.5 mg and 25 mg in the phase III trials is seen as a reasonable approach. In most of the pivotal studies, the effect difference between alogliptin 12.5 mg and 25 mg was not large, but the efficacy for alogliptin 25 mg was somewhat more pronounced. Therefore, the choice for alogliptin daily dose of 25 mg was considered acceptable.

The pharmacokinetic and pharmacodynamics study 101 showed that 12.5 mg alogliptin taken twice daily pharmacodynamic results did not differ from the ones obtained with 25 mg alogliptin taken once daily. Furthermore, clinical study 302 showed comparable efficacy results for alogliptin 12.5 mg twice daily, compared to alogliptin 25 mg taken once daily. Therefore, the proposed twice daily administration regimen for the FDC alogliptin/metformin is found acceptable.

No separate dose response studies were performed with metformin alone. This is acceptable, since the proposed dose of the metformin component is in line with the SmPC of metformin and with clinical practice.

Since metformin is contraindicated in patients with renal impairment (creatinine clearance < 60 ml/min), the FDC alogliptin/metformin is contraindicated in patients with creatinine clearance below 60 ml/min. Therefore, the proposed dosages for the FDC alogliptin/metformin 12.5 mg/ 850 mg BID and 12.5 mg/ 1000 mg BID are acceptable. In the initial application a lower dose of alogliptin (6.25mg BID) was included, as the applicant was of the opinion that there had been growing evidence that metformin is both efficacious and safe in patients with greater degree of renal impairment. The CHMP considered that the new evidence was not strong enough in order to impact in any way metformin contraindication in patients with severe renal dysfunction. Consequently the applicant decided to withdraw its application for the combinations that contained the lower alogliptin dose of 6.25mg BID.

Primary end-point (HbA1c)

In each of the studies, no meaningful differences across treatment groups were observed for any demographic or baseline characteristic. Change from baseline in HbA1c was the primary endpoint.

For the **combination with metformin**, relevant for the FDC alogliptin/metformin, two pivotal studies are submitted (studies 008 and 305). The first study is a 26-week, placebo-controlled study, while the second is a 2-year active controlled study, with interim 52 week data presented, in which glipizide was used as the active comparator. In combination with metformin, the treatment effect of alogliptin 25 mg was -0.48% (95% CI -0.67 to -0.30) in comparison to placebo after 26 weeks. In the non-inferiority trial 305, both alogliptin 25 mg and glipizide were associated with a clinically relevant reduction in HbA1c (-0.61% and -0.52%, respectively) after 52 weeks. However, the glipizide dose in the comparator group was relatively low (mean dose 5.2 mg). This is probably due to the dose titration algorithm. Following any dose-titration, a subject who experienced hypoglycaemia was allowed to reduce the dose to as low as 5 mg glipizide (or matching placebo) and continue the study on that dose. Following down titration, subjects were not allowed to increase the dose again. With such a low dose of glipizide, the CHMP concluded that non-inferiority of

alogliptin when compared to SU as add-on therapy to metformin has not been established. In addition, baseline HbA1c was relatively low in these patients (7.6%). This decreases the power to detect any differences between treatments.

For the **combination with TZD (with or without metformin)**, pivotal study 009 was submitted. The results of the patients on metformin therapy were also relevant for the FDC alogliptin/metformin. In this study, alogliptin is compared to placebo in patients treated with TZD (with or without metformin). In addition, supportive study 322OPI-004 is submitted. This is a 52 week active controlled study designed to evaluate the efficacy of alogliptin as triple therapy (add-on to pioglitazone 30 mg and MET), in which efficacy was compared with uptitration of pioglitazone, in subjects on pioglitazone 30 mg and MET. The combination with TZD and SU was not applied for. Nevertheless, a small number of patients treated with alogliptin in combination with TZD and SU was investigated in pivotal study 009. For the combination with TZD (with or without metformin), alogliptin 25 mg was associated with a reduction in Hba1c of -0.61% (95% CI -0.80 to -0.41) after 26 weeks in comparison to placebo. Treatment effects were clinically relevant for alogliptin 25 mg in combination with TZD only (-0.49%) and in combination with TZD and metformin (-0.72%). In addition, in study 322OPI-004, the effects of adding alogliptin 25 mg were not inferior compared to the ones obtained by increasing the dose of pioglitazone from 30 to 45 mg.

For the **combination with insulin**, study 011 was submitted. The objective of this study was to evaluate the efficacy of alogliptin administered in combination with insulin as compared with insulin alone. For the combination with insulin, treatment effect of alogliptin 25 mg was modest, but clinically relevant (-0.59%; 95% CI -0.80 to -0.37) after 26 weeks. There were no meaningful differences in the treatment groups in daily insulin dose before and after treatment with alogliptin. For the FDC alogliptin/metformin, results of the patients on metformin treatment (58.5%; n=227) were relevant. There were no important differences in the treatment effects of alogliptin 25 mg between patients with and without metformin. In this study, however, baseline HbA1c values were relatively high (9.3%). This may have resulted in an overestimation of the treatment effects of alogliptin on HbA1c. Nevertheless, in the individuals with HbA1c below 8.5%, the effect of alogliptin 25 mg on HbA1c was also clinically relevant (-0.68%). Combinations of alogliptin and insulin with other oral antidiabetic drugs were not investigated.

A monotherapy study (010) comparing alogliptin with placebo is submitted. Compared to placebo, alogliptin 25 mg was associated with a reduction in HbA1c of -0.57% (-0.80 to -0.35).

Secondary endpoints

The results of the analysis of the effects of alogliptin on fasting plasma glucose and the need for rescue therapy were in line with the effects on HbA1c. There were no important effects on weight and serum lipids. The presented data indicated a tendency towards effects on estimates of endocrine pancreatic function. However, these effects were not statistically significant in the majority of the studies. In addition, the serum measures (such as fasting proinsulin, fasting insulin, proinsulin/insulin ratio, C peptide and HOMA) are only surrogate estimates of pancreatic function. Therefore no conclusions can be drawn in regard to the effects of alogliptin on the pancreatic endocrine function. Compared with placebo, alogliptin 25 mg was associated with statistically significant reductions from baseline inHbA1c and postprandial total triglycerides levels.

Renal impairment

Renal dose adjustment recommendations of alogliptin 12.5 mg in patients with moderate to severe renal impairment are based on PK data. In the pivotal trials efficacy was not importantly influenced by mild or moderate renal impairment.

Metformin is contraindicated in patients with renal failure or dysfunction (creatinine clearance < 60 ml/min) or in patients with acute conditions that may alter renal function (e.g. dehydration, severe infection or shock) because of the risk of lactic acidosis. For patients with mild renal impairment (creatinine ≥ 60 ml/min), no dose adjustment is needed.

The CHMP agreed with the applicant's proposal to contraindicate alogliptin/metformin combination in patients with moderate-to-severe renal impairment or end-stage renal disease (ESRD) (SmPC sections 4.3 and 4.4).

Elderly

Diabetes is a disease that is especially prevalent in elderly individuals. In the pivotal trials, the treatment effect of alogliptin was not lower in patients >65 years compared to patients <65 years. However, only 2% of the patients treated with alogliptin were >75 years of age (n=124). Therefore, a study in elderly individuals was performed (study 303). Alogliptin 25 mg and glipizide were statistically non-inferior. However, baseline mean HbA1c values were relatively low (approximately 7.5%). This decreases the power to detect any differences between treatments. The overall results from supportive Study 303 showed minimal glycemic improvements in both the alogliptin and glipizide treatment arms after 52 weeks of treatment in an elderly T2DM population. The fact that these results were observed in both treatment groups indicates that the observed efficacy response was largely related to the specific study design, for example, the low baseline HbA1c and the inclusion of subjects on monotherapy (with a short period of background therapy washout). Importantly, results of the large pooled analysis of 2234 subjects from the 5 main phase III, 26 week, placebo-controlled studies, demonstrate relevant efficacy in the elderly. In patients aged ≥ 75 years alogliptin was associated with a treatment effect of -0.49% (95% CI-1.03, 0.06). Furthermore, efficacy results from the 2 main Phase III, active-controlled studies (total of 237 elderly subjects) demonstrated that HbA1c reductions at Week 52 were greater in subjects ≥ 65 years compared with subjects <65 years. In these two studies data interpretation in subjects ≥ 75 years who received alogliptin 25 mg is limited by the small numbers of subjects. The HbA1c reductions at Week 52 for these subjects were -0.29% in Study 305 (n=17) and -1.45% in study 322OPI 004 (n=4).

These results, taken together, suggest that alogliptin is a useful treatment option for elderly patients.

Effect of race

The majority of the patients were white. In the pooled data, the clinical relevance of the treatment effect of alogliptin in whites is of borderline significance (-0.44% and -0.50%) but still clinically relevant. In addition, subgroup analyses in the individual main studies demonstrate that the effect is of borderline relevance for some of the requested indications. Specifically, for alogliptin add-on to SU (study 007), the treatment effect of alogliptin 25 mg is -0.38%. For alogliptin add-on to

metformin (study 008), the treatment effect of alogliptin 25 mg is -0.36%. However, in these studies the differences between the races were small. In addition, the differences between the races were even less pronounced in the other studies.

Initial combination studies

In an initial combination study, both coadministration therapy regimens of alogliptin plus metformin (A12.5+ M500 BID and A12.5+ M1000 BID) resulted in larger reductions in HbA1c compared to their individual component regimens of alogliptin alone or metformin alone. Alogliptin 12.5 BID provided similar glycaemic control compared with alogliptin 25 once daily. In patients inadequately controlled with metformin, each individual combination of Alogliptin+Pioglitazone achieved larger reductions in HbA1c at Week 26 compared with the corresponding alogliptin and pioglitazone doses given alone. These differences were clinically relevant. The initial combination of alogliptin and pioglitazone was associated with a reduction in HbA1c that was larger than that with alogliptin and pioglitazone monotherapy. These data provide further support for the use of alogliptin in combination with metformin and/or pioglitazone, but initial combination therapy is not an indication requested by the applicant.

2.5.7. Conclusions on the clinical efficacy

In combination with metformin, the treatment effect of alogliptin 25 mg was -0.48% (95% CI -0.67 to -0.30) in comparison to placebo after 26 weeks. Overall, efficacy of alogliptin was found to be modest with an effect size with regard to lowering of HbA1C of about 0.5% - 0.6% as add-on therapy, but still being statistically significant and clinically relevant.

Since the bioequivalence of alogliptin/metformin 6.25 mg + 1000 mg tablet and 12.5 mg+1000 mg tablet to individual alogliptin and metformin tablets was demonstrated it can be considered that the efficacy of aloglitin/metformin fixed dose combination has been established.

Due to the low dose of glipizide and the low baseline HbA1c (study 305), non-inferiority of alogliptin compared to glipizide as add-on therapy to metformin has not been established.

Efficacy of the combination was further investigated specifically in subgroups, and found to be satisfactory, in caucasian patients, in elderly patients and patients with mild renal insufficiency.

2.6. Clinical safety

2.6.1. Submitted data

2.6.1.1. Alogliptin/metformin

The safety of the FDC alogliptin plus metformin was studied in the five main studies (008, 009, 011, 305 and 322OPI-004) and the 2 supporting studies (302 and 322OPI-001) for the FDC alogliptin/metformin. Because of the differences in background therapies, treatment groups, and lengths of exposure, the safety data were not pooled but are summarized individually by study.

Alogliptin data were pooled to allow for an opportunity to detect rare events and potential safety signals(see below).

2.6.1.2. Alogliptin

Data from all 55 clinical studies that comprise this MAA submission were used in the overall evaluation of safety. However, the focus of the safety assessment involves the Controlled Phase II and III Study Group and the main phase III studies.

Safety data from the 12 completed phase 2 and 3 studies (003, 007, 008, 009, 010, 011, 301, 302, 303, 322OPI-004, 322OPI-001, and 322OPI-002) and one phase III study (305), on-going at the time of evaluation of this application, were pooled into the Controlled Phase II and III Study Group. As the patient populations enrolled into these studies best represent the intended use of alogliptin, results from this Controlled Phase II and III Study Group are the primary focus of the evaluation of clinical safety. These data were pooled to allow for an opportunity to detect rare events and potential safety signals. Studies are also assessed individually for specific indications, as appropriate. In addition, data from four of the main phase III placebo-controlled studies (007, 008, 009, 010) were pooled to evaluate the safety data from a pool of main studies relevant to the proposed indications.

Study 012 is an uncontrolled safety extension study and the CV outcome (study 402) study is evaluating a specific subpopulation of patients with T2DM and recent ACS. Therefore, these two studies are excluded from the pooled data and are discussed separately, as appropriate.

2.6.1.3. Metformin

The safety profile of metformin has been well established based on pre and post approval clinical studies. Metformin safety information presented in this section was sourced from the harmonized metformin SmPCs, as well as scientific literature, as appropriate. Scientific literature was obtained through a search conducted in the following data-bases: Ovid Medline, Embase, and Biosis.

2.6.2. Patient exposure

2.6.2.1. Alogliptin/metformin

A total of 7150 subjects were randomized in the seven alogliptin/metformin studies. Across these studies, 4201 received alogliptin in combination with metformin either as a background medication or as one of the initial combination treatment assignments (Table 26).

Table 26. Number of Subjects on Combination Therapy (alogliptin plus metformin) – All Phase III Studies

	Main Studies										Supportive Studies
	008 Add-on to MET N=524		305 Add-on to MET N=2619 (a)		009 Add-on to TZD, with/without MET or SU N=494 (b)		322OPI-004 Add-on to PIO/MET N=803	011 Add-on to Insulin N=389		322OPI-001 ALO/PIO Add-on to MET N=1553		302 Initial combination ALO/MET N=768
Combination Therapy	A12.5 N=213	A25 N=207	A12.5 N=873	A25 N=877	A12.5 N=198 (c)	A25 N=199	A25 N=404	A12.5 N=131	A25 N=129	A12.5 N=518	A25 N=519	A12.5 BID N=220
Number (%) of subjects												
ALO+MET	213 (100.0)	207 (100.0)	873 (100.0)	877 (100.0)	-	-	-	-	-	128 (24.7)	129 (24.9)	220 (100.0)
ALO+MET+ PIO	-	-	-	-	107 (54.3) (b)	114 (57.3)	404 (100.0)	-	-	390 (75.3)	390 (75.1)	
ALO+MET+ Insulin	-	-	-	-	-	-	-	77 (58.8)	72 (55.8)			

Source: 008 Ad-hoc Table 1, 305 Table 15.1.1, 009 Ad-hoc Table 4, 322OPI-004 Table 15.1.1, 011 Ad-hoc Table 1, 322OPI-001 Table 15.1.1, and 302 Table 15.1.1.
(a) A total of 2621 subjects were included in the safety set, but 2 subjects did not receive study drug as randomized so are excluded from their assigned treatment groups and excluded from this table.
(b) 493 subjects were randomized but an additional subject (009/385-9015) was treated with double-blind study drug. This subject received ALO+MET+PIO (009 Appendix 16.2.4.4a) and when included brings the number of subjects receiving ALO+MET+PIO in Study 009 to 108. Note that this subject is not included in the total count of subjects receiving alogliptin in combination with MET.
(c) Percentages are based on N=197 (randomized set).

In Studies 008 (add-on to metformin) and 009 (add-on to TZD, with or without metformin or SU), the majority (≥52.0%) of subjects in each of the alogliptin groups were exposed to treatment for at least 26 weeks. Mean duration of exposure in the alogliptin 12.5 mg group was 23.78 and 22.93 weeks, respectively, and 23.35 and 23.46 weeks, respectively, in the alogliptin 25 mg group.

Median treatment duration in study 011 (add-on to insulin, with or without metformin) was longer in the alogliptin groups (25.86 weeks each) than in the placebo group (20.43 weeks), primarily because twice as many subjects in the placebo required hyperglycaemic rescue compared with the alogliptin groups. Mean duration of exposure was longer in the alogliptin 12.5 mg and 25 mg groups (21.86 weeks and 21.33 weeks, respectively) compared with the placebo group (19.01 weeks). In the alogliptin groups, ≥ 44.2% of subjects were exposed for at least 26 weeks compared with 26.4% in the placebo group.

In study 305 (add-on to metformin), median treatment duration and mean exposure were similar in all groups. Over 500 subjects in each group (≥ 59.3%) were exposed for at least 1 year.

In study 322OPI-004 (add-on to pioglitazone/metformin), 52-week study, mean duration of exposure was 43.14 weeks in the MET+A25+P30 group and 39.73 weeks in the MET+P45 group. The longer duration in the MET+A25+P30 was mainly due to fewer subjects requiring hyperglycaemic rescue therapy.

In the supportive studies, mean length of exposure was similar across treatment groups (20.56 to 23.78 weeks) in study 302 (initial combination alogliptin/metformin) and, in study 322OPI-001 (combination alogliptin and pioglitazone add-on to metformin), mean exposure was 24.28 weeks in

the alogliptin 12.5 mg + pioglitazone group and 24.08 weeks in the alogliptin 25 mg+ pioglitazone group.

2.6.2.2. Alogliptin

The number of subjects exposed to study drug, the duration of exposure, categorized duration of exposure, and cumulative exposure (subject-years) for subjects who participated in the phase II and III studies (the Controlled Phase II and III Study Group and Studies 012 and 402) are summarized below (Table 27). In study 402, all subjects are counted within the alogliptin 25 mg group, although different doses were assigned according to renal function, such that all subjects had equivalent exposure. Furthermore, higher numbers of subjects in the overall program were exposed to alogliptin 25 mg compared with 12.5 mg. Additionally, asymmetrical randomization schedules in the Phase III studies resulted in a proportionately smaller number of subjects in the placebo group compared with active comparator and the alogliptin groups. For these reasons, exposure-corrected rates for adverse events are included in key tables.

Table 27. Exposure by Dose and Duration – All Alogliptin Phase III Studies

Exposure	Placebo	Active Comparator	A12.5 mg	A25 mg	All Alogliptin (a)
Controlled Phase II and III Study Group					
	N=793	**N=2257**	**N=2476**	**N=3749**	**N=6354**
Cumulative exposure (subjects-years) (b)	307.76	1528.22	1453.25	2249.74	3725.98
Number (%) of subjects exposed for (c)					
<6 months	338 (42.6)	471 (20.9)	468 (18.9)	761 (20.3)	1358 (21.4)
≥6 months - <12 months	455 (57.4)	791 (35.0)	1355 (54.7)	1889 (50.4)	3244 (51.1)
≥12 months - <18 months	0	995 (44.1)	653 (26.4)	1099 (29.3)	1752 (27.6)
≥ 18 months	0	0	0	0	0
Study 402					
	N=1079	**N/A**	**N/A**	**N=1070**	**N/A**
Number (%) of subjects exposed for (c)					
<6 months	625 (57.9)	--	--	611 (57.1)	--
≥6 months - <12 months	358 (33.2)	--	--	360 (33.6)	--
≥12 months - <18 months	93 (8.6)	--	--	95 (8.9)	--
≥ 18 months	3 (0.3)	--	--	4 (0.4)	--
Study 012					
	N/A	**N/A**	**N=1394**	**N=1926**	**N/A**
Number (%) of subjects exposed for (c)(d)					
<6 months	--	--	47 (3.4)	109 (5.7)	--
≥6 months - <12 months	--	--	92 (6.6)	117 (6.1)	--
≥12 months - <18 months	--	--	112 (8.0)	168 (8.7)	--
≥18 months	--	--	1143 (82.0)	1532 (79.5)	--

(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).
(b) Cumulative exposure in subject-years is defined as the sum of days for all subjects within a grouping divided by 365.25.

(c) Duration of exposure in days is calculated as date of last dose - date of first dose+1. Last dose date is estimated from data available for subjects continuing study drug dosing in Study 305. Estimated dates are no later than the interim data cutoff date.
(d) Cumulative exposure from the double-blind feeder studies (and therefore also counted in the Controlled Phase 2 and 3 Study Group) and the open-label extension.

All subjects in the Controlled Phase II and III Study Group had a diagnosis of T2DM with inadequate glycaemic control. At the discretion of the investigator, subjects with a major illness or debility were excluded. Specific prohibited prior and concurrent conditions included New York Heart Association [NYHA] Class III or IV heart failure (Classes I-IV in study 322OPI-004); angioedema associated with angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers (except 301); treated diabetic gastro-paresis, laser-treated proliferative diabetic retinopathy (except 301), haemoglobinopathy (due to potential effect on HbA1c determination); history within 6 months (3 months for Studies 302 and 305) prior to Screening of coronary angioplasty, coronary stent placement, coronary bypass surgery, or MI; and history within 5 years prior to Screening of cancers other than squamous cell or basal cell carcinoma of the skin.

Demographic and other baseline characteristics were comparable among the treatment groups. The majority (79%) of subjects were less than 65 years, with a mean age ranging from 54.9 to 56.3 years, although there was an adequate representation of elderly subjects in the program. A total of 1990 subjects were at least 65 years, 224 were ≥ 75 years, and 2 subjects were ≥ 85 years. Most (69%) subjects were White. Slightly more than half (54%) of the subjects had a BMI greater than 30. At baseline, mean HbA1c ranged from 8.00% to 8.39% across treatment groups.

Across the main safety pool, approximately 20% of subjects were from Europe, 33% were from the US or Canada, 23% were from Latin/South America, and 23% were from other regions, mainly Asia/Pacific countries.

2.6.3. Adverse events

2.6.3.1. Alogliptin/Metformin

The percentages of subjects who experienced a treatment-emergent adverse event (TEAE) in **study 008** were comparable in the alogliptin 12.5 mg (62.9%) and 25 mg (57.0%) groups, and higher in the placebo group (66.3%). Most (72%) TEAEs were mild in intensity, and no TEAE was reported by ≥5% subjects overall.

In **study 009**, an ad-hoc analysis to support alogliptin add-on therapy to pioglitazone showed no clinically important differences in overall TEAE rates between the add-on to pioglitazone only and add-on to pioglitazone plus metformin groups. The percentages of subjects who experienced at least 1 TEAE were similar among treatment groups (placebo 64.9%; alogliptin 12.5 mg 69.7%; alogliptin 25 mg 72.4%). The most commonly reported TEAEs (experienced by ≥5% of subjects in the alogliptin 25 mg group) were nasopharyngitis, oedema peripheral, influenza, headache, and upper respiratory tract infection. The majority (62%) of TEAEs were mild in intensity.

For subjects receiving alogliptin as add-on to insulin (with or without metformin) in **study 011**, the percentages of subjects experiencing at least 1 TEAE were comparable across treatment groups (placebo-control 73.6%; alogliptin 12.5 mg 67.9%; alogliptin 25 mg 66.7%). The most commonly

reported TEAEs (experienced by ≥5% of subjects in the alogliptin 25 mg group) were urinary tract infection, diarrhoea, nasopharyngitis, and oedema peripheral. The majority (66%) of TEAEs were mild in intensity.

In **study 305**, again the proportions of subjects reporting at least 1 TEAE were comparable across treatment groups (metformin+alogliptin 12.5 mg, 72.2%; metformin+alogliptin 25 mg, 70.1%; metformin+glipizide, 71.7%). The most commonly reported TEAEs (experienced by ≥5% of subjects in the metformin+alogliptin 25 mg group) were upper respiratory tract infection, nasopharyngitis, headache, and diarrhea. The majority of TEAEs were of mild to moderate intensity; only 5.4% of subjects reported a TEAE of severe intensity.

In **study 322OPI-004**, the percentages of subjects who experienced at least 1 TEAE were comparable between groups (MET+A25+P30 71.5%; MET+P45 68.9%). The most commonly reported TEAEs in the MET+A25+P30 group were upper respiratory tract infection, nasopharyngitis, hypertension, and urinary tract infection. The majority (96%) of TEAEs were of mild to moderate intensity.

Results from **study 302**, showed that the TEAE profile was generally similar between the alogliptin once-daily and BID dosing regimens. The overall incidences of on-study TEAEs in the metformin groups were not dose dependent (metformin 500 mg BID [68.8%] and metformin 1000 mg BID [62.2%]), and were comparable to the alogliptin+metformin combination groups (alogliptin 12.5 mg+metformin 500 mg BID [63.2%] and alogliptin 12.5 mg+metformin 1000 mg BID [64.0%]). Most (71%) TEAEs were mild in intensity.

Generally, the pattern of AEs observed in the alogliptin/metformin phase III studies was consistent with the known safety profile of metformin, previous clinical trials with alogliptin, and conditions that are expected in this T2DM patient population. The most commonly (≥ 5% of subjects) reported with combination treatment were nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhoea, headache, oedema peripheral, influenza, hypertension, and arthralgia. Most TEAEs were considered mild or moderate in intensity and not related to study drug. TEAEs tended to occur more often within the system organ class (SOC) of infections and infestations and the incidence was generally similar among treatment groups.

At the CHMP request the applicant has presented a safety data pool of the seven alogliptin/metformin studies deemed relevant for the safety analyses. The most frequently reported TEAEs in the metformin only grouping were diarrhea (5.7%) and upper respiratory tract infection (4.7%). In the alogliptin only groupings, the most frequently reported TEAEs were edema peripheral, upper respiratory tract infection, dizziness, and hypertension in the A12.5 grouping (all reported by 4.8% of subjects) and hyperglycaemia (8.8%) and headache (4.7%) in the A25 grouping. In the combination groupings, the most frequently reported TEAEs were nasopharyngitis (6.2%) and upper respiratory tract infection (5.6%) in the A12.5+MET grouping and upper respiratory tract infection (6.1%), and nasopharyngitis (5.3%) in the A25+MET grouping (Alo/Met Day 120 Table 59.3).

The TEAEs with an incidence of ≥3% in any treatment group that occurred more frequently in the A12.5+MET grouping compared to A12.5 alone were diarrhea, upper respiratory tract infection, nasopharyngitis, influenza, dyslipidemia, hyperglycaemia, back pain, arthralgia, and headache. Dyslipidemia was the only common (≥3%) TEAE that occurred in the A12.5+MET grouping at twice the rate of the A12.5 grouping, but this was not considered to be a clinically relevant difference.

For alogliptin, TEAEs reported in ≥ 1% of subjects treated with alogliptin (with metformin with or without pioglitazone or insulin) and occurring with a frequency twice the rate of placebo or active comparator (with at least 2 subjects if zero in the comparator group) were identified for consideration as possible adverse drug reactions (ADRs). For metformin, identified ADRs were those presented in the SmPC. The ADRs identified for each of the single agents and in combination (dual and triple therapies) are listed below:

- headache, diarrhea, pruritus, and myalgia for alogliptin;
- lactic acidosis, vitamin B12 deficiency, metallic taste, abdominal pain, diarrhea, loss of appetite, nausea, vomiting, hepatitis, liver function test abnormalities, erythema, pruritus, and urticaria for metformin;
- pruritus, rash, and musculoskeletal pain for alogliptin/metformin;
- nasopharyngitis, abdominal pain, nausea, pruritus, and back pain for alogliptin/metformin with insulin; and
- nasopharyngitis, insomnia, abdominal pain, dyspepsia, gastroesophageal reflux disease, nausea, muscle spasms, musculoskeletal pain, hypersensitivity, headache, and rash for alogliptin/metformin with pioglitazone.

2.6.3.2. Alogliptin

An overview of treatment-emergent adverse events (TEAEs), TEAEs that led to discontinuation of study drug, serious adverse events (SAEs), and deaths for subjects in the Controlled Phase II and III Study Group is summarized by treatment group in the table below.

Table 28 Overview of TEAEs and SAEs - Controlled Phase II and III Study Group

	Number (%) of Subjects [Events per 100 Subject-Years]				
Event Type	**Placebo N=793**	**Active Comparator N=2257**	**A12.5 N=2476**	**A25 N=3749**	**All Alogliptin (a) N=6354**
Any TEAE	514 (64.8) [438.0]	1548 (68.6) [330.1]	1672 (67.5) [333.2]	2497 (66.6) [342.1]	4234 (66.6) [340.5]
Leading to discontinuation of study drug	18 (2.3) [5.8]	132 (5.8) [8.7]	88 (3.6) [6.5]	155 (4.1) [7.1]	248 (3.9) [7.0]
SAEs	25 (3.2) [9.4]	117 (5.2) [9.9]	100 (4.0) [8.5]	175 (4.7) [9.9]	277 (4.4) [9.3]
Deaths	0	4 (0.2) [0.3]	5 (0.2) [0.3]	4 (0.1) [0.2]	9 (0.1) [0.2]

(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).

The incidence of TEAEs was comparable across treatment groups (68.6% active comparator vs 66.6% alogliptin), although slightly lower in subjects receiving placebo (64.8%). However, in terms of events per 100 subject-years, the numbers were higher in the placebo group (438.0) than in the other groups (330.1 active comparator vs 340.5 alogliptin). The incidence of SAEs was slightly higher in the active comparator group (5.2%) than in the alogliptin 25 mg group (4.7%), the

alogliptin 12.5 mg group (4.0%) or the placebo group (3.2%). For TEAEs leading to discontinuation of study drug, more subjects were withdrawn in the active comparator group (5.8%) than in the alogliptin group (3.9%) or the placebo group (2.3%). The incidence of deaths within the study period was low, with no deaths reported in the placebo group, 4 deaths in the active comparator group (0.2%), and 9 deaths (0.1%) in the alogliptin group.

TEAEs reported by ≥3% of subjects in the Controlled Phase II and III Study Group are summarized in the table below.

Table 29 Common TEAEs (≥3% of Subjects in any Presented Group) – Controlled Phase II and III Study Group

	Number (%) of Subjects				
)C Preferred Term	**Placebo N=793**	**Active Comparator N=2257**	**A12.5 N=2476**	**A25 N=3749**	**All Alogliptin (a) N=6354**
Any TEAE (b)	514 (64.8)	1548 (68.6)	1672 (67.5)	2497 (66.6)	4234 (66.6)
Headache	30 (3.8)	113 (5.0)	110 (4.4)	203 (5.4)	321 (5.1)
Upper respiratory tract infection	36 (4.5)	95 (4.2)	121 (4.9)	196 (5.2)	320 (5.0)
Nasopharyngitis	35 (4.4)	99 (4.4)	141 (5.7)	192 (5.1)	334 (5.3)
Urinary tract infection	35 (4.4)	93 (4.1)	102 (4.1)	157 (4.2)	268 (4.2)
Hypertension	26 (3.3)	102 (4.5)	88 (3.6)	147 (3.9)	236 (3.7)
Diarrhea	32 (4.0)	121 (5.4)	91 (3.7)	143 (3.8)	237 (3.7)
Back pain	19 (2.4)	86 (3.8)	86 (3.5)	125 (3.3)	214 (3.4)
Influenza	17 (2.1)	86 (3.8)	67 (2.7)	105 (2.8)	173 (2.7)
Arthralgia	20 (2.5)	72 (3.2)	69 (2.8)	102 (2.7)	171 (2.7)
Dyslipidemia	12 (1.5)	87 (3.9)	35 (1.4)	94 (2.5)	129 (2.0)
Dizziness	19 (2.4)	68 (3.0)	63 (2.5)	84 (2.2)	151 (2.4)
Hyperglycaemia	32 (4.0)	43 (1.9)	10 (0.4)	53 (1.4)	63 (1.0)
Hypoglycaemia	0	80 (3.5)	13 (0.5)	11 (0.3)	24 (0.4)

(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).
(b) Ordered by descending frequency in the alogliptin 25 mg group.

Percentages of subjects who experienced at least 1 TEAE were comparable among treatment groups. The most common TEAEs reported in ≥ 5% of subjects treated with alogliptin 25 mg and more frequently than in subjects who received placebo or active comparators were headache, nasopharyngitis, and upper respiratory tract infection.

The majority of the TEAEs experienced were considered by the investigator as either mild or moderate in intensity. No specific TEAE of severe intensity occurred in > 1.0% of subjects in any group.

TEAEs reported in ≥ 1% of subjects treated with alogliptin 25 mg and occurring with a frequency twice the rate of placebo or active comparator (with at least 2 subjects if zero in the comparator group) were identified for consideration as possible adverse drug reactions. Compared with placebo, events meeting the criteria were upper respiratory tract infection, nasopharyngitis, influenza, headache, abdominal pain, diarrhoea, nausea, pruritus, rash, back pain, musculoskeletal pain, and myalgia. Compared with active comparator, events meeting the criteria were nasopharyngitis, insomnia, abdominal pain, dyspepsia, gastroesophageal reflux disease, nausea, muscle spasms, musculoskeletal pain, hypersensitivity, headache, and rash.

2.6.3.3. Metformin

Acute, reversible AEs occur in 5% to 20% of patients taking MET, although it is estimated that less than 5% of patients cannot tolerate the drug. The most common adverse reactions are gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite, which are very common (>10%). Taste disturbance is also listed as a common AE (3%). The table below shows common AEs reported for metformin.

Table 30 Common AEs (% Patients) (Belcher et al, 2005)

	Monotherapy				Combination Therapy			
	Study 1		Study 2		+SU		+MET	
	Pio N=597	MET N=597	Pio N=624	Glic N=626	Pio N=319	MET N=320	Pio N=317	Glic N=313
Diarrhea	3.2	11.1	2.9	3.4	2.5	12.5	1.3	3.8
Nausea	2.3	4.2	4.3	5.1	2.5	3.1	2.2	2.2
Nasopharyngitis	4.2	3.2	6.6	5.3	2.2	2.2	2.2	3.5
Back pain	2.3	2.8	6.4	5.0	1.6	3.8	3.2	2.9
Hypertension	2.5	2.8	3.4	3.8	0.9	3.8	1.9	4.5
Headache	4.4	2.3	8.7	8.9	3.8	3.4	4.1	3.8
Arthralgia	1.5	2.0	7.1	6.2	4.1	2.8	1.6	3.8
Dizziness	2.3	1.8	4.0	6.5	1.3	2.8	2.8	1.3
Edema	6.7	1.8	8.1	4.2	6.9	1.6	6.3	2.2
Hypoglycaemia	1.5	1.3	3.5	10.1	10.7	14.1	1.3	11.2

Glic=gliclazide
Note: AEs are listed in order of decreasing frequency for MET monotherapy in Study 1.

2.6.4. Serious adverse events and deaths

2.6.4.1. Alogliptin/metformin

Among the seven pivotal studies in the alogliptin/metformin clinical program, 13 (0.2%) deaths were reported, of which, 6 occurred in subjects who received alogliptin/metformin. The majority of deaths (7/13) were CV in nature, and two were considered by the investigator to have a possible relationship to study drug: sudden death reported study 009 (alogliptin 12.5 mg+pioglitazone 30 mg) and acute pulmonary edema reported in study 305 (alogliptin 25 mg+metformin).

The incidence of serious adverse events (SAEs) from the main studies was low (2.5% [study 009, alogliptin 12.5 mg] to 6.8% [Study 305, metformin+glipizide]) among the treatment groups, with no meaningful differences observed with respect to the specific types of events reported in the treatment groups. With the exception of Study 305 with a larger population, individual SAEs were not reported by more than 2 subjects in any treatment group. SAEs were reported most frequently in the cardiac disorder SOC and the infections and infestations SOC. In addition, no apparent dose response relationship was seen.

The percentage of subjects who experienced a TEAE that led to discontinuation from the main studies ranged from 0.8% [study 011, alogliptin 12.5 mg] to 8.4% [Study 305, metformin+glipizide], and were similar among the treatment groups within the studies. There was no distinct pattern of discontinuations with respect to type of TEAE. Overall, with the exception of study 305, most TEAEs leading to study drug discontinuation only occurred in 1 subject within each study.

2.6.4.2. Alogliptin

Fifteen deaths were reported in the Controlled Phase II and III Study Group (11/6354 in the alogliptin group [0.17%]; 4/2257 in the active comparator group [0.18%]; and none in the placebo group). Most deaths were CV in nature. Only 2 of the 15 deaths (both in the alogliptin group) were considered by the investigator to have a possible relationship to the study drug.

In the CV outcomes study 402, deaths were reported for 26 subjects who received placebo (26/1079; 2.4%), 17 subjects who received alogliptin (17/1070; 1.6%), and 1 subject whose treatment assignment is unknown at this time (occurred after the clinical database cut for the interim analysis). None of these deaths was considered to be related to the administration of study drug.

A total of 44 deaths occurred in the open-label safety extension study 012 (44/3320; 1.3%). Ten of the deaths were considered to have a possible relationship to study drug by the investigator.

An additional 5 deaths occurred in the Japanese studies (5/1649; 0.3%), all considered unrelated to study drug.

Overall, a low and similar percentage of subjects across treatment groups experienced at least 1 SAE (placebo 3.2%; active comparator 5.2%; alogliptin 12.5 mg 4.0%, alogliptin 25 mg 4.7%; see table below). SAEs were reported most frequently in the cardiac disorder SOC, followed by the infections and infestations SOC. The incidence of SAEs associated with cardiac disorders was comparable between the alogliptin 25 mg and active comparator groups (1.0% and 1.2%, respectively) and greater compared with placebo (0.4%).

A slightly higher percentage of subjects discontinued due to a TEAE in the alogliptin 25 mg group (4.1%) than the alogliptin 12.5 mg (3.6%) group. There was no distinct pattern of discontinuations with respect to any type of TEAE. Notably, the percentage of subjects in the alogliptin groups (3.9%) that discontinued due to a TEAE was lower than for subjects who received active comparator (5.8%).

2.6.5. Adverse Events of Special Interest

Special-interest TEAEs were predefined based on observations made during the clinical program, conditions in the T2DM patient population, and known or suspected effects of the drug class.

CV Safety

<u>Alogliptin/metformin</u>

For the five main phase III studies in alogliptin/metformin program, potential CV events were retrospectively adjudicated. Events adjudicated as MACE (CV death, nonfatal MI, and nonfatal stroke) are presented in the table below.

Table 31 Summary of Adjudicated MACE (studies 008, 305, 009, 322OPI-004, and 011)

	Number (%) of Subjects				
Study	Placebo n/N (%)	Active Comparators n/N (%)	Alogliptin 12.5 mg n/N (%)	Alogliptin 25 mg n/N (%)	All Alogliptin (a) n/N (%)
008	0/104	N/A	1/213 (0.5)	1/210 (0.5)	2/423 (0.5)
305	N/A	6/873 (0.7)	4/880 (0.5)	5/885 (0.6)	9/1765 (0.5)
009	0/97	N/A	2/197 (1.0)	2/199 (1.0)	4/396 (1.0)
322OPI-004	N/A	3/399 (0.8)	N/A	2/404 (0.5)	2/404 (0.5)
011	1/130 (0.8)	N/A	1/131 (0.8)	0/129	1/260 (0.4)

(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table)

The MACE data show no increase in MACE with alogliptin or with alogliptin in combination with metformin.

Alogliptin

In the Controlled Phase II and III Study Group, the percentages of subjects who experienced a TEAE from the SOC of cardiac disorders were comparable between the alogliptin 25 mg and active comparator groups (4.5% and 4.9%, respectively) and greater compared with placebo (2.5%). The most frequently reported cardiac disorder TEAEs in the alogliptin 25 mg group were angina pectoris and palpitations. The incidence of SAEs associated with cardiac disorders was comparable between the alogliptin 25 mg and active comparator groups (1.0% and 1.2%, respectively) and greater compared with placebo (0.4%). The most frequently reported cardiac disorder SAE in subjects receiving alogliptin 25 mg was angina pectoris. The incidence of events of hypertension was slightly higher in the active comparator group (4.5%) than for subjects receiving alogliptin 12.5 mg (3.6%) and 25 mg (3.9%), but slightly lower in the placebo group (3.3%).

In the adjudicated MACE analysis for the Controlled Phase II and III Study Group, the incidence of CV death and nonfatal MI was similar and low in the alogliptin (0.1% and 0.2%, respectively) and active comparator groups (0.1% and 0.3%, respectively), while no subject receiving placebo reported CV death or nonfatal MI. The incidence of nonfatal stroke was lower for alogliptin-treated (< 0.1%) subjects than for active comparator-treated (0.2%) and placebo (0.3%) subjects.

Using a Cox Proportional Hazards (CPH) model for adjudicated MACE for the Controlled Phase II and III Study Group, the hazard ratio of alogliptin against all comparators (placebo and active) was 0.806.

During the procedure, the CHMP did seek clarification on the cases of cardiac failure and myocardial infarction designated as non-serious. The applicant stated that there were 20 subjects in total in the alogliptin clinical studies who experienced adverse events (AEs) of cardiac failure/cardiac failure congestive (14 subjects) or myocardial infarction (6 subjects) in which the event had been classified by the investigator as non-serious. The applicant did provide details of the definition of SAEs , which was consistently applied by the investigators in all studies and also provided detailed case narratives for these 20 subjects; a clinical review of the available data was performed and a rationale for the non-serious designation has been determined based on that data. The review of

the 6 subjects with non-serious AEs of myocardial infarction indicated that these were reported by investigators as such on the basis of ECG findings, suggestive of myocardial ischaemia, rather than following hospital admission of patients with typical chest pain (and confirmatory cardiac enzyme rise). The majority of these AEs were supported with sufficient clinical information indicating that the non-serious classification was appropriate. Similarly, reassuring descriptions were provided by the applicant for the cases of heart failure, and therefore the CHMP considered this concern as being resolved.

The CV risk of alogliptin is also being assessed in the CV outcomes Study 402. In that study, potential CV events are being collected and independently and prospectively adjudicated (by a blinded cardiovascular endpoint committee [CEC]). The incidence of CV death (1.0%) and nonfatal stroke (0.5%) in the interim analysis were the same for alogliptin and placebo in this study, with the incidence of nonfatal MI higher in the placebo group (2.8%) than in the alogliptin group (2.0%). MACE results from the interim analysis of Study 402 were consistent (hazard ratio alogliptin vs placebo, 0.814) with the MACE analysis done for the Controlled Phase II and III Group. When urgent revascularization due to unstable angina is added to adjudicated events, the hazard ratio is lower at 0.750. The proportion of subjects requiring urgent revascularization was lower in the alogliptin group (0.4%) than in the placebo group (0.8%).

Metformin

Lactic acidosis is a severe reaction to biguanide therapy and is fatal in 50% of cases, although it is described as a very rare (<1/10,000) adverse reaction in the harmonized SmPC, with an incidence of 0.3 cases per 1,000 patient-years. Most cases of lactic acidosis with MET occur exclusively in patients with contraindication(s) to its use. The risk for developing lactic acidosis is increased in patients with renal impairment, hepatic impairment, and advancing age. MET therapy is contraindicated in patients with renal dysfunction characterized by serum creatinine levels $\geq$ 132.6 μmol/L in men and $\geq$ 123.8 μmol/L in women; congestive heart failure requiring pharmacologic treatment; and acute or chronic metabolic acidosis, including diabetic ketoacidosis.

Hypersensitivity reactions

Hypersensitivity reactions are of special interest as they have been associated with the use of other DPP-4 inhibitors. Administration of some DPP-4 inhibitors has been associated with dose- and duration-dependent necrotic peripheral skin lesions in monkeys. Such lesions have not been observed in alogliptin nonclinical studies or in humans.

Preferred terms were identified by severe cutaneous adverse reactions Standardized Medical Query (SMQ) (narrow-scope terms only), angioedema SMQ (narrow-scope terms only), and anaphylactic reaction SMQ (narrow-scope terms only).

Overall, the frequency of hypersensitivity reactions was low (≤ 0.8%) and balanced across the treatment groups. There were no serious hypersensitivity reactions in subjects receiving alogliptin 12.5 mg or 25 mg. 13 patients (0.2%) developed an anaphylactic reaction during alogliptin, whereas no patient developed an anaphylactic reaction during treatment with placebo. Although not part of the hypersensitivity reaction event search by SMQ, it is noted that a subject in the Phase

III program (on alogliptin 25 mg) had an SAE of serum sickness that resulted in discontinuation of study drug.

While safety results for alogliptin indicate a low incidence of hypersensitivity reactions, a warning is included in section 4.4 of the SmPC and such reactions are included as an undesirable effect in section 4.8 of the SmPC. This approach is consistent with the labeling of the other DPP-4 inhibitors. In addition, hypersensitivity reactions are listed as a potential risk in the RMP.

No subjects in the main alogliptin/metformin studies experienced an SAE within the SMQs described above. One subject in the alogliptin 25 mg group of study 011 reported an angioedema TEAE (urticaria) that led to discontinuation. Based on the results from the alogliptin/metformin studies, there is no evidence to suggest that the combination of alogliptin and metformin is associated with an increased risk of hypersensitivity reactions, compared to alogliptin therapy alone. As additional pharmacovigilance activity the cardiovascular outcome study 402 is further investigating hypersensitivity reactions. The final study report is expected to be in the first quarter of 2014.

Acute Pancreatitis

Alogliptin/metformin

Three subjects from the main phase III studies supporting the combination of alogliptin/metformin reported an AE of pancreatitis. Two subjects had a preferred term from the pancreatitis acute SMQ reported as an SAE. None of these subjects were treated with the combination alogliptin plus metformin.

Based on the results of the alogliptin/metformin main studies, there is no evidence to suggest that the combination of alogliptin and metformin is associated with an increase in incidence or severity of acute pancreatitis. However, alogliptin itself is associated with an increased risk (see below).

Alogliptin

No toxicological effects in the pancreas or pancreatic cells were observed in non-clinical studies of alogliptin. No evidence of pancreatitis was noted in the chronic toxicity studies in rats and dogs or in a 2-year carcinogenicity studies in mice and rats.

In the Controlled Phase 2 and 3 Study Group, the percentage of subjects reporting at least 1 acute pancreatitis TEAE was low in all groups, reported in 5 subjects (0.1%) treated with alogliptin 25 mg and 2 subjects (< 0.1%) with alogliptin 12.5 mg compared with 1 subject (< 0.1%) treated with an active comparator. Among the 7 alogliptin-treated subjects reporting at least 1 acute pancreatitis TEAE, 3 subjects had SAEs and 2 subjects had TEAEs (pancreatitis acute and pancreatitis) that led to study drug discontinuation.

In addition to the 8 subjects in the Controlled Phase 2 and 3 Study Group with pancreatitis TEAEs, as of 23 August 2011, pancreatitis TEAEs were reported for 6 subjects in study 402 (3 and 3 subjects, respectively, in the alogliptin 25 mg and placebo groups), 13 subjects in study 012 (9 and 4 subjects, respectively, in the alogliptin 25 and 12.5 mg groups), and 2 subjects in the regional studies (1 subject on placebo in study 308 [China] and 1 subject on alogliptin 25 mg in OCT-001 [Japan]).

After adjusting for exposure, rates of pancreatitis adverse events were 0, 0.1, 0.1, and 0.3 events per 100 subject-years, respectively, for the placebo, active comparator, and alogliptin 12.5 and 25 mg groups in the Controlled Phase 2 and 3 Study Group. These rates are comparable to epidemiological studies that have shown that diabetic subjects have an increased incidence of 0.05 to 0.4 events per 100 patient-years vs 0.02 to 0.15 events per 100 patient-years in non-diabetic subjects.

The frequency of pancreatitis events is low but there is an increased risk with alogliptin treatment.

The risk of pancreatitis is indicated in the SmPC section 4.4 (Warnings and Precautions), and acute pancreatitis is listed as an adverse reaction in Post-marketing Reports in SmPC, Section 4.8. Moreover, pancreatitis is included as an identified risk in the Risk Management Plan. As additional pharmacovigilance activity the cardiovascular outcome study 402 is further investigating pancreatitis. The final study report is expected to be in the first quarter of 2014.

Malignancies

Alogliptin/metformin

A total of 37 subjects from the 5 main Phase III studies supporting the combination of alogliptin/metformin reported an AE from the malignancy SMQ. The number of malignancy events reported in the alogliptin/metformin main studies was slightly higher in subjects receiving A12.5 and placebo compared to active comparator and A25: 3 subjects (3/330 [0.9%]) receiving placebo;. 7 subjects (7/1268 [0.6%]) receiving active comparator; 15 subjects (15/1415 [1.1%]) receiving A12; and 12 subjects (12/1816 [0.7%]) receiving A25.

Alogliptin

Malignancies are considered special-interest TEAEs for long-term use of DPP-4 or GLP-1 therapies. Alogliptin was not genotoxic in non-clinical in vitro and in vivo genotoxic studies, and no evidence of carcinogenicity occurred in the non-clinical studies with alogliptin. In preclinical studies a minimal to mild simple transitional cell hyperplasia in the urinary bladder was noted in male rats at 27-fold higher than the intended human exposure. Pioglitazone has been associated with bladder cancer, and therefore an interaction with pioglitazone cannot be excluded. However, no cases of bladder cancer were reported in the clinical trials.

The percentage of subjects reporting at least 1 malignancy TEAE was low in all groups (0.9% placebo, 0.4% active comparator, 0.8% alogliptin 12.5 mg, 0.5% alogliptin 25 mg) with no imbalance in individual cancers.

Based on these results showing low overall incidence, no special warning/precaution is included for "malignancies" in the SmPC.

Pancreatic Cancer

Uncertainties remained during the procedure regarding effects of alogliptin on the pancreas, as long term safety data are limited. Besides, during the procedure data had been published that gave rise

to additional concerns on inflammatory and proliferative pancreatic effects of the therapy with another DPP-4 inhibitor, sitagliptin, (Butler et al. Diabetes, March 2013). Therefore the applicant was asked during the procedure to provide further analyses with regard to pancreatic risk.

In the controlled clinical studies, including the long-term studies OPI-004 (52 weeks) and 305 (104 weeks), there were no TEAEs of pancreatic cancer in alogliptin treatment groups. A PV database search found that 5 subjects had pancreatic cancer events that occurred outside of the study treatment period: 4 subjects had events that occurred during run-in before randomization (prior to study drug exposure) and 1 subject who received placebo and pioglitazone had an event spontaneously reported 1 year after study completion.

As of November 2012, in Study 402, there were no TEAEs of pancreatic cancer.

A total of five subjects with events were reported with alogliptin in uncontrolled studies, and the incidence rates of pancreatic cancer for the alogliptin uncontrolled studies was considered to be consistent with the incidence expected in the T2DM population.

Most post-marketing cases reported a time to onset less than 2 months from the start of alogliptin treatment or had pre-existing pancreatic cancer before receiving alogliptin.

Based on these additional data the CHMP considered that there was no clear evidence for an association of pancreatic cancer and alogliptin treatment. Nevertheless, CHMP considered that a targeted follow-up is needed. This has now been reflected in the RMP as 'Pancreatic cancer' has been included as an important potential risk (in line with the recommendation given by CHMP at the July 2013 meeting for this class of products in the conclusions of the Art. 5(3) referral for GLP 1 based therapies).

Hypoglycaemia

Investigators were asked to record episodes of hypoglycaemia on a dedicated case report form (CRF). Three criteria were identified:

- Symptomatic hypoglycaemic episode and blood glucose < 3.33 mmol/L (Mild to Moderate).
- Symptomatic or asymptomatic hypoglycaemic episode and blood glucose <2.78 mmol/L (Mild to Moderate).
- Any hypoglycaemic episode that required assistance, associated with a documented blood glucose < 3.33 mmol/L (Severe).

Alogliptin/metformin

From the main individual placebo-controlled study covering use as add-on to metformin (**008**), there was no consistent indication of an increase in hypoglycaemia risk or severity by the addition of alogliptin 25 mg. The level of HbA1c on entry, being at the lower end of the diabetic range, did not appear to unduly influence hypoglycaemia rates or severity.

In **study 009** (add-on to TZD), accurate interpretation of hypoglycaemic episode rates is complicated by the permitted variations in background therapy with respect to MET and SU. Given the rate seen in the placebo arm (5.2%), however, there is little to suggest a clinically relevant rate increase in the alogliptin 25 mg group (7.0%). The incidence of hypoglycaemia was markedly

higher in subjects on triple therapy with concomitant SU (5.6% for placebo+SU+TZD and 27.3% for alogliptin 25 mg+SU+TZD) compared with subjects on triple therapy with concomitant MET (3.6% for placebo+MET+TZD and 1.8% for alogliptin 25 mg+MET+TZD). No severe hypoglycaemic events occurred, and no events of hypoglycaemia were reported as SAEs or led to permanent discontinuation of the study drug.

In **study 011** (add-on to insulin, with or without metformin), the incidence of hypoglycaemic episodes was higher in the alogliptin 25 mg (27.1%) and 12.5 mg (26.7%) groups vs placebo (24.0%), but the incidence of severe cases was similar.

In **study 305** (alogliptin vs SU in a general adult T2DM population, on metformin monotherapy), hypoglycaemia rates with metformin+alogliptin 25 mg vs metformin+glipizide were > 10-fold lower (1.4% vs 23.8%, respectively). Similarly, the incidence of severe hypoglycaemic episodes was greater in the metformin+glipizide group (0.5%) compared with the metformin+alogliptin 12.5 mg and metformin+alogliptin 25 mg groups (0.1% and 0, respectively).

In the case of alogliptin 25 mg used to form triple therapy with metformin and pioglitazone in **study 322OPI-004**, there was an increased rate of hypoglycaemic episodes (4.5%) vs dual therapy with metformin and a higher dose of pioglitazone (1.5%). A similar trend was also seen in study 322OPI-001, which compared pioglitazone and alogliptin alone and in combination as add-on therapy to metformin, but with lower rates. The increased risk of hypoglycaemia when alogliptin is used in combination with pioglitazone is indicated in section 4.4 of the SmPC.

Alogliptin

The incidence of hypoglycaemic episodes in the Controlled Phase II and III Study Group (excluding study 301 as detailed information regarding hypoglycaemic episodes was not collected in this study) was 12.9% in the active comparator group, 3.6% in the alogliptin 25 mg group, and 6.2% in the placebo group. Within each treatment group, the highest numbers of hypoglycaemic episodes were classified as symptomatic hypoglycaemic episodes with a blood glucose < 3.33 mmol/L. Although the incidence of severe hypoglycaemic episodes was low overall, the percentages in the placebo and active comparator groups (both 0.4%) were higher than for subjects treated with alogliptin (0.1%). From this pooled analysis, across the alogliptin clinical development program, alogliptin treatment does not lead to an increased risk of hypoglycaemia when compared with placebo or active comparator.

In elderly subjects ≥65 years in study 303, hypoglycaemia rates were approximately 5-fold lower for alogliptin 25 mg vs glipizide (5.4% vs 26.0%). There were no severe episodes of hypoglycaemia in the alogliptin 25 mg group, and the rate of hypoglycaemia was in line with the hypoglycaemia rates in the placebo and alogliptin groups reported in the Controlled Phase II and III Study Group, predominantly in subjects < 65 years. As elderly patients with T2DM are considered more susceptible to episodes of hypoglycaemia than younger patients, a pooled analysis of the data from 12 studies was performed comparing these age groups. The overall incidence of any episode of hypoglycaemia was similar between subjects ≥ 65 years and < 65 years (3.8% and 3.6%, respectively) treated with alogliptin 25 mg.

2.6.6. Comparative safety by dose

In most of the alogliptin phase III studies, both alogliptin 12.5 mg and 25 mg were evaluated; however, in some studies, particularly the longer duration studies, only 25 mg dose was evaluated. Therefore, for the alogliptin 25 mg group, there were more subjects exposed overall and for longer periods of time compared with the alogliptin 12.5 mg group.

Incidence of TEAEs was similar between the alogliptin 12.5 and 25 mg dose groups. In the Controlled Phase II and III Study Group, the incidence of TEAEs was 67.5% in the alogliptin 12.5 mg group (333.2 events per 100 subject-years) and 66.6% in the alogliptin 25 mg group (342.1 events per 100 subject-years). For SAEs, the incidence was 4.0% in the alogliptin 12.5 mg group (8.5 events per 100 subject-years) vs 4.7% in the alogliptin 25 mg group (9.9 events per 100 subject-years). For TEAEs leading to discontinuation of the study drug, the incidence was 3.6% in the alogliptin 12.5 mg group (6.5 events per 100 subject-years) vs 4.1% in the alogliptin 25 mg group (7.1 events per 100 subject-years).

Common TEAEs (experienced by ≥ 3% of subjects in either dose group) were experienced by similar proportions of subjects in the 12.5 and 25 mg dose groups and included nasopharyngitis (5.7% vs 5.1%, alogliptin 12.5 mg vs 25 mg), upper respiratory tract infection (4.9% vs 5.2%), headache (4.4% vs 5.4%), urinary tract infection (4.1% vs 4.2%), hypertension (3.6% vs 3.9%), diarrhoea (3.7% vs 3.8%), and back pain (3.5% vs 3.3%). No meaningful differences were observed between the dose groups in the analysis of common TEAEs by time to onset or by duration of exposure to treatment. In addition, no single type of event emerged in only one of the 2 dose categories and not in the other.

Similarly, the incidences of TEAEs of special interest, including hypersensitivity, acute pancreatitis, malignancies, and CV events were comparable between exposure-corrected dose groups. Overall, the safety and tolerability profile of alogliptin was similar between the 12.5 and 25 mg groups.

2.6.7. Laboratory findings

For both the fixed dose combination alogliptin/metformin and for alogliptin alone, laboratory evaluations of haematology, clinical chemistry and urinalysis, mean changes from baseline to endpoint measurement time were generally small and consistent across the treatment groups. The incidence of markedly abnormal values for renal function parameters during treatment was low overall and similar across treatment groups.

During treatment, the incidence of alanine aminotransferase (ALT) > 3× upper limit of normal (ULN) was higher in the active comparator group (2.2%) than in alogliptin or placebo groups (1.3% and 0.9%, respectively). The incidence of ALT >5×ULN in subjects receiving active comparator, alogliptin or placebo was 0.5%, 0.3%, and 0.1%, respectively. ALT >10×ULN only occurred in subjects receiving active comparator or alogliptin (0.2% and 0.1% respectively).

The incidence of total bilirubin > 34.2 µmol/L was low and similar across groups (active comparator 0.5%, alogliptin 0.4%). The incidence of ALT > 3×ULN concurrent with total bilirubin > 34.2 µmol/L was 0.1% in the active comparator group and < 0.1% in subjects receiving alogliptin.

For the alogliptin-treated subjects with an ALT > 10×ULN, all had an alternative (non-study drug) aetiology. Minor, transient and isolated elevations in hepatic parameters were observed in other

subjects but most were not considered clinically meaningful in terms of observed absolute values within expected physiological fluctuation of these enzymes in the context of underlying liver comorbidity.

Overall, the data indicate alogliptin alone or taken in combination with metformin is associated with a low risk of hepatic toxicity.

2.6.8. Vital signs and electrocardiogram evaluations

No clinically meaningful trends were observed in vital sign measures (pulse, blood pressure, respiratory rate, and temperature) in the FDC alogliptin/metformin studies or the alogliptin studies. In addition, alogliptin was found to be weight neutral.

Non-clinical electrophysiological studies did not raise any safety concerns. Study 019 investigated the effects of alogliptin on cardiac repolarization (QT/QTc) and concluded that alogliptin had no clinically meaningful effect on cardiac repolarization. Electrocardiogram (ECG) parameters showed no clinically meaningful trends.

2.6.9. Safety in special populations

No specific subpopulation investigations have been conducted with the FDC alogliptin/metformin; however, the FDC is expected to have a similar efficacy profile as the individual components. To determine whether certain factors predispose subgroups of individuals to experience specific TEAEs with alogliptin, analyses were performed using the Controlled Phase II and III Study Group for a number of intrinsic (sex, age, race, BMI, and renal function) factors. No important differences were noted.

2.6.9.1. Elderly

TEAEs in the Controlled Phase II and III Study Group were reviewed by age group (< 65, 65-74, 75-84, and ≥85 years). Dizziness, headache, urinary tract infection, diarrhoea, and dyslipidaemia were consistently reported by a greater percentage of subjects 75-84 years compared with subjects < 65 years and subjects 65-74 years in the alogliptin 25 mg group. This trend was also evident in the active comparator group for dizziness. This finding is consistent with the known propensity for these conditions observed in the general population of elderly patients and is not attributable per se to alogliptin treatment.

In addition, creatinine renal clearance decreased was reported by a greater percentage of subjects 75-84 years of age compared with subjects < 65 years and subjects 65-74 years in the alogliptin 25 mg group. This trend was also evident in the active comparator group. This subgroup difference is not unexpected and is unlikely to be attributable to alogliptin treatment.

In the Controlled Phase II and III Study Group, no safety signals were observed in subgroup populations stratified by age, but exposure in subjects older than 85 years of age is very limited.

Study 303 was a randomized, double-blind, active-controlled study designed to further explore the efficacy and safety of alogliptin compared with glipizide over a longer period of time (up to 52 weeks) in an older T2DM subject population (age, 65 to 90 years). Overall, compared with glipizide,

alogliptin was well tolerated, showed less hypoglycaemia, and no body weight increases. The safety and tolerability results evaluated in this study were consistent with the safety profile established for alogliptin in previous studies within its clinical development program. The most frequently reported TEAEs included urinary tract infection, dizziness, and headache, all of which are similar to glipizide and consistent with what has been reported in previous studies. Most other TEAEs occurred in less than 1% of subjects, were considered by the investigator not drug related, and were mild or moderate in intensity.

2.6.9.2. Subjects with impaired renal function

In the phase I study 006 (renal pharmacokinetic study), compared with healthy subjects, systemic exposure to alogliptin was 71%, 112%, 251% and 377% higher in subjects with mild, moderate, or severe renal impairment, and with ESRD, respectively, following administration of a single alogliptin 50 mg dose. While no change in dose is anticipated for patients with mild renal impairment, dose reductions proportional to the increases in exposure in subjects with moderate or severe renal impairment or end-stage renal disease (ESRD) are recommended (SmPC section 4.2). The majority of TEAEs reported in this study were judged to be mild in intensity and unrelated to study drug. The percentage of TEAEs was similar between each renal impairment group and their respective healthy matched controls. As expected, several subjects with renal impairment exhibited serum chemistry and urinalysis abnormalities consistent with their underlying condition; however, no clinically meaningful changes in any of these values were observed.

The majority of subjects in the Controlled Phase II and III Study Group had mild or moderate renal impairment based on estimated glomerular filtration rate (eGFR) using the MDRD calculation. The relatively small number of subjects with severe baseline renal impairment limits the ability to make meaningful comparisons in this subgroup (no subjects receiving placebo or active comparator, 1 subject in the alogliptin 12.5 mg group, and 3 subjects in the alogliptin 25 mg group when defined by MDRD formula).

In the Controlled Phase II and III Study group, urinary tract infection was the only common TEAE reported by ≥ 1% of subjects in the alogliptin 25 mg group for which the incidence in subjects with moderate renal impairment at baseline was higher than that in subjects with normal renal function or mild renal impairment at baseline. A similar trend was evident for subjects who received active comparator, indicating that this difference is not necessarily attributable to treatment with alogliptin. Similarly, pruritus was the only TEAE of interest reported by ≥1% of subjects overall in the alogliptin 25 mg group for which the incidence in subjects with either mild or moderate renal impairment at baseline was at least twice that in subjects with normal renal function at baseline.

Of the TEAEs reported by ≥ 1% of subjects with severe renal impairment in study 402, compared to placebo, alogliptin was associated with a similar percentage TEA's (87.9 % vs. 87.9%). As expected with multiple comparisons, some numerical imbalances remain with the updated data set, including events in which incidence was lower for alogliptin compared with placebo and those with an incidence higher for alogliptin compared with placebo. Among the most common TEAEs (≥ 5% incidence), a 2-fold difference between treatment groups was observed for anemia, urinary tract infection, and angina pectoris (higher for alogliptin) and diarrhea, edema peripheral, and blood creatine phosphokinase increased (higher for placebo). In line with the SmPC of metformin, the FDC

is contraindicated in patients with moderate or severe renal failure (creatinine clearance < 60 ml/min) (SmPC sections 4.3 and 4.4).Subjects with impaired hepatic function

Results from phase I study 023 demonstrated that mild or moderate hepatic impairment did not affect exposure to alogliptin; therefore, subgroup analyses were not performed for hepatic function. The effect of severe hepatic impairment on the pharmacokinetics of alogliptin was not studied. As a result, use of alogliptin in patients with severe hepatic impairment is not recommended.

Moreover, according with the harmonized SmPC of metformin, metformin is contraindicated in patients with hepatic impairment.

2.6.10. Safety related to drug-drug interactions and other interactions

No differences in exposure to alogliptin or to metformin were observed when alogliptin and metformin were coadministered, and no clinically meaningful changes in exposure to a number of drugs that are metabolized by CYP isozymes (pioglitazone [2C8]; glyburide, tolbutamide and (S)-warfarin [2C9]; midazolam, atorvastatin, ethinyl estradiol, and norethindrone [3A4]; caffeine and (R)-warfarin [1A2]; dextromethorphan [2D6], transported by Pgp (fexofenadine and digoxin) or OCT2 (metformin), or drugs that are excreted unchanged in urine (metformin, cimetidine, a OCT2 inhibitor, and digoxin) were observed when these drugs were administered with alogliptin.

Alogliptin was devoid of any clinically meaningful drug or food interactions, which suggests a favourable safety profile in patients with T2DM who are likely to be receiving multiple concomitant medications.

The SmPC for MET includes specific recommendations for administration of MET with drugs that tend to cause hyperglycaemia, cationic drugs that are eliminated by renal tubular secretion, and intravascular iodinated contrast agents. All of these are considered relevant for the FDC aogliptin/metformin and are appropriately reflected in the SmPC.

2.6.11. Post marketing experience

The FDC alogliptin/metformin was not marketed in any country.

Alogliptin was approved for use in the treatment of T2DM in Japan in April 2010 and commercially launched (6.25, 12.5, and 25 mg) in June 2010.

As of 15 October 2011, cumulative exposure for alogliptin is estimated to be 117,359 patient-years. A total of 271 post-marketing cases were included in the 3 PSURs, 37 of which were serious. The most common events reported post-marketing were in the skin and subcutaneous disorders SOC (18 serious and 124 non-serious cases) and included 1 case of Stevens-Johnson syndrome.

Hepatotoxicity was reported post-marketing in 5 cases. An independent committee concluded that the relationship between alogliptin and hepatotoxicity in three of the five cases was deemed "probable" (50-74% probability) and in the remaining two was deemed "possible" (25-49% probability).

There were 6 serious post-marketing cases of acute pancreatitis (as of 27 October 2011). All except 1 serious post-marketing case had a possible alternative aetiology that likely precipitated the event.

One fatal case of necrotizing pancreatitis was reported, which occurred in a patient with multiple gallbladder stones as evidenced by dilation of the extrahepatic common bile duct on autopsy.

No new information affecting the safety profile of alogliptin has been identified post-marketing and no changes have been made to the Company Core Safety Information (CCSI). To date, no regulatory action has been taken by the Japanese regulatory authority with respect to safety labelling, which is based on the clinical trial program.

PSURs have been produced every 6 months since approval in Japan. Categories of medically significant adverse reactions reviewed within each PSUR include those relating to skin and subcutaneous tissue disorders, hypoglycaemia, pancreatitis, and hepatotoxicity.

2.6.12. Discussion on clinical safety

2.6.12.1. Alogliptin/metformin

The safety profile of the FDC alogliptin/metformin is derived from five main phase III clinical studies (008, 009, 011, 305, 322OPI-004) and from two supportive studies. A total of 4201 subjects received alogliptin in combination with metformin either as a background medication or as one of the initial combination therapies. Treatment duration ranged from 16 to 52 weeks in the phase III studies.

Generally, the pattern of AEs observed in the alogliptin/metformin phase III studies was consistent with the known safety profile of metformin, previous clinical trials with alogliptin (see below), and conditions that are expected in this T2DM patient population. The most commonly (≥ 5% of subjects) reported with combination treatment were nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhoea, headache, oedema peripheral, influenza, hypertension, and arthralgia. Most TEAEs were considered mild or moderate in intensity and not related to study drug. TEAEs tended to occur more often within the system organ class (SOC) of infections and infestations and the incidence was generally similar among treatment groups.

The number of treatment emergent deaths in the alogliptin/metformin program was low (13/7150 [0.2%]). Six of the deaths were in subjects taking alogliptin in combination with MET (6/4201 [0.1%]).

Special interest AEs for alogliptin/metformin are based on the AEs of special interest for the single components and include hypersensitivity reactions (severe cutaneous adverse reactions, angioedema, and anaphylaxis reactions), acute pancreatitis, malignancy, CV events, and lactic acidosis. There is no evidence to suggest that the combination of alogliptin and MET is associated with an increase in incidence or severity of these AEs of special interest. There have been no reports of lactic acidosis in the alogliptin or alogliptin/metformin clinical programs.

The cardiovascular safety was retrospectively adjudicated as MACE (CV death, nonfatal MI, and non-fatal stroke) in the five main phase III trials. The number of subjects with MACE was low, ranging from one (1/260; 0.4%) patient in study 011 to 9 (9/1765; 0.5%), with the highest percentage in study 009 (4/396; 1.0%) for the alogliptin groups. In the placebo groups there was only one subject reported with MACE event in study 011 (1/130; 0.8%) and none in studies 008 and 009. However, in the active comparator studies there was a higher adjudicated MACE event rate

with 6/873 (0.7%) in study 305 and 3/399 (0.8%) in study 322OPI-004. Currently, there is a cardiac vascular study on-going (study 402).

2.6.12.2. Alogliptin

Overall, for alogliptin, a comprehensive clinical program was submitted comprising 55 clinical studies involving approximately 1000 healthy adult subjects and more than 11,000 adult subjects with T2DM. The patient population can be considered representative of the European population of diabetes patients..

The most common TEAEs reported in ≥ 5% of subjects treated with alogliptin 25 mg and more frequently than in subjects who received placebo or active comparators were headache, nasopharyngitis, and upper respiratory tract infection. In comparison to other DPP-4 inhibitors, no potential new adverse events emerged. However, in order to increase the precision of adverse event rates and to achieve a higher validity, the applicant was requested to generate a safety data pool containing all seven pivotal phase III studies (5 placebo-controlled and 2 active-comparator studies) and to present a table of adverse events which is to be reflected in the tabulated list of adverse reactions (SmPC section 4.8). The applicant presented the requested data. It is agreed that the pattern of TEAEs observed in the polled "pivotal phase III controlled studies was similar to the one observed in the polled "controlled phase II and IIIstudy group". The tabulated list of ADRs in SmPC section 4.8 was updated accordingly to reflect data from pooled phase III studies instead of individual studies in accordance with the SmPC guideline.

Reported serious adverse events had higher frequency with alogliptin compared to placebo, but lower compared to active comparators. There was no discernible pattern in the type of adverse events. The applicant was requested to discussion in depth the relevance of the following the 7 fatal cases, considered to be related to alogliptin treatment; 1 acute pancreatitis, 1 sudden death and 1 acute pulmonary oedema in the Controlled Phase 2/3 Group and 4 fatal cases with CV outcome in the study 012.

After review of the cases, it was considered that these individual cases (seven classified as possibly related and one as not related) do not reflect an association with alogliptin. Such events are expected in a population with T2DM and occurred at rates consistent with other studies. No apparent patterns, trends, were observed and it is considered that they do not indicate a new safety concern. Moreover, further results from the CV outcome study 402, for which a final study report is expected to be available during the first quarter of 2014, should allow a further in-depth characterisation of the CV profile of alogliptin-cotaining products.

Pre-defined special-interest AEs for alogliptin were CV (MACE), hypersensitivity reactions (severe cutaneous adverse reactions, angioedema, and anaphylaxis reactions), acute pancreatitis, and malignancies.

Cardiovascular safety

In the Controlled Phase II and III Study Group, when compared to placebo, alogliptin was associated with a higher cardiovascular event rate (Hazard ratio 1.33). However, in the controlled Phase II and III Study Group, cardiovascular event rate was lower compared to active comparators

(Hazard ratio 0.66). In addition, interim analyses of the cardiovascular outcome study demonstrated that alogliptin was associated with a lower cardiovascular risk (Hazard ratio 0.81).

Owing to the differences in the number of events for MI (10 vs. 6), cardiac failure (7 vs. 1) and cardiac failure congestive (14 vs. 7) in the table presenting TAES vs. the table presenting serious TEAEs in the SOC cardiac disorders, the CHMP did seek clarification on the cases of cardiac failure and myocardial infarction designated as non-serious. The applicant stated that there were 20 subjects in total in the alogliptin clinical studies who experienced adverse events (AEs) of cardiac failure/cardiac failure congestive (14 subjects) or myocardial infarction (6 subjects) in which the event had been classified by the investigator as non serious. The applicant did provide satisfactory details of the definition of SAEs, a clinical review of the available data that was performed and a rationale for the non serious designation. Similarly, reassuring descriptions were provided by the applicant for the cases of heart failure, and therefore the CHMP considered this concern as being resolved.

Based on results showing no increase in MACE with alogliptin, no special warning/precaution regarding CV events is needed for the alogliptin component. According to metformin SmPC cardiac failure is a contraindication therefore alogliptin/metformin FDC is contraindicated in patients with congestive heart failure (NYHAI-IV).

Hypersensitivity reactions

Safety results for alogliptin indicate a low incidence of hypersensitivity reactions. Nevertheless, 13 patients (0.2%) developed an anaphylactic reaction during alogliptin, whereas no patient developed an anaphylactic reaction during treatment with placebo. During postmarketing surveillance in Japan, skin disorders, including Stevens Johnson, were reported. Consistent with labelling for other DPP-4 inhibitors the occurrence of such reactions has been indicated in section 4.4 of the SmPC.

Pancreatitis

The frequency of pancreatitis events is low, but alogliptin was associated with a higher risk for pancreatitis in comparison to comparators. Several cases of pancreatitis were reported postmarketing of which one was fatal. Given the increased risk of pancreatitis reported with other DPP-4 inhibitors, the risk of pancreatitis is indicated in the SmPC section 4.4 (Warnings and Precautions), and acute pancreatitis is listed as an adverse reaction in Post-marketing Reports in SmPC, Section 4.8. The risk of pancreatitis is indicated in the SmPC section 4.4 (Warnings and Precautions), and acute pancreatitis is listed as an adverse reaction in Post-marketing Reports in SmPC, Section 4.8. Moreover, new pancreatitis data have been integrated during the procedure and hence pancreatitis is now included as an identified risk in the Risk Management Plan.

Malignancies

There is no safety signal for malignancies with alogliptin. Therefore, no special warning/precaution is necessary for malignancies.

Pancreatic Cancer

Uncertainties remained during the procedure regarding effects of alogliptin on the pancreas, as long term safety data are limited. Besides, during the procedure data had been published that gave rise to additional concerns on inflammatory and proliferative pancreatic effects of the therapy with another DPP-4 inhibitor, sitagliptin, (Butler et al. Diabetes, March 2013). Therefore the applicant was asked during the assessment procedure to provide further analyses with regard to pancreatic risk.

In the controlled clinical studies, including the long-term studies OPI-004 (52 weeks) and 305 (104 weeks), there were no TEAEs of pancreatic cancer in alogliptin treatment groups. A PV database search found that 5 subjects had pancreatic cancer events that occurred outside of the study treatment period. As of November 2012, in Study 402, there were no TEAEs of pancreatic cancer. In uncontrolled studies, the incidence rates of pancreatic cancer associated with the use of alogliptin were low and considered to be consistent with the incidence expected in the T2DM population.

Based on these additional data the CHMP considered that there was no clear evidence for an association of pancreatic cancer and alogliptin treatment. Nevertheless, CHMP considered that a targeted follow-up is needed. This has now been reflected in the RMP as 'Pancreatic cancer' has been included as an important potential risk (in line with the recommendation given by CHMP at the July 2013 meeting for this class of products in the conclusions of the Art. 5(3) referral for GLP 1 based therapies).

Hypoglycaemia

There was no increase in hypoglycaemia rate vs placebo when alogliptin 25 mg was administered alone, added on to SU, or added on to metformin. In the case of alogliptin 25 mg used to form triple therapy with metformin and pioglitazone in study 322OPI-004, there was an increased rate of hypoglycaemic episodes. In study 009 (add-on to TZD), there was a small increase in the rate of hypoglycaemic episodes in the alogliptin 25 mg group. In study 011 (add-on to insulin, with or without metformin), the incidence of hypoglycaemic episodes was higher with alogliptin 25 mg vs placebo. This increased rate of hypoglycaemia in combination with metformin/TZD and insulin is reflected in the SmPC.

Vital signs and ECG

There were no relevant changes in vital signs and ECG. There were no relevant changes in laboratory findings.

Subgroups

In patients with mild to moderate renal insufficiency, no safety signals were observed with alogliptin. The number of patients with severe renal insufficiency in the pivotal studies was negligible. In the cardiovascular outcome study 402, a number of patients with severe renal insufficiency was included. Of the TEAEs reported by ≥ 1% of subjects with severe renal impairment, compared to placebo, alogliptin was associated with a similar percentage TEA' s (87.9

% vs. 87.9%). The applicant does not apply for an indication of the FDC alogliptin/metformin in patients with moderate and severe renal impairment, since metformin is contraindicated in patients with renal dysfunction (creatinine clearance < 60 ml/min). In T2DM patients with mild renal impairment (creatinine clearance between 60-90 ml/min) no dose adjustment is proposed or needed. This is appropriately reflected in the SmPC sections 4.3 and 4.4.

No safety signals for alogliptin were observed in subgroup populations stratified by age. Some adverse events were more common with alogliptin in elderly individuals. However, the number of patients was limited, and the differences between alogliptin and placebo were small. Overall, no safety signals were observed with alogliptin in subgroup populations stratified by race. In addition, no safety signals were observed with alogliptin in subgroup populations stratified by BMI.

Patients with hepatic disease were excluded in the phase II and III studies. In a pharmacokinetic study in patients with moderate hepatic impairment, there were no adverse events and no clinically meaningful changes in laboratory tests were reported. However, the use of alogliptin in patients with severe hepatic impairment cannot be recommended. In addition, five cases of hepatotoxicity, including one case of hepatic failure were reported post-marketing. An independent committee concluded that the relationship between alogliptin and hepatotoxicity in three of the five cases was deemed "probable" (50-74% probability) and in the remaining two was deemed "possible" (25-49% probability). Although no causal relationship between alogliptin and hepatic dysfunction has been established, these 5 cases provide important knowledge about the risks of alogliptin in clinical practice. Therefore, the occurrence of hepatic dysfunction has been reflected in the SmPC in section 4.4 (warnings and precautions) and 4.8 (undesirable effects). In addition, since hepatic impairment has been associated with lactic acidosis, the use of metformin/alogliptin FDC in patients with hepatic impairment is contraindicated. Furthermore, hepatotoxicity is included in the RMP as important potential risk.

Drug interactions

No dose adjustment is required due to drug interactions.

2.6.12.3. Metformin

The safety profile of metformin has been well established based on pre and post-approval clinical studies and post-marketing experience.

One of the most common side effects of metformin is gastrointestinal intolerance, which can hinder maximizing the dose as well as lessen patient compliance. The most important adverse effect associated with metformin therapy is lactic acidosis, which mandates cessation of treatment.

Metformin therapy is contraindicated in patients with renal dysfunction, congestive heart failure requiring pharmacologic treatment and acute or chronic metabolic acidosis, including diabetic ketoacidosis. Additionally, since hepatic impairment has been associated with lactic acidosis, the use of MET in patients with hepatic insufficiency is contraindicated. The above mentioned metformin contraindications are reflected in Vipdomet's SmPC section 4.3.

All safety issues are appropriately reflected in the SmPC and in the RMP.

2.6.13. Conclusions on the clinical safety

In comparison to other DPP-4 inhibitors, no potential new adverse events emerged for the alogliptin component.

Generally, the pattern of AEs observed in the alogliptin/metformin phase III studies was consistent with the known safety profile of metformin, previous clinical trials with alogliptin, and conditions that are expected in this T2DM patient population. The most commonly (≥ 5% of subjects) reported with combination treatment were nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhoea, headache, oedema peripheral, influenza, hypertension, and arthralgia.

The applicant does not apply for an indication of the FDC alogliptin/metformin in patients with moderate and severe renal impairment, since metformin is contraindicated in patients with renal dysfunction (creatinine clearance < 60 ml/min). In T2DM patients with mild renal impairment (creatinine clearance between 60-90 ml/min) no dose adjustment is proposed or needed. This is appropriately reflected in the SmPC sections 4.3 and 4.4.

There is no safety signal for malignancies with alogliptin.The cases of hepatotoxicity, observed post-marketing in Japan, are relevant. Therefore, the occurrence of hepatic dysfunction has been reflected in the SmPC in section 4.4 (warnings and precautions) and 4.8 (undesirable effects). In addition, since hepatic impairment has been associated with lactic acidosis, the use of metformin/alogliptin FDC in patients with hepatic impairment is contraindicated. Furthermore, hepatotoxicity is included in the RMP as important potential risk.

Hypersensitivity reactions, pancreatitis and hypoglycaemia (in combination with TZD and insulin) are reflected in the SmPC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4.0, the PRAC considers by consensus that the risk management system for alogliptin/metformin (Vipdomet) for the above mentioned indication is acceptable.

Proposed indication:

Treatment of adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycaemic control in adult patients, inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin.
- in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.
- in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

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

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Hypersensitivity reactions. - Pancreatitis. - Lactic acidosis.
Important potential risks	- Hepatotoxicity - Peripheral necrotic skin lesions - Gastrointestinal disorders - Infections
Missing information	- Patients with concurrent CVD. - Patients with severe renal impairment or End-Stage Renal disease (ESRD) requiring dialysis - Patients with severe hepatic impairment. - Pregnant and/or breastfeeding women - Children and adolescents - Malignancies

The PRAC agreed.

- **Pharmacovigilance plans**

Ongoing and planned studies in the PhV development plan

Activity/Study title	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of final reports**
CV outcome study 402 - A multicenter, randomized, doubleblind, placebo-controlled	*To evaluate CV outcomes following treatment with alogliptin in addition to standard of care in*	*Investigate hypersensitivity reactions, pancreatitis, skin lesions,*	*Ongoing*	*January 2014*

Activity/Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of final reports
study	*subjects with type 2 diabetes and ACS*	*hepatotoxicity, GI disorders and infections, effects in patients with concurrent CV disease and effects in patients with renal impairment.*		

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

- **Risk minimisation measures**

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity Reactions	*SmPC Sections 4.3, 4.4 and 4.8 provide data and recommendations*	*None*
Pancreatitis	*SmPC Sections 4.4 and 4.8 provide data and recommendations*	*None*
Lactic acidosis	*SmPC Sections 4.3, 4.4, 4.5 and 4.8 describe metformin related risks and provide data and recommendations.*	*None*
Hepatotoxicity	*SmPC Section 4.4 and 4.8 provide data and recommendations*	*None*
Peripheral necrotic skin lesions	*None required*	*None*
Gastrointestinal disorders	*SmPC Section 4.8 provides data.*	*None*
Infections	*SmPC Section 4.8 provides data.*	*None*
Patients with concurrent cardiovascular disease	*SmPC Section 4.3 provides a contraindication concerning use in patients with cardiac failure*	*None*
Patients with severe renal impairment or End-Stage Renal disease (ESRD) requiring dialysis	*SmPC Section 4.2 and Section 4.4 Provide a contraindication and warnings around use in patients with renal impairment*	*None*
Patients with severe hepatic impairment	*SmPC Sections 4.3 and 4.4 provide warnings concerning use in patients with severe hepatic impairment.*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pregnant and/or breastfeeding women	*SmPC Section 4.6 provides information on the absence of data.*	*None*
Children and adolescents	*SmPC Section 4.2 provides information on the absence of pediatric data.*	*None*
Malignancies	*None required*	*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(s).

In addition the PRAC considered that the applicant should address the following points

- Pancreatic cancer should be included in the RMP as missing information
- Pancreatic cancer should be added as an adverse event of special interest in the CV outcome study 402.

The CHMP endorsed this advice with changes.

These changes concerned the following elements of the Risk Management Plan:

- Pancreatic cancer should be included in the RMP as an important potential risk

The CHMP justified these changes as follows:

The Article 5 (3) referral procedure assessing the available data concerning the potential relationship between pancreatic cancer and GLP-1 agonists and DPP-4 inhibitors treatment, was concluded during July 2013 CHMP meeting. In line with the recommendation given by CHMP in the conclusion of the above mentioned Art. 5(3) referral procedure, "pancreatic cancer" should be seen as an important potential risk associated with alogliptin treatment and reflected as such in all alogliptin containing products' RMPs.

All issues identified by the PRAC and the CHMP were properly addressed by the applicant and an updated RMP version 5 was submitted.

The CHMP endorsed the updated RMP without changes.

2.9. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Vipdomet is a Fixed Dose Combination of a new DDP-4 inhibitor, alogliptin, and the biguanide metformin.

Pharmacokinetics

In study 322MET-103, the pivotal BE study, the developed fixed dose combination tablets containing the lowest and highest amount of metformin (500 mg and 1000 mg, respectively) and the tablets containing the lowest and highest amount of alogliptin (6.25 and 12.5, respectively) were compared with individual corresponding alogliptin and metformin tablets.

In all cases the 90% CI of the AUC and C_{max} was within the 80%-125% range. Therefore, it can be considered that bioequivalence of the FDC alogliptin/metformin 6.25mg + 1000mg and 12.5mg+1000mg tablets has been demonstrated.

The applicant used a bracketing approach by making only an evaluation of the highest and lowest dose strengths in humans *in vivo*, as was previously advised by the CHMP during scientific advice. Therefore, a biowaiver for the applicated alogliptin/metformin 6.25mg+850mg and 12.5mg+850mg tablet can be granted.

No changes in exposure to alogliptin and no clinically meaningful changes in exposure to metformin (an OCT2 substrate that is primarily excreted unchanged in the urine) were observed when alogliptin and metformin were co-administered.

Twice daily dosing compared with once daily dosing of alogiptin resulted in identical exposure (AUC) but resulted in a lower C_{max} of approximately 35%. However, DPP-4 inhibition with BID dosing of alogliptin was similar to that with once daily dosing (both > 80% at 24 hours post-dose) and in a clinical study (**302**, see below) efficacy was similar between the two dose regimens.

Clinical

Five clinical trials were considerd pivotal for the fixed dose combination of alogliptin and metformin: (008, 009, 011, 305, and 322OPI-004) and two supportive trials (302 and 322OPI-001). Study 010 was included to show the efficacy and safety of alogliptin as monotherapy.

Pivotal **study 008** (alogliptin add-on to metformin) demonstrated that the combination treatment of alogliptin 25 mg with metformin was clinical relevant with HbA1c changes from baseline of -0.48% (95% CI -0.67 to -0.30) in comparison to placebo with metformin after 26 weeks.

In pivotal **study 009**, in which alogliptin was added to pioglitazone with or without metformin, alogliptin 25 mg was associated with a reduction in HbA1c of -0.61% (95% CI -0.80 to -0.41) after 26 weeks in comparison to placebo. Treatment effects were clinically relevant for alogliptin 25 mg in combination with TZD only (-0.49%) and in combination with TZD and metformin (-0.72%), which is relevant for this FDC. In **study 322OPI-004**, the effects of adding alogliptin 25 mg, in

patients already on metformin treatment, were non-inferior compared with increasing the dose of pioglitazone from 30 to 45 mg.

Study 011 was submitted to show the effect of alogliptin as add-on to insulin in patients with or without metformin. Treatment effect of alogliptin 25 mg was modest, but clinically relevant (-0.59%; 95% CI -0.80 to -0.37) after 26 weeks. In the subgroup of patients on metformin treatment (58.5%; n=227), which is relevant for the FDC alogliptin/metformin, mean Change (SD) from baseline in HbA1c at Week 26 was -0.77 (0.933). baseline HbA1c values were relatively high (9.3%). This may have resulted in an overestimation of the treatment effects of alogliptin on HbA1c. Nevertheless, in the individuals with HbA1c below 8.5%, the effect of alogliptin 25mg on HbA1c was also clinically relevant (-0.68%).

In an initial combination study (**302**), both co-administration therapy regimens of alogliptin plus metformin (A12.5+ M500 BID and A12.5+ M1000 BID) resulted in larger reductions in HbA1c compared to their individual component regimens of alogliptin alone or metformin alone. Alogliptin 12.5 BID provided similar glycaemic control compared with alogliptin 25 once daily.

In patients inadequately controlled with metformin (**322OPI-001**), each individual combination of alogliptin+pioglitazone achieved larger reductions in HbA1c at Week 26 compared with the corresponding alogliptin and pioglitazone doses given alone. These differences were clinically relevant. These data provide further support for the use of alogliptin in combination with metformin.

In addition to the specific combination trials of alogliptin with metformin, efficacy and safety of alogliptin were studied in an extensive number of double blind randomized trials, including trials with placebo and active comparators, and in combination with several other antidiabetic agents. HbA1c was used as the primary endpoint. In the placebo controlled studies, the treatment effect of alogliptin is modest (0.5-0.6%). These results have been discussed further in the marketing application of alogliptin that is still pending and will not be repeated here.

Uncertainty in the knowledge about the beneficial effects

Cardiovascular beneficial effects

In the five main FDC trials, there was a numerically higher incidence of CV outcomes. However, the numbers were very low. Alogliptin, when compared to placebo, was associated with a higher cardiovascular event rate (Hazard ratio 1.33). However, in the Controlled Phase II and III Study Group, cardiovascular event rate was lower compared to active comparators (Hazard ratio 0.8). In addition, interim analyses of the cardiovascular outcome study demonstrated that alogliptin was associated with a lower cardiovascular risk (Hazard ratio 0.81).

Elderly

Initially, there was uncertainty regarding alogliptin in elderly individuals and is also considered relevant for the application of this FDC. In the pivotal alogliptin trials, the treatment effect of alogliptin was not lower in patients > 65 years compared to patients < 65 years, but only 2% of the patients treated with alogliptin were > 75 years of age (n=124). Therefore, a study in elderly individuals was performed (study 303). Although alogliptin 25 mg and glipizide were statistically non-inferior, the absolute changes in HbA1c after 1 year were clinically not relevant. The fact that these results were observed in both treatment groups indicates that the observed efficacy response

might be related to the specific study design, for example, the low baseline HbA1c and the inclusion of subjects on monotherapy (with a short period of background therapy washout). Importantly, results of the large pooled analysis of the 5 main Phase III, 26-week, placebo-controlled studies, demonstrate relevant efficacy in the elderly, also in patients aged ≥75 years.

Non-inferiority compared to glipizide

For the combination with metformin, in the non-inferiority trial (**322OPI-004**), both alogliptin 25 mg and glipizide were associated with a clinically relevant reduction in HbA1c (-0.61% and -0.52%, respectively) after 52 weeks. However, the glipizide dose in the comparator group was relatively low (mean dose 5.2 mg). This is probably due to the dose titration algorithm. Following any dose-titration, a subject who experienced hypoglycaemia was allowed to reduce the dose to as low as 5 mg glipizide (or matching placebo) and continue the study on that dose. Following down titration, subjects were not allowed to increase the dose again. With such a low dose of glipizide, the CHMP concluded that non-inferiority of alogliptin when compared to SU as add-on therapy to metformin has not been established. In addition, baseline HbA1c was relatively low in these patients (7.6%). This decreases the power to detect any differences between treatments.

Long term effects

Although the extension study (study **012**) was not intended for efficacy evaluation, after 4 years, the increase in HbA1c with alogliptin 25 mg was clinically relevant (+0.61%). In addition, in study 303 in elderly individuals, efficacy after 1 year was small, but stable. In the two main non-inferiority trials (study **322OPI-004** and **305**) after 1 year, treatment effects of alogliptin were relatively stable compared to glipizide (study **305**) and compared to increasing the dose of pioglitazone (study **322OPI-004**).

Effects on beta cell function

There tended to be effects on estimates of endocrine pancreatic function. However, these effects were not statistically significant in the majority of the studies. In addition, these serum measures (such as fasting proinsulin, fasting insulin, proinsulin/insulin ratio, C peptide and HOMA) are only surrogate estimates of pancreatic function.

Risks

Unfavourable effects

The safety profile of the FDC alogliptin/metformin is derived from five main phase III clinical studies (008, 009, 011, 305, 322OPI-004) and from two supportive studies. A total of 4201 received alogliptin in combination with metformin either as a background medication or as one of the initial combination therapy. Treatment duration ranged from 16 to 52 weeks in the phase III studies.

Generally, the pattern of AEs observed in the alogliptin/metformin phase III studies was consistent with the known safety profile of metformin, previous clinical trials with alogliptin (see below), and conditions that are expected in this T2DM patient population. The most commonly (≥ 5% of subjects) reported with combination treatment were nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhoea, headache, oedema peripheral, influenza, hypertension, and arthralgia. Most TEAEs were considered mild or moderate in intensity and not related to study

drug. TEAEs tended to occur more often within the system organ class (SOC) of infections and infestations and the incidence was generally similar among treatment groups.

Regarding the mono components, the safety of metformin is sufficiently known. Regarding alogliptin, the following safety topics were identified:

Hypersensitivity reactions

Safety results for alogliptin indicate a low incidence of hypersensitivity reactions. Nevertheless, 13 patients (0.2%) developed an anaphylactic reaction during alogliptin, whereas no patient developed an anaphylactic reaction during treatment with placebo. During post marketing surveillance in Japan, skin disorders, including Stevens Johnson, were reported. Consistent with labeling for other DPP-4 inhibitors such reactions are now mentioned in the SmPC.

Pancreatitis

The frequency of pancreatitis events is low, but alogliptin was associated with a higher risk for pancreatitis in comparison to comparators. Several cases of pancreatitis were reported post marketing of which one was fatal. Given the increased risk of pancreatitis reported with other DPP-4 inhibitors, the risk of pancreatitis is included as Warning and Precautions in the SmPC, Section 4.4, and acute pancreatitis is listed as an adverse reaction in Postmarketing Reports in the SmPC, Section 4.8. Moreover, pancreatitis is now included as an identified risk in the Risk Management Plan.

Malignancies

There is no safety signal for malignancies with alogliptin. Therefore, no special warning/precaution is necessary for malignancies.

Pancreatic cancer

Based on all available data the CHMP considered that there was no clear evidence for an association of pancreatic cancer and alogliptin treatment. Nevertheless, 'Pancreatic cancer' has been included in the Risk Management Plan as an important potential risk (in line with the recommendation given by CHMP at the July 2013 meeting for this class of products in the conclusions of the Art. 5(3) referral for GLP 1 based therapies).

Hypoglycaemia

There was no increase in hypoglycaemia rate vs placebo when alogliptin 25 mg was administered alone, or added on to metformin. In the case of alogliptin 25 mg used to form triple therapy with metformin and pioglitazone in Study 322OPI-004, there was an increased rate of hypoglycaemic episodes. In study 009 (add-on to TZD), there was a small increase in the rate of hypoglycaemic episodes in the alogliptin 25 mg group. In study 011 (add-on to insulin, with or without metformin), the incidence of hypoglycaemic episodes was higher with alogliptin 25 mg vs placebo.

Subgroups

No specific safety signals for alogliptin were observed in subgroup populations stratified by age. Some adverse events were more common with alogliptin in elderly individuals. However, the number of patients was limited, and the differences between alogliptin and placebo were small.

Overall, no specific safety signals were observed with alogliptin in subgroup populations stratified by race. In addition, no specific safety signals were observed with alogliptin in subgroup populations stratified by BMI.

Uncertainty in the knowledge about the unfavourable effects

Patients with renal insufficiency

In patients with mild to moderate renal insufficiency, no safety signals were observed with alogliptin. The number of patients with severe renal insufficiency in the pivotal studies was very low. In the cardiovascular outcome study, 87 patients with severe renal insufficiency were studied for 6 months (43 treated with alogliptin and 44 treated with placebo). Of the TEAEs reported by ≥ 1% of subjects with severe renal impairment, compared to placebo, alogliptin was associated with a similar percentage TEA' s (87.9 % vs. 87.9%).

Metformin is contraindicated in patients with renal failure or dysfunction (creatinine clearance < 60 ml/min), therefore the FDC alogliptin/metformin can not be prescribed in these patients. No dose reductions are recommended for patients with mild renal impairment (creatinine clearance ≥ 60 ml/min).

Patients with hepatic disease

Patients with hepatic disease were excluded in the phase II and III studies. In a pharmacokinetic study in patients with moderate hepatic impairment, there were no adverse events and no clinically meaningful changes in laboratory tests were reported. However, this was only a small group of patients and alogliptin was administered only as a single dose. In addition, five cases of hepatotoxicity, including one case of hepatic failure were reported postmarketing. An independent committee concluded that the relationship between alogliptin and hepatotoxicity in three of the five cases was deemed "probable" (50-74% probability) and in the remaining two was deemed "possible" (25-49% probability). Within the context of the reassuring hepatic safety database for the controlled clinical trials, and the lack of a "signature" presentation among alogliptin associated liver events according to the committee treatment does not reach a "threshold of concern regarding black box warnings, restrictions on usage, or monitoring requirements". Although no causal relationship between alogliptin and hepatic dysfunction has been established,these 5 cases provide important knowledge about the risks of alogliptin in clinical practice. Therefore, hepatic dysfunction has been included in the SmPC in section 4.4 (warnings and precautions) and 4.8 (undesirable effects). Furthermore, hepatotoxicity is included in the RMP as important potential risk.

Metformin is contraindicated in patients with hepatic failure, therefore the FDC alogliptin/metformin is contraindicated prescribed in hepatic impaired patients.

Benefit-risk balance

Importance of favourable and unfavourable effects

The applicant performed several clinical pharmacology studies and literature studies to show the pharmacokinetics and pharmacodynamics of alogliptin and metformin administered alone or in

combination. Additionally specific studies with the combination products were performed including bioequivalence studies and a food-effect study. Overall, an additive, clinically relevant effect of the combination of alogliptin and metformin compared to the monocomponents with respect to its HbA1C lowering effect has been demonstrated.

The combination was not associated with weight gain, and there were no detrimental effects on blood pressure and serum lipids. For the FDC alogliptin/metformin, no indication for T2DM patients with moderate or severe renal insufficiency is requested by the applicant and the FDC is not recommended for this subgroup. For T2DM patients with mild renal impairment no dose reduction of the alogliptin component was proposed (in line with Vipidia).

The main goal of treatment of diabetes is the prevention of cardiovascular events. HbA1c is only a surrogate endpoint. A beneficial effect of alogliptin on cardiovascular events has not been shown. Nevertheless, interim analyses of the cardiovascular outcome study demonstrated that alogliptin was associated with a lower cardiovascular risk (Hazard ratio 0.81). A final study report is expected to be available during the 1st quarter of 2014

Generally, the pattern of AEs observed in the alogliptin/metformin phase III studies was consistent with the known safety profile of metformin and previous clinical trials with alogliptin. Alogliptin was associated with several relatively minor adverse events, such as headache, nasopharyngitis, and upper respiratory tract infection. In comparison to other DPP-4 inhibitors, no potential new adverse events emerged.

DPP-4 inhibitors in general have been associated with a potential risk of developing acute pancreatitis. Similar to other DPP-4 inhibitors, alogliptin is associated with pancreatitis. In addition, there have been spontaneously reported adverse reactions of acute pancreatitis with alogliptin in the postmarketing setting in Japan. However, these events were rare, and consistent with labeling for other DPP-4 the risk of pancreatitis is included as Warning and Precautions in the SmPC, Section 4.4, and acute pancreatitis is listed as an adverse reaction in Postmarketing Reports in SmPC, Section 4.8.

The risk of hypoglycaemia for alogliptin in combination with metformin and SU is only slightly increased.

There is insufficient knowledge about efficacy and safety of alogliptin in patients with severe hepatic disease. However, as metformin is contraindicated in patients with hepatic impairment, the FDC alogliptin/metformin cannot be prescribed in these patients.

Discussion on the benefit-risk balance

The CHMP considered that the benefit-risk balance of alogliptin/metformin fixed dose combination is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vipdomet in the treatment of of adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycaemic control in adult patients, inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin.
- in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.
- in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, 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.

When the submission of a PSUR and the update of a RMP coincide, they should 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.

New Active Substance Status

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