EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Incresync

International non-proprietary name: alogliptin / pioglitazone

Procedure No. EMEA/H/C/002178/0000

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
Ae	total amount of drug excreted
A/G	albumin/globulin
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
API	Active Pharmaceutical Ingredient
ADR	adverse drug reactions
AR	Assessment Report
ASM	Active Substance Manufacturer
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC(0-inf)	area under the plasma concentration-time curve from time 0 to time infinity
BA	bioavailability
BID	twice per day
%CV	percent coefficient of variation
Caco-2	human colonic adenocarcinoma
CHO	Chinese hamster ovary
CI	confidence interval
CK	creatine kinase
Cl	chloride
CL	clearance
CLr	renal clearance
Cmax	maximum observed plasma concentration
CNS	central nervous system
Cr	serum creatinine
CrCl	creatinine clearance
CRP	C-reactive protein
CYP	cytochrome P-450
DASH	DPP-4 activity and/or structure homologues
DPP-2,-4…	dipeptidyl peptidase-2, 4, …
E2	estradiol
EC50	half-maximal effective concentration
ECG	electrocardiogram
FDC	fixed-dose combination
GC	Gas Chromatography
GD	Gestation Day
GFR	glomerular filtration rate
GGT	γ-glutamyl transferase
GHb	glycosylated hemoglobin
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
Glut2	glucose transporter 2
GMP	Good Manufacturing Practice
HbA1c	glycosylated hemoglobin
HCl	Hydrochloric acid
HCT	hematocrit
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol

HGB	haemoglobin
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation
IC50	50% inhibitory concentration
IDL	intermediate-density lipoprotein
IP	intraperitoneal
IPC	In-process control
IR	Infrared
IR	immunoreactivity
ITT	intent to treat
IV	intravenously
ka	absorption constant
KF	Karl Fischer
LD	Lactation Day
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDPE	Low Density Polyethylene
LH	luteinizing hormone
LS	least squares
M-I, M-II, …	metabolite I, I …
LYM	lymphocytes
MAA	Marketing Authorisation Application
MET	metformin
MON	monocytes
MS	Mass Spectrometry
MTD	maximum tolerated dose
N/A	not applicable
ND	Not detected
NOAEL	no-observed-adverse-effect level
NT	Not tested
OGTT	oral glucose tolerance test
OAT	organic anion transporters
PCTFE	Polychlorotrifluoroethylene
pdx-1	insulin promoter transcription factor
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PO	by mouth
PPARγ	peroxisome proliferator–activated receptorγ
Ppg	postprandial glucose
PSUR	Periodic Safety Update Report
PT	prothrombin time
PVC	Polyvinylchloride
QTc QT	interval corrected for heart rate
RBC	red blood cell
RET	reticulocytes
RH	Relative Humidity
RV	residual variability
SAE	serious adverse event
SC	subcutaneous
SCr	serum creatinine
%SEM	standard error of the parameter estimate divided by the parameter estimate 100%
STZ	streptozotocin
SU	sulfonylurea
T1/2 or T1/2, z	terminal elimination half-life
T2DM	type 2 diabetes mellitus
TFA	triflouroacetate salt

TG	triglycerides
TLC	Thin Layer Chromatography
Tmax	time to reach Cmax
TS	tosylate salt
TZD	thiazolidinedione
ULN	upper limit of normal
UN	urea nitrogen
USP	United States Pharmacopoeia
UV	Ultraviolet
WBC	white blood cells

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 Incresync, 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:

Incresync is indicated to improve glycaemic control in adult patients (⩾ 18 years old) with type 2 diabetes mellitus:

- when diet and exercise plus pioglitazone alone do not provide adequate glycaemic control.
- in combination with metformin when diet and exercise plus dual therapy with pioglitazone and metformin do not provide adequate glycaemic control.

In addition, Incresync can be used to replace separate tablets of alogliptin and pioglitazone in those adult patients (⩾ 18 years old) with type 2 diabetes mellitus already being treated with this combination.

After initiation of therapy with Incresync, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, Incresync should be discontinued. In light of potential risks with prolonged pioglitazone therapy, prescribers should confirm at subsequent routine reviews that the benefit of Incresync is maintained (see section 4.4).

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/60/2008 on the granting of a class 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 repeated Scientific Advice from the CHMP during 2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Incresync has been given a Marketing Authorisation in Japan on 1 July 2011, in the US on 25 January 2013, and Mexico on 23 May 2013

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

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 reviewers: Harald Enzmann and Patrick Salmon

- 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 19

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 19 October 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 Incresync.

2. Scientific discussion

2.1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has increased dramatically throughout the world, and is expected to continue to rise 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 (i.e. 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 pioglitazone. The applicant proposed the following strengths: 25 mg/ 30 mg, 25 mg/ 45 mg, 12.5 mg/ 30 mg and 12.5 mg/ 45 mg. Alogliptin belongs to the class of DPP-4 inhibitors. Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist and member of the thiazolidinediones (TZD) class of oral antiglycaemic agents.

Pioglitazone is currently approved for use in the treatment of T2DM in 107 countries (including the European Union, the US, and Japan). The initial EU Marketing Authorisation for pioglitazone was granted in October 2000 via the centralized procedure and a 10-year renewal was approved in August 2010.

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.

For this MAA, key guidance documents considered in the design of the clinical development program included the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (CPMP/EWP/1080/00). The program is also largely consistent with the adopted revision 1 (CPMP/EWP/1080/00 Rev 1). Specifically relevant for this FDC is the Guideline on fixed combination medicinal products (CPMP/EWP/240/95). This guideline was in general followed.

2.2. Quality aspects

2.2.1. Introduction

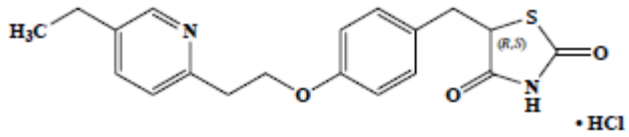
The finished product is manufactured as immediate-release, round, biconvex, film-coated tablets for once daily oral administration containing alogliptin (as benzoate) and pioglitazone (as hydrochloride) as active substances. Four tablet strengths are proposed for commercial use containing 12.5mg+30mg, 12.5mg+45mg, 25mg+30mg, or 25mg+45mg of alogliptin and pioglitazone, respectively. All strengths of the drug product have the same dimensions (diameter: approximately 8.7 mm; thickness: approximately 5.0 mm) and weight. The 4 strengths are distinguished by film color, printing ink color, and dose-specific imprinted markings on one side of the tablet.

The composition is further detailed in section 6.1 of the SmPC.

The product is available in aluminum blister strips using push-through aluminum lidding as described in section 6.5 of the SmPC.

2.2.2. Active Substance Pioglitazone

The active substance pioglitazone (INN) is a white crystalline powder, odourless, slightly bitter, melting at 193 C, freely soluble in dimethylsulfoxide, soluble in dimethlyformamide and methanol, sparingly soluble in solvents such as acetonitrile, acetone, insoluble in diethyl ether and hexane, practically insoluble in water. Partition coefficients were provided. Pioglitazone is non-hygroscopic. Pioglitazone has one asymmetric carbon but is manufactured as the racemate (optical rotation in dimethylformamide of 0.0°).Pioglitazone is crystalline but does not exhibit polymorphism.



The active substance is packed in well-closed polyethylene bags placed in fibre drums. Specifications for the packaging components are provided. The materials are in compliance with EU regulation 10/2011 and Ph. Eur. 3.1.11 where applicable.

Manufacture

The five-step chemical synthesis of pioglitazone (as hydrochloride) involves two main steps synthesis of a key intermediate and the conversion to pioglitazone hydrochloride and its subsequent purification. The synthetic routes used at all the manufacturing sites are identical. The equipment and process controls used at each site are very similar.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented. The molecular structure of Pioglitazone hydrochloride has been confirmed by Elemental analysis UV, IR, MS, 13C-NMR and 1H-NMR. Additional supportive data are provided by studies characterising the key intermediate in which the comparative IR absorption spectroscopy and X-ray diffraction data showed that the chemical and physical properties of the intermediates remain the same from all manufacturing sites. Equivalency was demonstrated including results for impurity profile and stability studies.

Pioglitazone hydrochloride has one asymmetric carbon but is synthesised as a racemate.

Information about related substances including potential genotoxic impurities, residual solvents and residual catalyst has been provided. Impurity level results show that most potential impurities are not detected or below the limit of quantitation and that the potential for carry-through of impurities and starting materials to the final drug substance is low. The impurity levels do not raise any safety concern. Comparative data demonstrate that the impurity profiles of intermediate and pioglitazone hydrochloride are similar for all manufacturing sites.

Specification

The specification for pioglitazone hydrochloride (applicable to all manufacturing sites) includes test for: description (visual), identification (IR, UV, HPLC, chloride ion test Ph.Eur.), heavy metals (Japan. Ph.), related substances (HPLC), residual solvents (GC), water (USP method), residue on ignition (USP), assay (HPLC) and particle size (laser diffraction). The analytical procedures have been described for each manufacturer of the final drug substance. Reference to compendial methods (USP, JP and Ph.Eur.) is made where relevant. The different manufacturers apply the same methods. Analytical methods have been described and non-compendial methods have been validated in accordance with ICH guidelines.

The specification is based on batch analyses of the drug substance prepared by the commercial process, and batches used for clinical, toxicological and stability studies. The limits established for the impurities including related substances, heavy metals, and residual solvents are in line with the relevant ICH guideline. The related substances are toxicologically qualified and do not raise any safety concern. With regards to the particle size, specification was set due to the low aqueous solubility of pioglitazone.

Stability

Stability studies have been performed on 17 batches obtained from the different manufacturers (six pilot-scale batches and 11 production-scale batches) in well-closed polyethylene packs

The parameters tested were description, identity, clarity & colour of solution, water content, assay, related substances and optical isomeric ratio. The methods were the same as for release testing; methods of parameters additional to release testing (e.g. optical isomer ratio) were described and validated.

Studies were conducted under long- term (25°C/60% RH) for up to 48 months, and accelerated (40°C/75% RH) for up to 6 months stability testing ICH conditions. In addition, stress stability testing was conducted under various conditions (heat, humidity, acid and basic, oxidising, and photostability). Photostability studies were in line with ICH requirements.

The analytical procedures were fully described, validated and stability indicating. All the stability batches were manufactured using the proposed route of synthesis.

No significant change could be observed under any of the storage conditions (long-term and accelerated). Similarly there were no significant changes under the specified stress conditions.

The stability data provided support the proposed the re-test period of 48 months when stored in the commercial storage container at a temperature not exceeding 30°C.

2.2.3. Active Substance Alogliptin

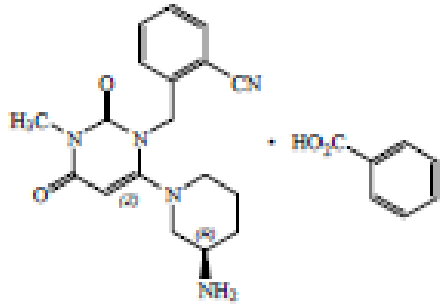
The active substance alogliptin benzoate (INN: alogliptin) is a white crystalline odourless powder, soluble in i.e dimethylsulfoxide, sparingly soluble in methanol, slightly soluble in e.g. tetrahydrofuran, and practically insoluble in e.g. toluene and diethyl ether. The aqueous solubility is high and independent of the 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 monobenzoateand 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 three 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.

Alogliptin benzoate is packaged in double low-density polyethylene (LDPE) bags closed by a plastic tie. The bags are then stored in a fiberboard drum for further protection. The information on the container closure system is considered acceptable and supports the stability of alogliptin benzoate. The plastic materials in direct contact with the substance are stated to be in compliance with the EU regulations.

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 ICH guidelines including ICH Q3A(R2) and ICH Q3C for residual solvents. The potential effect of particle size on the dissolution properties of alogliptin 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 °C), 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.

2.2.4. Finished Medicinal Product

Pharmaceutical Development

Alogliptin benzoate is identified as a single stable crystal form, which is manufactured for use in the finished product. Although particle size has been shown not to influence exposure to alogliptin, specifications are in place to control the particle size distribution of the active substance to ensure uniformity of content.

Pioglitazone is always obtained as a racemic mixture.Given its low aqueous solubility particle size limits have been established for the commercial pioglitazone. These limits provide adequate manufacture and controls to ensure consistent physical and biological properties of the drug product.

Key physicochemical characteristics of the active substances such as particle size distribution and stereochemistry are controlled through the respective specifications.

The two active substances have been shown to be chemically incompatible in mixtures under stressed and accelerated stability conditions; therefore, separate granulations were prepared and compressed into bi-layer tablets to minimize physical interaction between the drug substances.

All excipients are used in concentrations based on historical experience, and are conventional for their pharmaceutical function. The excipients are: mannitol, cellulose microcrystalline, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate. For the film-coating solution the excipients are: hypromellose , talc, titanium dioxide, iron oxide yellow, iron oxide red. For the polishing solution, macrogol is used and for the printing ink solution printing red and gray inks are used. Both substances alogliptin and pioglitazone demonstrate good compatibility with all excipients used in their respective granulations and with the excipients used for film-coating. Each excipient was chosen based on its required function for the formulation and on successful demonstration of compatibility with the relevant active substance. The amounts of excipients were selected based on experiments performed to study excipient ranges and their effects on drug product performance and manufacturability. All excipients are compendial (Ph.Eur, Commission Directive 95/45/EC or the USP/NF) except the printing inks. These inks are prepared from components that meet compendial specifications on an individual basis or comply with relevant regulatory standards.

During the formulation development, six dosage strengths were developed, containing 12.5 mg or 25 mg of alogliptin and 15 mg, 30 mg, or 45 mg of pioglitazone, in an immediate-release, fixed-dose combination (FDC), oral tablet. Only four strengths have been applied for in this submission. The development resulted in evaluation of 2 distinct formulations, both based on the requirement to separate the alogliptin and pioglitazone.

Formulation development proceeded in parallel with clinical development; co-administered individual alogliptin and pioglitazone tablets were used in the Phase III clinical program while the fixed dose combination product was being developed. As such, formulation development for the fixed dose combination product required demonstration of bioequivalence (BE) to the reference alogliptin and pioglitazone products.

The concentrations of the ingredients used in the film-coating were determined on the basis of historical knowledge gained by the applicant, and conventional pharmaceutical practice. The effect of film-coating on the dissolution of alogliptin was negligible, and was minimal for pioglitazone. There were no significant differences in the dissolution results observed between film-coated and uncoated tablets by the 10 minute sample time.

The dissolution profiles of alogliptin and pioglitazone from the bi-layer (BL) tablets (12.5mg+15mg and 25mg+45mg, respectively) were similar to those of the corresponding individual tablets. Equivalency was confirmed on laboratory-scale, pilot-scale and commercial-scale. Subsequently, comparative dissolution studies were performed that established the similarity of all dosage strengths relative to the 25mg+45mg strength, based on difference and similarity factors f1 and f2, which justifies the biowaiver for the intermediate strengths of BL tablets that were not tested in the in-vivo pivotal BE study.

The process for the manufacturing of the finished product followed conventional pharmaceutical practices, and consists of individual granulation of the active substances, mixing, tabletting and film-coating. The manufacturing steps were studied during the pilot-scale manufacturing campaigns. All results indicated that the operating parameters and ranges selected for these batches will produce acceptable product.

To ensure that manufacturing conditions used at the commercial scale are appropriate to produce BL tablets with properties equivalent to those achieved at the pilot scale, optimization studies were performed for the individual operations to develop the appropriate operating parameters for use with the larger commercial scale equipment. All equipment intended for commercial manufacturing was either the same or equivalent to that used during pilot scale manufacturing. All results from the commercial scale process optimization batches showed acceptable results for each manufacturing stage using the selected operating ranges.

The primary packaging consists of nylon/ aluminium /PVC (NYL/alu/PVC) blister strips using push-through aluminum lidding as described in the SmPC. The materials comply with the Ph.Eur. requirements and is adequate to support the stability and the use of the tablets.

Bulk packaging for the tablets included a primary heat-sealed polyethylene bag, a silica gel desiccant bag, a secondary heat-sealed, laminated aluminum bag, and a tertiary fiberboard or metal drum for storage and shipment to the commercial packaging facility. Stability in the bulk packaging has been established for 24 months.

Adventitious agents

The only component from animal origin is lactose monohydrate. It is certified that the magnesium stearate used will be of plant origin only. Furthermore, Takeda certifies that lactose monohydrate used is sourced from milk collected under the same conditions as that for human consumption and comply with the latest Note for Guidance on minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and veterinary medicinal products.

Manufacture of the product

The manufacture of the finished product is a standard process and consists of individual granulation of the active substances, mixing, tabletting and film-coating.

Consistency of the manufacturing process for the tablets is maintained by the combination of controls established for operating parameters and routine in-process tests of selected physical attributes of the process materials. Although no manufacturing steps are defined as critical, operating parameters of key processes are controlled, and testing of in-process materials is performed.

Validation of the commercial manufacturing process was performed to confirm the reproducible quality of the manufacturing process. The process consists of conventional pharmaceutical unit operations; therefore, the general properties were evaluated on three full-scale production batches of each strength manufactured under fixed processing conditions. All results demonstrated that the manufacturing process consistently produces a product that meets its pre-determined specifications and quality attributes.

Product specification

The release and shelf-life specifications for the 12.5mg+30mg, 12.5mg+45mg, 25mg+30mg, and 25mg+45mg of alogliptin and pioglitazone film-coated tablets include appropriate tests for: appearance (visual), identification (UV and HPLC), assay for each active substance (HPLC), content uniformity (Ph.Eur. 2.9.40), related substances (HPLC) and microbiological test (Ph.Eur. method). Analytical methods have been described and when non-compendial have been adequately validated in accordance with ICH Guideline, Q2B. The release and shelf-life specifications have been adequately justified based on product development, batch analyses, stability data for clinical and primary stability batches, and are in compliance with general pharmacopoeial standards (including Ph Eur) and ICH guidelines (Q3B and Q6A).

Batch analysis results were provided for 13 pilot-scale batches of the finished product (12.5mg+30mg, 12.5mg+45mg, 25mg+30mg, and 25mg+45mg of alogliptin+pioglitazone, respectively). Tests were performed using the same analytical procedures proposed for testing of commercial product, except for dissolution. All results met the proposed commercial specifications.

Stability of the product

Stability studies have been performed on three pilot-scale batches of each strengths 12.5mg+30mg, 12.5mg+45mg, 25mg+30mg, and 25mg+45mg of alogliptin and pioglitazone, respectively, in the proposed commercial package stored under long-term (25°C/60%RH) for up to 48 months, accelerated (40°C/75%RH) for 6 months according to ICH conditions. Photostability testing was conducted on one batch of each strength according to ICH Q1B guidance, Option 1. Based on results presented, the drug product is not sensitive to light.

Additional studies were performed under accelerated and long-term conditions for the bulk tablets packaged in an inner polyethylene bag sealed within an outer aluminum laminated bag with desiccant.

The parameters studied were appearance, assay, related substances, dissolution, hardness, and loss on drying for all time points; microbial examination at significant intervals (6 months at accelerated, annually at long term).

No significant change could be observed for any of the parameters tested. Three commercial-scale batches have been tested for 18 months under long-term storage and the results are satisfactory. Bulk stability studies showed that the product remained stable after 24 months under long-term and 3 months under accelerated conditions.

Based on the stability data generated, the proposed shelf-life for the tablets and storage conditions as stated in the SmPC are acceptable.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, and control applied to the active substances (pioglitazone and alogliptin) and the finished product has been presented in a satisfactory manner. The two active substances have been shown to be chemically incompatible in mixtures under stressed and accelerated stability conditions. Therefore, separate granulations were prepared and compressed into bi-layer tablets to minimize physical interaction between the drug substances.

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.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Incresync film-coated tablets is considered to be acceptable when used in the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of this fixed-dose combination tablets have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendation for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The alogliptin/ pioglitazone fixed-dose combination (FDC) tablet containing alogliptin and pioglitazone hydrochloride is being developed by Takeda for the treatment of type 2 diabetes mellitus (T2DM). Proposed strengths are 25 mg/ 30 mg; 25 mg/ 45 mg; 12.5 mg/ 30 mg; and 12.5 mg/ 45 mg.

Alogliptin is a potent and highly selective inhibitor of the dipeptidyl peptidase (DPP)-4 enzyme that is being developed as an antihyperglycaemic agent. 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.

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

Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist and member of the thiazolidinediones (TZD) class of oral antiglycaemic agents.

Pioglitazone is currently approved for use in the treatment of T2DM in 107 countries (including the European Union, the US, and Japan). The initial EU Marketing Authorisation for pioglitazone was granted in October 2000 via the centralized procedure and a 10-year renewal was approved in August 2010.

Pioglitazone is approved in the EU for the treatment of T2DM as monotherapy, as dual therapy in combination with metformin or a SU, as triple therapy in combination with metformin and a SU, or in combination with insulin. The Marketing Authorization (MA) for pioglitazone was granted by the European Commission in October 2000 and 5-year renewals received European Commission decisions in October 2005 and August 2010.

With the exception of minor editorial changes and the inclusion of three studies conducted to evaluate the in vitro protein binding of pioglitazone and its active metabolite AD-4833 M-IV with glimepiride to human serum albumin (HSA) as well as the toxicity studies conducted to evaluate the mechanism for bladder cancer in male rats, the written and tabulated summaries for pioglitazone are the same as those that were submitted with the pioglitazone/metformin FDC MAA in 2005. Five studies supported the evaluation of the mechanism for bladder cancer in male rats.

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.

Pioglitazone

The binding affinity of pioglitazone for recombinant human (h) PPARγ was examined in vitro by competitive binding assays. Pioglitazone demonstrated low micromolar affinity for PPARγ but not for PPARα. Assays for PPARα and PPARγ transactivation activity of pioglitazone indicated 50% effective concentration (EC50) values for hPPARγ1 of 420 nmol/L, 490 nmol/L, and 680 nmol/L. Pioglitazone produced rat PPARγ activation, with an EC50 value of 470 nmol/L. There was also some (relatively weak) activation of human PPARα by pioglitazone. There was no activation of human

retinoid X receptor (RXR)α or retinoic acid receptor (RAR)α by pioglitazone. Transactivation activity of hPPARγ was also demonstrated with metabolites M-II, M-III, and M-IV, with EC50 values ranging from 1.0 to 7.0 µmol/L.

Pioglitazone does not bind to insulin receptors. Pioglitazone appears to reduce insulin resistance by effects that are mediated at postbinding sites, but without increasing the expression of signaling molecules.

Insulin-stimulated glucose incorporation was increased in diaphragmatic muscle and adipocytes obtained from KKAy mice after dietary administration of pioglitazone. Insulin-stimulated glycogen synthesis and glycolysis were increased in soleus muscle preparations obtained from male Wistar fatty rats after administration of pioglitazone (3 mg/kg/day) for 10 days. Insulin sensitivity, glucose oxidation, and lipid synthesis were augmented when adipocytes prepared from the epididymal fat pads of the same animals were incubated in the presence of glucose. Pioglitazone also potentiated the action of insulin mimickers, such as vitamin K5 and vanadate in adipocytes obtained from pioglitazone treated male Wistar fatty rats. The hepatic activity of glucokinase was increased, glucose-6-phosphatase (G6Pase) was decreased, and pyruvate kinase activity was unchanged when pioglitazone was administered to Wistar fatty rats at 3 mg/kg/day and their lean litter mates at 10 mg/kg/day. Administration of pioglitazone (3 mg/kg/day) for 7 days accelerated the disappearance of exogenous TG from plasma and increased hepatic TG output in male Wistar fatty rats.

Daily treatment of male Zucker fatty rats with pioglitazone (10 mg/kg/day) decreased their fasting plasma glucose and insulin concentrations, normalized their responses to an oral glucose load, and increased the glycemic response to insulin. Administration of pioglitazone to Wistar fatty rats, at a dose of 3 mg/kg/day, improved glucose tolerance and insulin hypersecretion in response to oral glucose loading (2 g/kg) and augmented the glycemic response to exogenous insulin.
Pre-treatment for 7 days with pioglitazone (3 mg/kg/day) improved hepatic and peripheral insulin sensitivity as assessed by isotopic measurement of hepatic production and peripheral utilization of glucose in combination with euglycemic clamping.

The hypoglycemic and hypotriglyceridemic activities of (+), (-), and (±) pioglitazone after 7 days of treatment at 1 mg/kg/day have been compared using the Wistar fatty (insulin resistant) rat model of T2DM. No differences in pharmacological activity were observed.

Six metabolites (M-I, M-II, M-III, M-IV, M-V, and M–VI) of pioglitazone have been isolated from pioglitazone-treated animals and synthesized. The ability of each of the identified metabolites to reduce plasma glucose and TG was investigated in Wistar fatty rats dosed by the IP route. Metabolites M-II, M-III, and M-IV showed hypoglycemic and hypotriglyceridemic activities whereas metabolites M-I, M-V, and M-VI were inactive at doses up to the maximal dose tested (ie, 3 mg/kg/day). None of the pharmacologically active metabolites were as potent as the parent compound in lowering plasma glucose levels. M-II was more potent in lowering plasma TG levels and metabolites M-III and M-IV were only slightly lower in potency.

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.

Pioglitazone

Efficacy is apparent against hyperglycaemia, hyperinsulinemia, and hypertriglyceridemia in animal models of obesity/hyperglycaemia that mimic aspects of T2DM. Pioglitazone may also be effective in reducing the onset and severity of hypertension and nephropathy that occur in hyperinsulinemic states. The mechanism of action has yet to be clarified but involves modulation of intracellular signaling mediated via nuclear PPARγ. No potential has been identified for pioglitazone to elicit unintended pharmacological effects in non-target tissues.

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 μ mol/L. At concentrations up to 30 μ mol/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.

Pioglitazone

In vitro and/or in vivo studies were conducted to evaluate the effect of pioglitazone on the CNS, cardiovascular system, autonomic nervous system, renal function, and digestive system.

Doses of 100 and 300 mg/kg pioglitazone demonstrated slight anticonvulsive effects in male ICR mice whereas phenytoin significantly prevented seizures. No effects were noted at 30 mg/kg.

There were no pioglitazone-related effects on the autonomic nervous system in anesthetized cats.

At 100 μmol/L, pioglitazone produced a rightward shift in the concentration-response curve of the contraction of the isolated guinea pig ileum in response to acetylcholine, histamine, and barium and slightly inhibited the maximum contraction. Spontaneous motility of the isolated rabbit ileum was inhibited at a concentration of 100 μmol/L. Since these in vitro effects were not apparent at concentrations <100 μmol/L, there is a considerable margin of safety with respect to clinically attainable plasma concentrations of pioglitazone. Pioglitazone did not elicit unintended pharmacological actions when administered orally or intraduodenally at large multiples of the clinically relevant doses.

The potential for pioglitazone to modify cardiac action potential duration has not been evaluated; however, literature describes the effects of several antidiabetic TZDs on the action potential and membrane currents of rabbit ventricular myocytes. Pioglitazone had no significant effect on ventricular myocyte excitability, action potential configuration, or membrane currents over the concentration range 1 to 10 µmol/L.

AD-4833 (HCl) had no significant effect on gastric emptying in rats.

Pioglitazone had no significant effect on intestinal transport or urine volume or urinary excretion of sodium or potassium in rats.

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.

Pioglitazone

The effects of coadministration with pioglitazone and metformin, glibenclamide, or voglibose on diabetic indices were evaluated in Wistar fatty rats. Combination treatment with pioglitazone and insulin was evaluated in Goto-Kakizaki rats.

Oral administration of 1 mg/kg/day pioglitazone or 300 mg/kg/day metformin for 14 days decreased plasma glucose levels to 57% and 78% of control, respectively; coadministration of the same doses of AD-4833 (HCl) and metformin decreased plasma glucose levels to 38% of control. Combined treatment resulted in a marked reduction in hemoglobin A1 (82% of control).

Combined treatment with pioglitazone and glibenclamide markedly improved glucose intolerance and slightly suppressed the oversecretion of insulin.

Combined treatment with pioglitazone and voglibose decreased plasma glucose and TG levels more markedly than either compound separately. The combined treatment significantly decreased hemoglobin A1 levels, which were not decreased by either compound individually.

Combined treatment of both pioglitazone and insulin decreased plasma glucose, TG and cholesterol levels more markedly than treatment with AD-4833 or insulin separately. Combined treatment normalized hemoglobin A1.

Alogliptin combined with pioglitazone

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 [322/000178]. 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.

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 conduced 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.

Pioglitazone

The pharmacokinetics of pioglitazone were determined after oral or IV administration to mice, rats, dogs, and cynomolgus monkeys. Extensive pharmacokinetic evaluations were conducted in rats, dogs, and monkeys, since these were the major species used in the toxicology program. The concentrations of pioglitazone and its six identified metabolites in plasma samples from a number of nonclinical pharmacokinetic and toxicology studies in mice, rats, rabbits, dogs, and monkeys were assayed using validated and acceptable analytical methods.

Alogliptin combined with pioglitazone

A toxicity study showed no toxicokinetic interactions between alogliptin and pioglitazone after a single oral administration of alogliptin with pioglitazone to rats. Therefore, nonclinical pharmacokinetic studies were not conducted using a combination of alogliptin and pioglitazone as test articles.

2.3.3.2. Absorption

Alogliptin

Caco-2 permeability

Alogliptin has low permeability as the apparent permeability (Papp) coefficients were comparable to those of mannitol, which is a reference compound for low permeable compounds. The Papp 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 AUC0-24hr values. In rats, ~30% of the dose radioactivity was absorbed via the jejunal loop within 2 hours after administration of 14C-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 14C-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, Cmax and AUC0-24hr 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. Tmax 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 Tmax 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, AUC0-24hr 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.

Pioglitazone

Single-dose PO studies were conducted in mice, rats, dogs, monkeys and humans. Values for CL and volume of distribution were derived after a single IV dose of 0.5 mg/kg in rats, dogs, monkeys and humans.

Pioglitazone was well absorbed in the non-clinical species following oral administration of 0.5 mg/kg. Oral bioavailability was 81% in mice and monkeys, 85% in rats, 94% in dogs and 83% in humans. Hepatic first-pass effect was insignificant in rats, although an in vitro study did show that pioglitazone was partly metabolized in rat duodenum. In an absorption site study, pioglitazone was well absorbed from all segments of the gastro-intestinal (GI) tract, and absorption was greatest form the small intestine in rats.

Maximum plasma concentrations were achieved within 1, 4, 0.5, 4.3 and 1.5 hour of dosing in mice, rat, dog, monkey and human, respectively, indicating a slower rate of absorption in monkeys. The elimination of pioglitazone was rapid with an estimated T½ of 2.1-5.7 hours in all species. The volume of distribution was comparable across species, ~0.22-0.47 L/kg. Clearance was more rapid in dogs (~329 mL/h/kg) than in rat (~60 mL/h/kg), monkey (~77 mL/h/kg) or humans (~33 mL/h/kg).

The linearity of plasma kinetics of pioglitazone after single doses was examined in the rat over the concentration range 0.5 to 30 mg/kg. Cmax and AUC values increased with rising dose and were almost proportionally increased in relation to the dose increase.

Pharmacokinetics after repeated dosing were studied in male rats given 7 consecutive daily oral doses of 0.5 mg/kg radiolabeled pioglitazone HCl. The kinetics of total radioactivity were not changed by 7 days dosing at a pharmacologically relevant dose.

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.

Pioglitazone

Protein binding

[14C]pioglitazone exhibited relatively high (>98%) plasma protein binding in all species, including humans, and binding was broadly concentration-independent in all species.

Red blood cell partitioning

There was no preferential partitioning into red blood cells.

Tissue distribution

The volume of distribution of pioglitazone ranged from approximately 0.22 to 0.47 L/kg across species. These values were relatively small, suggesting that pioglitazone was not extensively partitioned into tissues, which was confirmed in tissue distribution studies with [14C]pioglitazone in male rats. Radioactivity was detectable in a wide range of tissues and the highest values were recorded at 6 hours after dosing except in the case of stomach. Except liver, tissue:plasma radioactivity ratios were less than one. These results indicated a wide distribution of [14C]pioglitazone without extensive uptake in any specific tissues. At 6 hours, the concentration of radioactivity in the liver was 1.60 µg equivalents/g and 0.97 µg equivalents/mL in plasma. Radioactivity declined to low but quantifiable levels by 24 hours and was undetectable except in Harder's gland, thyroid, liver, adrenal gland, kidney, and fat at 72 hours. In the pigmented rats, the 14C was distributed in the choroidea and skin (pigment) with relatively high concentrations but disappeared within 72 hours after dosing. In other tissues, no apparent differences were observed between albino and pigmented rats. After repeated dosing for 14 days, most tissues attained steady state exposure. The highest tissue concentrations were found in the liver and brown fat.

Placental transfer

Following oral administration, radioactivity was quickly absorbed and transferred to fetal tissues. Pioglitazone and metabolites M-II, M-III, M-IV, and M-V were quantifiable in fetal plasma. Radioactivity was consistently higher in maternal plasma than in fetal tissues, amniotic fluid and placenta.

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.

Pioglitazone

Pioglitazone exhibits chirality, with chiral inversion between (+) and (-)-enantiomers of pioglitazone observed in plasma of rats and humans. No obvious differences in the absorption and elimination between the two enantiomers were observed in rats.

In vivo, pioglitazone was extensively metabolized in all species investigated, including humans and the metabolic profile was found to be similar across species. Six metabolites were identified in animals and human plasma, urine, or feces samples, mainly arising from hydroxylation of the 2 side-chain attached to the pyridine ring of pioglitazone. After oral administration, all species, including humans, were systemically exposed to the active metabolite M-IV and to other metabolites. None of the pharmacologically active metabolites were as potent as parent compound in lowering plasma glucose. Humans were found to be primarily exposed to pioglitazone and M-IV, with less exposure to other metabolites. Mice, rats, dogs, and monkeys were also primarily exposed to pioglitazone and M-IV.

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.

Pioglitazone

Excretion balance data were provided for mice, rats, dogs, cynomolgus monkeys, and humans. Excretion was primarily urinary in the monkey but the fecal route predominated in the other species. Following oral administration of [14C]pioglitazone, excretion of radioactivity was rapid, with most excretion occurring within 24 to 48 hours post dose. Good recovery of radioactivity was observed in all studies. The primary route of elimination of total radioactivity after oral administration to mice, rats, dogs was via fecal excretion (76%, 63% and 81%, respectively), while in monkeys the primary route of excretion was urinary excretion (77%). (In humans urinary excretion was 32% and fecal excretion 39% in a study where total excretion of the administrated dose was 71%.) In all species, including humans, only a very small amount of unchanged pioglitazone was excreted into urine, indicating that renal clearance of pioglitazone was a minor elimination pathway, and that pioglitazone was mainly eliminated by metabolism. Following excretion into bile in rats, pioglitazone-related radioactivity was shown to be re-absorbed significantly.

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)

Pioglitazone

The effect of oral administration of pioglitazone at doses of 0.5, 3 and 30 mg/kg for 7 days on the activity of hepatic microsomal drug-metabolizing enzymes was investigated in male rats and compared with the inducible effects of phenobarbital. No changes in total hepatic CYP and cytochrome b5 levels, and activities of 4-nitroanisole O-demethylation, 4-nitrophenol hydroxylation, regio- and stereoselective testosterone hydroxylation, and 4-nitrophenol glucuronidation were observed. Thus pioglitazone was devoid of any induction effects on hepatic microsomal drug-metabolizing enzymes in this mode.

Competitive protein binding to human serum albumin (HSA) between pioglitazone and 12 concomitant drugs (glibenclamide, gliclazide, acetohexamide, buformin HCl, furosemide, manidipine HCl, delapril HCl, pravastatin, bezafibrate, cimetidine, digoxin and warfarin) was studied. Results indicated that there is no interaction in protein binding between pioglitazone and the 12 drugs at anticipated therapeutic concentrations.

The effects of pioglitazone on the in vitro binding of glimepiride to HSA were investigated. At about 10 times the therapeutic concentration of pioglitazone, the concentration of unbound glimepiride was slightly increased to 1.18-fold. The therapeutic concentration of pioglitazone did not affect the concentration of unbound glimepiride. These results show that the plasma protein binding of glimeripide did not change significantly with concomitant dosing with pioglitazone HCl in clinical use. Effect of glimepiride on the in vitro binding of pioglitazone and its active metabolite M-IV to HSA were investigated. The presence of glimepiride had no effect on the plasma protein binding ratio of pioglitazone and M-IV to HSA.

No transporter-based drug-drug interactions with pioglitazone have been conducted. Pioglitazone did not show any inhibition towards P-gp and BCRP in vitro.

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.

Toxicology studies conducted with pioglitazone include single- and escalating-dose studies in rats and monkeys; repeat-dose toxicity studies of durations up to 13 weeks in mice, and 1 year in rats, dogs, and monkeys; in vitro and in vivo genotoxicity studies; and reproductive toxicity studies. Two-year carcinogenicity bioassays were conducted in mice and rats. Special toxicity studies were conducted to further clarify urinary bladder, heart, and ovarian findings, to compare toxicities in lean vs fatty animals, and general toxicity and genotoxicity testing served to qualify the potential product impurities.

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.

Pioglitazone

There were no mortalities or abnormal clinical signs after oral dosing at doses up to 2000 mg/kg in mice or rats. Signs of acute intoxication were apparent within 5 to 30 minutes after an IP dose of ≥ 90 mg/kg in mice, and after a dose of ≥ 260 mg/kg in rats. Deaths occurred between Days 0 and 5 in mice after IP doses of 180 and 250 mg/kg and between Days 2 and 6 in rats at doses of ≥ 360 mg/kg. Calculated LD50 values derived following IP dosing were 181 mg/kg for mice of both sexes and 558 and 587 mg/kg for male and female rats, respectively.

Alogliptin combined with pioglitazone

Male Sprague-Dawley rats (3/group, 6 weeks of age) were administered oral gavage doses of 3.6 and 14.5 mg/kg pioglitazone, 30 and 100 mg/kg alogliptin, 100 mg/kg alogliptin with 3.6 mg/kg pioglitazone, and 30 mg/kg alogliptin with 14.5 mg/kg pioglitazone. There were no toxicokinetic interactions resulting from concomitant treatment with alogliptin and pioglitazone.

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.

Pioglitazone

Plasma volume expansion producing hemodilution (decreased RBC counts and decreased HCT and HGB) and eccentric cardiac hypertrophy occurred after repeated dosing in mice, rats, dogs, and monkeys, a response suggested being adaptive and compensatory in nature, and reversible. The plasma volume expansion appears to be a consequence of enhancement of the natriuretic properties of insulin resulting in increased Na retention mediated via the renal tubular Na+, K+ ATPase system. The NOAELs for Pioglitazone (HCl) derived from 52-week repeat-dose toxicity

studies were defined as the highest doses that did not produce increased heart weight, and were 1 mg/kg/day(rats), 1.1 mg/kg/day (male dogs), 3.4 mg/kg/day (female dogs), and 35.6 mg/kg/day (monkeys).

Changes in the size and location of fat depots and, at high doses, vacuolar and vascular changes in adipose tissue and changes in the bone marrow fat:cell ratio seen in rodents was considered to be due to an exaggeration of the pharmacological effect of pioglitazone. Enlargement of the liver seen after administration of high doses in mice and rats was not associated with elevation of liver enzymes or pathology. An approximately 2-fold elevation of ALT, when compared with concurrent control values, was reported for dogs treated with Pioglitazone (HCl) at 11.4 mg/kg/day for 3 months or one year but not at 10 mg/kg/day for 6 months. There were no associated histopathologic changes and ALT values were reversible.

Alogliptin combined with pioglitazone

Combination treatment with alogliptin and pioglitazone for up to 13 consecutive weeks in rats did not produce unanticipated toxicities, and did not exacerbate any pioglitazone-related findings.

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.

Pioglitazone

Pioglitazone was inactive in an Ames Salmonella microsomal plate incorporation assay using strains TA98, TA100, TA1535, TA1537 and TA1538 over the concentration range 250 to 2000 µg/plate. Negative results were obtained in an additional bacterial mutation assay in which concentrations over the range 156 to 5000 µg/plate were tested against E coli WP2uvrA and S typhimurium (strains TA100, TA1535, TA98, and TA1537). Pioglitazone was also negative at the tk locus (5-trifluorothymidine resistance) in mouse lymphoma cells.

In the CHO/HPRT and AS-52/XPRT mammalian cell forward mutation assays, there were no increases in mutation frequency in either cell line. An in vitro cytogenetic test using Chinese Hamster Lung (CHL) cells also proved negative. An unscheduled DNA synthesis (UDS) assay using primary rat hepatocyte cultures revealed no increase in UDS at concentrations up to 100 µg/mL.

A bone marrow micronucleus assay in mice given IP doses of pioglitazone, dissolved in DMSO, at 1250, 2500, and 5000 mg/kg, showed no statistically significant increases in micronuclei in polychromatic erythrocytes at any dose at any time point.

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.

Pioglitazone

There was no indication of any carcinogenic potential in mice. There was an increased incidence of urinary bladder benign/malignant transitional cell tumors in male rats administered doses of 4 mg/kg/day and higher.

Additional mechanistic studies were conducted to further evaluate the mechanisms of the bladder carcinogenesis observed in rats. Investigative studies were conducted to assess mRNA expression of the PPARs in the urinary bladder of rats, mice, and humans, to evaluate methodologies for detection of the microcrystals and hyperplastic changes, and to provide information about the optimal concentration for the acidified diet. These studies were followed by a 2-year mechanistic study in male rats that was conducted to provide evidence that the microcrystal hypothesis as described by Cohen was the causative factor of the urinary bladder hyperplasia seen in male rats . The chronic mechanistic study of the effects of pioglitazone with or without NH4Cl dietary acidification demonstrated that although the incidence of proliferative lesions in the urinary bladder was increased in rats administered pioglitazone, the incidence of advanced proliferative lesions, ie, carcinoma, papilloma, and/or nodular and papillary hyperplasia were suppressed when the urinary pH was lowered by feeding the rats an acidified diet.

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.

Pioglitazone

There was no effect of pioglitazone on male or female fertility in rat (NOEL for reproductive performance was 11.1 mg/kg/day - the highest dose used in the study).

Pioglitazone was not teratogenic in rats or rabbits. However, embryotoxicity, increased incidences of skeletal and visceral variants, retarded fetal growth and development, and delayed attainment of reproductive capacity were apparent. In rats Pioglitazone was embryotoxic at 44.9 mg/kg/day; fetal body weight and crown-rump length were decreased, and the incidences of skeletal and visceral variants were increased at 11.2 and 22.5 mg/kg/day. The body weight gains of the

offspring of rats treated at 22.5 and 44.9 mg/kg/day were reduced and the high dose animals required 3 breeding periods to achieve fertility rates that were comparable with control rates. In rabbits doses of 0, 44.5, 89.0, and 178 mg/kg/day administered on Days 6 through 18 of gestation embryotoxicity was only evident at the dose of 178 mg/kg/day pioglitazone and there was no evidence of developmental toxicity. The findings in the animal studies were suggested to be secondary to effects on the maternal organism via the pharmacological activity of Pioglitazone and not to be indicative of primary selective developmental toxicity.

Alogliptin combined with pioglitazone

Fertility and early embryonic development and pre- and postnatal development studies were conducted with alogliptin and pioglitazone alone; no additional studies were conducted with the combination alogliptin/pioglitazone.

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.

Pioglitazone / Alogliptin combined with pioglitazone

In a 4 week study pioglitazone induced hypertrophy of adipocytes in the brown adipose and bone marrow, and hyperplasia of the adipocytes in the white adipose tissue, changes which are considered to be due to the pharmacological action of this compound. The changes in adipocytes, together with decreased ovary weights, which were also seen in rats treated with pioglitazone alone, were also seen in rats after the combined alogliptin-pioglitazone treatment. However, the magnitude and incidence was similar after the combined treatment as compared to treatment with piaglitazone alone, indicating that there was no toxicological interaction between these compounds. Treatment-related changes were observed in the heart in males, bone marrow (femur and sternum) in both sexes, and brown and white adipose tissue in both sexes in a 13-week study, but again no

differences in magnitude or incidence were detected in rats treated with the combination as compared to rats treated with pioglitazone alone.

No toxicological interaction between alogliptin and pioglitazone was thus detected in the 4- and 13-week repeat dose toxicity studies performed. However, based on results obtained in an embryo-fetal toxicity study it is concluded that the combined administration of alogliptin and pioglitazone may potentiate the effects of pioglitazone alone in terms of fetal growth and most of visceral variation. No embryo-fetal mortality or fetal anomalies were induced in this study.

There was an increased incidence of urinary bladder benign/malignant transitional cell tumors in male rats at ≥4 mg/kg/day. Effects on urinary pH, crystalluria, and cell proliferation markers confirmed the absence of a marked hyperplastic response over 13-week dosing periods, but trends for increases in urinary pH and microcrystalluria were detected. Calculi obtained from affected rats were composed of amorphous material likely to be spontaneously precipitated in male rat urine with increased pH. This may be the result of chronic irritation following formation and retention of urinary bladder calculi and other urinary solids in male rats treated with pioglitazone and fed traditional rodent diet. This hypothesis was supported in a battery of mechanistic studies, including a 2-year study in which pioglitazone-related effects in the urinary bladder were evaluated in male rats fed diet that was acidified with NH_4Cl. The underlying non-genotoxic mechanism is considered to have no predictive significance for humans.

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.

Pioglitazone

No local tolerance studies were conducted with pioglitazone since the clinical formulation is an oral tablet.

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 were seen in the nonclinical 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 non-selective 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 behaviour and activity were observed in rats at doses of up to 300 mg/kg/day for 4 consecutive weeks.

2.3.4.8.5. Effects on peroxisome proliferation

Pioglitazone

Enzymatic activities of catalase and acyl CoA oxidase, primary enzymes that index peroxisome proliferation, were measured for pioglitazone, clofibrate (a typical PPARα agonist), and Wy-14643 (a potent PPARα agonist) in human derived liver cells (HepG2 and primary culture cells). Pioglitazone did not increase the enzymatic activity of the human hepatocyte peroxisome, and did not cause proliferation of peroxisomes.

2.3.4.8.6. Echocardiographic analysis of pioglitazone-induced cardiac hypertrophy

Pioglitazone

Echocardiography was used to investigate the morphological and functional changes in the hearts of male Sprague-Dawley rats after 2, 4, and 6 weeks treatment with pioglitazone at doses of 0, 4, 16, and 64 mg/kg/day and male beagle dogs treated at 64 mg/kg/day for 13 weeks. The echocardiography findings in both species were consistent with eccentric hypertrophy resulting from volume overload and quite distinct from the pattern associated with the concentric hypertrophy resulting from thickening of the ventricular wall because of pressure overload. There was no functional evidence of heart failure or histological evidence of myocardial damage, indicating that the echocardiographic changes were reflective of an adaptive or compensatory state that had not progressed to overt irreversible pathology.

2.3.4.8.7. Insulin sensitivity, plasma volume, and cardiac hypertrophy

Pioglitazone

Insulin is known to promote renal sodium retention in euglycaemic rats. Increased plasma and blood volume was apparent at 4 hours after a single dose and at 4 and 8 hours after 7 daily doses of long acting insulin (0.06 IU/kg) in male Sprague-Dawley rats. Increased heart weight, attributable to increased left ventricular mass, was also apparent after repeated dosing of insulin.

Pioglitazone had no effect on the in vitro rate of RNA synthesis in cultured cardiac myocytes and did not modify the extent of insulin-stimulated RNA synthesis in the same system. Heart weight was increased in male rats given 160 mg/kg/day for five weeks, but there was no change in the ratio of components (moisture:fat:fat free mass). There was also no change in the quantities of extracellular matrix components (fibronectin, laminectin) and transforming growth factor (TGF)β1 in the hearts of rats treated at 64 mg/kg/day for 2 weeks or 160 mg/kg/day for 5 weeks.

Increased plasma volume, with consequent hemodilution and increased heart weight was not apparent in male rats treated with pioglitazone (64 mg/kg/day) that were allowed access only to the same quantity of food as consumed by their controls. There was a slight increase in plasma volume, no hemodilution, and no increase in heart weight in rats with STZ-induced insulin deficiency even at a dose of 480 mg/kg/day. Treatment of Wistar fatty rats at 160 mg/kg/day for 12 days normalized blood glucose and increased plasma volume with resultant hemodilution, but heart weight remained similar to that of untreated rats. Administration of pioglitazone (160 mg/kg/day) to Goto-Kakizaki rats with relatively high plasma insulin levels, induced plasma volume increase, hemodilution, and increased heart weight but did not normalize plasma glucose.

Co-administration of the diuretic furosemide (30 mg/kg/day BID) did not affect the TG lowering activity of pioglitazone (160 mg/kg/day) but increased urinary sodium excretion and prevented or ameliorated the plasma volume increase, hemodilution, and cardiac enlargement induced by pioglitazone alone. In renal proximal convoluted tubules obtained from rats given pioglitazone (160 mg/kg/day) for 5 to 7 days, mean values (nmol/5 µg/hr) for Na+, K+ ATPase activity were 12.6±2.1 (controls) and 20.5±4.0 (pioglitazone, 160 mg/kg/day).

2.3.4.8.8. Estradiol and progesterone levels

Pioglitazone

Decreased ovary weights were noted in the 13-week toxicity studies in rats. In an in vitro study, there were no pioglitazone or rosiglitazone-related effects on the production of estradiol or progesterone from cultured rat ovarian cells. However, a concentration of 30 µmol/L, troglitazone suppressed estradiol and progesterone production along with morphological changes in the ovarian cells. In an in vivo study, there were no pioglitazone related functional changes in estrus cycle, plasma estradiol and progesterone levels, estradiol: progesterone ratios, or ovary weights. The Cmax and AUC values at the highest dose tested were 43.29 µg/mL and 601.9 µg·hr/mL, respectively.

2.3.4.8.9. 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.

Pioglitazone

The single dose toxicity of pioglitazone and its pharmacologically active metabolites M-II, M-III, and M-IV as well as its inactive metabolite M-V were compared after IP dosing in mice (ICR strain) of both sexes. The severity and incidence of signs inducible with pioglitazone metabolites at 250 mg/kg were either comparable to or not as severe as those seen with pioglitazone at the same dose.

In the light of the findings from the rat 2-year carcinogenicity study, the mutagenic potential of the main metabolites (M-I, M-IV, M-V, and M-VI) found in the urine of rats were evaluated. M-I, M-IV, M-V and M-VI showed no mutagenic potential in S typhimurium (strains TA100, TA1535, TA98, and TA1537) and E coli strain WP2uvrA.

Pioglitazone and its metabolites M-I, M-IV, M-V, and M-VI showed no structural alerts of carcinogenic potential using computer automated structure evaluation (CASE/MULTICASE) programs incorporating validated structure activity relationship (SAR) models.

2.3.4.8.10. 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.

Pioglitazone/Alogliptin in combination with pioglitazone

Pioglitazone-related impurities, designated related Substances I, II, and III, may be present in the clinical formulation. Related Substances II and III were present in the material used for the pivotal toxicity studies and are therefore qualified at the impurity levels set in the analytical specification. Related substance I was not detectable in the material used for toxicity tests. Neither impurity elicited a mutagenic response.

The impurity profiles of alogliptin drug substance and pioglitazone 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 Incresync (alogliptin/ pioglitazone 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

Based on the above results alogliptin doesn't meet the screening criterion for the bioaccumulation. It can be concluded that alogliptin is not qualifying for PBT (persistence, bioaccumulation, and toxicity) assessment.

Calculation of $PEC_{surface\ water}$

$$PEC_{SW} = \frac{DOSE_{ai} \cdot F_{pen}}{WASTEW_{inhab} \cdot DILUTION}$$

*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	(–)

Pioglitazone, a thiazolidinedione, is an authorised medicinal product in the European Union and has been marketed since 2000. The maximum daily pioglitazone dose is 45 mg and this dose was used in the initial calculations of the PECsurfacewater presented in Phase I, Estimation of Exposure of the ERA. The CHMP opinion on the ERA submitted in support of pioglitazone was that, "Overall pioglitazone is not considered to represent an environmental risk and no special precautions and safety measures are considered to be necessary".

Incresync is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus. Incresync will be available in different strengths; however, the maximum daily dose of 25 mg alogliptin and 45 mg pioglitazone will not be exceeded. Incresync will be used as an alternative to taking alogliptin and pioglitazone as separate medications.

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

2.3.5.2. Phase II, Tier A

The applicant performed a phase II Tier A ERA for alogliptin.

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.

Pioglitazone

Pioglitazone, a thiazolidinedione, is an authorised medicinal product in the European Union and has been marketed since 2000. The maximum daily pioglitazone dose is 45 mg and this dose was used in the initial calculations of the PECsurfacewater presented in Phase I, Estimation of Exposure of the ERA. The CHMP opinion on the ERA submitted in support of pioglitazone was that, "Overall pioglitazone is not considered to represent an environmental risk and no special precautions and safety measures are considered to be necessary".

No increased environmental exposure of pioglitazone hydrochloride is expected based on the use pattern of Incresync.

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 DPP4-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.

Pioglitazone

Pioglitazone is an orally active antihyperglycemic agent that acts as an insulin sensitizer. Both (+) and (-) pioglitazone are pharmacologically active and it has been established that epimerization, with attainment of equilibrium of chiral inversion, occurs in the plasma of humans and animals. Efficacy is apparent against hyperglycaemia, hyperinsulinemia, and hypertriglyceridemia in animal models of obesity/hyperglycaemia that mimic aspects of T2DM. Pioglitazone may also be effective in reducing the onset and severity of hypertension and nephropathy that occur in hyperinsulinemic states. The mechanism of action has yet to be clarified but involves modulation of intracellular signaling mediated via nuclear PPARγ. No potential has been identified for pioglitazone to elicit unintended pharmacological effects in non-target tissues.

Alogliptin in combination with pioglitazone

Combination pharmacodynamic studies showed additive and synergistic effects of concomitant treatment with alogliptin and pioglitazone.

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.

Pioglitazone

Orally administered pioglitazone is rapidly absorbed with high bioavailability, ranging from 81% in monkeys and mice to 94% in dogs, has a low volume distribution and is highly protein bound. The $T_{1/2}$ of the parent compound in plasma varies between 2 to 5 hours in animals as compared with 5 to 6 hours in humans, but the metabolites persist for longer durations in animals, especially in dogs. Excretion is predominantly fecal in mice, rats, and dogs, and urinary in monkeys. Tissue uptake in rats is low and depletes rapidly with the highest tissue concentrations being found in liver and fat. Six metabolites, that are all present in the plasma of mice, rats, dogs, and monkeys have been identified. The routes of biotransformation include cleavage of aliphatic bonds, hydroxylation of methylene groups, and oxidative reactions.

Alogliptin in combination with pioglitazone

When alogliptin and pioglitazone are administered concomitantly, there are no direct interactions expected on metabolism level. The effect of co-administration of alogliptin and pioglitazone on the absorption kinetics of both compounds could not be assessed as no 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. Interactions on the distribution level may occur as protein displacement may lead to a relatively large increase in the free fraction of pioglitazone. There were however no indications of protein displacement in the clinical setting. Further, as in humans both drugs are mainly eliminated via renal clearance interactions altering the excretion kinetics of alogliptin and/or pioglitazone cannot be excluded. As alogliptin is also excreted via other routes in the rat, this pre-clinical model is not a good predictive model of the clinical situation.

No transporter-based drug-drug interactions with pioglitazone have been reported. Pioglitazone did not show any inhibition towards P-gp and BCRP in vitro. A clinical drug-drug interaction study of pioglitazone with digoxin (as a substrate of P-gp) confirmed that pioglitazone is not an inhibitor of P-gp. A pivotal bioequivalence study of 12.5 mg alogliptin +15 mg pioglitazone and 25 mg alogliptin +45 mg pioglitazone bilayer tablets suggested that there are no drug-drug interactions between alogliptin and pioglitazone, consequently suggesting that there are no transporter-based drug-drug

interactions between these 2 drugs. Based on these results, it is concluded that the occurrence of clinically relevant interactions for alogliptin and pioglitazone at the transporter level is very unlikely.

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.

Pioglitazone

Single oral doses of up to 2000 mg/kg pioglitazone were well tolerated without manifestations of toxicity in rats and mice. Repeated dosing in mice, rats, dogs, and monkeys showed plasma volume expansion producing hemodilution and eccentric cardiac hypertrophy, which was adaptive and compensatory in nature, and reversible. The NOAELs for pioglitazone derived from the 52-week toxicity studies were defined as the highest doses that did not produce increased heart weight, and were 1 mg/kg/day (rats), 1.1 mg/kg/day (male dogs), 3.4 mg/kg/day (female dogs), and 35.6 mg/kg/day (monkeys). Safety monitoring during the clinical program has included echocardiography assessments that confirm the lack of adverse effects on cardiac morphology and function at therapeutic doses in the target patient population.

Pioglitazone increases insulin-stimulated glucose metabolism in muscle and adipose tissue and is a potent hypotriglyceridemic agent. Exaggeration was manifest in rodent studies as changes in the size and location of fat depots and, at excessively high doses, as vacuolar and vascular changes in adipose tissue and changes in the bone marrow fat:cell ratio.

Enlargement of the liver seen after administration of high doses in mice and rats was not associated with elevation of liver enzymes or pathology and most probably represented an adaptive response. A 2-fold elevation of ALT was reported for dogs treated with pioglitazone at 11.2 mg/kg/day for 3 months or 1 year but not at 10 mg/kg/day for 6 months. There were no associated histopathological changes and ALT values decreased on cessation of treatment.

Pioglitazone and its metabolites M-I, M-IV, M-V, and M-VI showed no genotoxic potential, and no carcinogenic potential in mice. There was an increased incidence of urinary bladder benign/malignant transitional cell tumors in male rats at $\geq$ 4 mg/kg/day. Effects on urinary pH, crystalluria, and cell proliferation markers confirmed the absence of a marked hyperplastic response over 13-week dosing periods, but trends for increases in urinary pH and microcrystalluria were detected. Calculi obtained from affected rats were composed of amorphous material likely to be spontaneously precipitated in male rat urine with increased pH. This may be the result of chronic irritation following formation and retention of urinary bladder calculi and other urinary solids in male rats treated with pioglitazone and fed traditional rodent diet. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded. Pioglitazone showed embryotoxicity, increased incidences of skeletal and visceral variants, retarded

fetal growth and development, and delayed attainment of reproductive capacity. No observable effect doses were defined and the data should be evaluated in the context of the physiological changes in insulin secretion and sensitivity that occur during pregnancy. Hyperinsulinemia and increased insulin resistance are normal features of pregnancy ensuring that competition between maternal and fetal tissues for glucose and carbohydrates is biased in favor of the fetus. Thus, stimulation of maternal insulin sensitive tissues in healthy animals by pioglitazone simulates the fetal growth syndrome reported in spontaneously increased insulin sensitivity. The findings in the animal studies are therefore secondary to effects on the maternal organism and not indicative of primary selective developmental toxicity.

Alogliptin in combination with pioglitazone

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. A combination of alogliptin with pioglitazone only showed a slight potentiation of foetal growth inhibition.

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

Pioglitazone

The CHMP opinion on the ERA submitted in support of pioglitazone was that, "Overall pioglitazone is not considered to represent an environmental risk and no special precautions and safety measures are considered to be necessary".

It can be concluded that no increased environmental exposure of pioglitazone hydrochloride is expected based on the use pattern of Incresync.

2.3.7. Conclusion on the non-clinical aspects

The applicant has investigated the non-clinical properties of alogliptin and pioglitazone 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 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 alogliptin

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Tabular overview of clinical studies

In addition to the clinical pharmacology program and to the studies already submitted for the application of the monoproduct alogliptin (Vipidia) the applicant included several studies concerning pioglitazone, which have already been included in the MAA for pioglitazone (Actos) and assessed by the CHMP preceding the authorization in 2000 and in several variations thereafter. Only a brief summary of the performed studies are mentioned here.

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 3 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 3)

All subjects were healthy unless otherwise stated.

The clinical pharmacology program for the Fixed Dose combination alogliptin/pioglitazone comprises 1 pivotal bioavailability study (study 322OPI-101) and a pivotal food effect studies (322OPI-006) and is supported by a drug-interaction study between alogliptin and pioglitazone (study 017) that was conducted as part of the alogliptin program. Additional supporting studies are 322OPI-005, 322OPI-007, 322OPI-102, 322-4833/CPH-001, and 322-4833/CPH-002).

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) Studies ongoing at the time of the evaluation of this application; interim results are presented in this document. At the time of the CHMP opinion for this procedure, the applicant has already made available a summary of the results from study 305 and confirmed that the results are in line with the interim data formally assessed in this report (however, a full assessment is pending and will be carried out once a final study report is available) and the clinical phase of study 402 has been already completed as the calculated number of events had been reached; a final study report of study 402 is expected to be available in the first quarter of 2014.

2.4.2. Pharmacokinetics

Pharmacokinetics of alogliptin and pioglitazone FDC tablet

Introduction

The application concerns a FDC of alogliptin and pioglitazone. Proposed strengths are 25 mg/ 30 mg; 25 mg/ 45 mg, 12.5 mg/ 30 mg, and 12.5 mg/ 45 mg.

The clinical pharmacology program for alogliptin/pioglitazone comprises 1 pivotal bioavailability study (study 322OPI-101) and 1 pivotal food effect study (322OPI-006) and is supported by a drug-interaction study between alogliptin and pioglitazone (017) that was conducted as part of the alogliptin program. Additional supporting studies are 322OPI-005, 322OPI-007, 322OPI-102, 322-4833/CPH-001, and 322-4833/CPH-002).

Pharmaceutical development

For the combination tablet, a bilayer formulation developed for the alogliptin/pioglitazone FDC, and 6 dose strengths of alogliptin/pioglitazone BL were used: A12.5+P15, A12.5+P30, A12.5+P45, A25+P15, A25+P30, and A25+P45. All 6 tablet strengths are of the same mass and size and contain the same quantities of inactive ingredients, with the exception of mannitol, lactose, titanium dioxide, and yellow and red iron oxides. The diluents mannitol and lactose are varied proportionally to coincide with the quantity of active ingredients in their respective layers; titanium dioxide and the iron oxides are varied to impart different colors to each dosage strength.

Bioequivalence

In study 322OPI-101, the pivotal BE study, the bioequivalence of alogliptin and pioglitazone when dosed orally as the highest proposed dosage strength (A25+P45) and lowest dosage strength that was developed (A12.5+P15) of the FDC product (alogliptin/pioglitazone BL), was compared with individual alogliptin and pioglitazone tablets.

- *Bioequivalency assessment of A12.5+P15 Tablets*

Plasma pharmacokinetic parameters of alogliptin and serum pharmacokinetic parameters of pioglitazone following administration of an A12.5+P15 tablet and co-administered individual alogliptin 12.5 mg and pioglitazone 15 mg tablets are presented in the table below. The 90% CIs for the ratios of the LS means for AUC(0-tlqc), AUC(0-inf), and Cmax values of both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the A12.5+P15 BL tablet met the standards for bioequivalence to individual alogliptin 12.5 mg and pioglitazone 15 mg tablets.

No statistically significant differences for the median T_{max} values for either alogliptin or pioglitazone were observed between the A12.5+P15 BL tablet, and individual alogliptin 12.5 mg and pioglitazone 15 mg tablets.

Table 3 Pharmacokinetic Parameters of Alogliptin and Pioglitazone Following Administration of an A12.5+P15 BL Tablet and Individual Alogliptin 12.5 mg and Pioglitazone 15 mg Tablets: Study 322OPI-101

		LS Mean		
Analyte (matrix) Parameter (units)	**N**	**A12.5+P15 BL (T)**	**Alogliptin 12.5 mg + Pioglitazone 15 mg (R)**	**Ratio T/R·100 (90% CI) (a)**
Alogliptin (Plasma)				
AUC(0-tlqc) (ng·hr/mL)	68	826.83	824.23	100.32 (99.00, 101.65)
AUC(0-inf) (ng·hr/mL)	66	904.72	904.17	100.06, (98.68, 101.46)
Cmax (ng/mL)	68	48.23	50.28	95.94 (91.83, 100.23)
Tmax (hr) (b,c)	68	3.00	2.99	N/A
Pioglitazone (Serum)				
AUC(0-tlqc) (ng·hr/mL)	68	5707.70	5774.19	98.85 (95.42, 102.40)
AUC(0-inf) (ng·hr/mL)	59	6399.01	6429.75	99.52 (96.58, 102.55)
Cmax (ng/mL)	68	612.22	626.25	97.76 (91.82, 104.08)
Tmax (hr) (b,d)	68	1.77	1.50	N/A

AUC(0-inf)=area under the concentration-time curve from time 0 to infinity, AUC(0-tlqc)=area under the concentration-time curve from time 0 to time of last quantifiable concentration, Cmax=maximum observed concentration, N/A=not applicable, R=reference treatment, T=test treatment, Tmax=time to reach Cmax.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as the median.
(c) p=0.586.
(d) p=0.264.

- *Bioequivalency assessment of A25+P45 Tablets*

Plasma pharmacokinetic parameters of alogliptin and serum pharmacokinetic parameters of pioglitazone following administration of an A25+P45 tablet and co-administered individual

alogliptin 25 mg and pioglitazone 45 mg tablets are presented in the table below. The 90% CIs for the ratios of the LS means for AUC(0-tlqc), AUC(0-inf), and Cmax values for both alogliptin and pioglitazone were within the 80% to 125% range. Therefore, the A25+P45 BL tablet met the standards for bioequivalence to individual alogliptin 25 mg and pioglitazone 45 mg tablets.

Table 4 Pharmacokinetic Parameters of Alogliptin and Pioglitazone Following Administration of an A25+P45 BL Tablet and Individual Alogliptin 25 mg and Pioglitazone 45 mg Tablets: Study 322OPI-101

		LS Mean		
Analyte (matrix) Parameter (units)	**N**	**A25+P45 BL (T)**	**Alogliptin 25 mg + Pioglitazone 45 mg (R)**	**Ratio T/R·100 (90% CI) (a)**
Alogliptin (Plasma)				
AUC(0-tlqc) (ng·hr/mL)	67	1582.33	1601.99	98.77 (97.58, 99.98)
AUC(0-inf) (ng·hr/mL)	66	1694.76	1719.46	98.56 (97.40, 99.74)
Cmax (ng/mL)	68	104.10	106.15	98.07 (93.33, 103.06)
Tmax (hr) (b,c)	68	2.50	2.98	N/A
Pioglitazone (Serum)				
AUC(0-tlqc) (ng·hr/mL)	67	14978.78	14369.87	104.24 (98.62, 110.18)
AUC(0-inf) (ng·hr/mL)	47	16789.67	15961.30	105.19 (98.19, 112.69)
Cmax (ng/mL)	68	1276.53	1303.92	97.90 (89.34, 107.28)
Tmax (hr) (b,d)	68	3.00	2.00	N/A

N/A=not applicable, T=test treatment, R=reference treatment,
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as the median.
(c) p=0.830.
(d) p<0.001.

Bioequivalence between the individual alogliptin 12.5 mg and pioglitazone 15 mg tablets and the A12.5+P15 BL was sufficiently shown in study 322OPI-101. Additionally, bioequivalence between the individual alogliptin 25 mg and pioglitazone 45 mg tablets and the A25+P45 BL was sufficiently shown. In all cases the 90% CI of the AUC and C_{max} was within the 80%-125% range.

Food interaction

The effect of food on the single-dose pharmacokinetics of alogliptin and pioglitazone when dosed orally as the highest proposed dosage strength (A25+P45) of the proposed commercial formulation of the FDC product (alogliptin/pioglitazone BL) was determined in study 322OPI-006.

Subjects who received the fed treatment were given a high-fat breakfast and were given 30 minutes to consume it. Study drug was administered immediately after completion of the meal. Subjects who received the fasted treatment continued to fast for at least 4 hours after dosing.

Plasma pharmacokinetic parameters of alogliptin and serum pharmacokinetic parameters of pioglitazone following administration of an A25+P45 BL tablet under fed and fasted conditions are presented in the table below.

Table 5 Pharmacokinetic Parameters of Alogliptin and Pioglitazone When Administered as an A25+P45 BL Tablet Under Fed and Fasted Conditions: Study 322OPI-006

			LS Mean		
Analyte (matrix) Parameter (units)	**N (T)**	**N (R)**	**A25+P45 BL Fed (T)**	**A25+P45 BL Fasted (R)**	**Ratio T/R·100 (90% CI) (a)**
Alogliptin (plasma)					
AUC(0-tlqc) (ng·hr/mL)	23	23	1508.08	1484.57	101.58 (99.02, 104.21
AUC(0-inf) (ng·hr/mL)	23	23	1630.19	1607.20	101.43 (99.05, 103.87
Cmax (ng/mL)	23	23	104.44	94.77	110.21 (101.61, 119.54)
Tmax (hr) (b,c)	23	23	3.00	2.00	N/A
Pioglitazone (serum)					
AUC(0-tlqc) (ng·hr/mL)	23	23	14493.66	14561.85	99.53 (90.87, 109.02
AUC(0-inf) (ng·hr/mL)	20	19	15210.31	15696.40	96.90 (87.05, 107.87
Cmax (ng/mL)	23	23	1531.59	1478.31	103.60 (90.49, 118.61
Tmax (hr) (b,d)	23	23	4.00	2.00	N/A

R=reference treatment, T=test treatment, N/A=not applicable.
(a) Ratios and CIs are presented as percentages.
(b) Tmax is presented as median.
(c) p=0.290.
(d) p<0.001.

The food interaction study (322OPI-006) with highest proposed dosage strength (A25+P45) of the proposed commercial formulation of the FDC product (alogliptin/pioglitazone BL) did not show any influence of food on the pharmacokinetics of pioglitazone and alogliptin as the 90% CIs for AUC and C_{max} of alogliptin and of pioglitazone were within the 80% to 125%. This was supported by food interaction studies 322-4833/CPH-001 and 322-4833/CPH-002 in Japanese subjects.

Interaction between alogliptin and pioglitazone

The effect of multiple doses of pioglitazone on the multiple-dose pharmacokinetics of alogliptin and M-I and the effect of multiple doses of alogliptin on the multiple-dose pharmacokinetics of pioglitazone were assessed in a randomized, multiple-dose, open-label, 6-sequence, 3-period crossover study (study 017). Thirty subjects enrolled in the study, and 27 subjects completed the study. Subjects were randomized to 1 of 6 treatment sequences and received alogliptin 25 mg once daily for 12 days, pioglitazone 45 mg once daily for 12 days, and alogliptin 25 mg + pioglitazone 45 mg once daily for 12 days. Study 017 showed that when alogliptin and pioglitazone (CYP2C8 substrate) were co-administered, no changes in the exposures to alogliptin, pioglitazone, or pioglitazone metabolites were observed.

Pharmacokinetics of alogliptin

Introduction

Four tablet strengths of alogliptin were developed: 3.125, 6.25, 12.5 and 25 mg. The 3.125 mg and the 6.25 mg dose strengths were developed for the purpose of dose reduction in patients with severe renal impairment, but the registration of these dose strengths is not being sought for the FDC alogliptin/pioglitazone. Instead the 12.5 mg dose strength is for patients with moderate renal impairment.

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.

Bioequivalence

Four formulations of alogliptin were used in the clinical program. The formulation of the phase 3 tablet that was used in the main studies and the proposed commercial tablet differed substantially. Bioequivalence between the alogliptin phase 3 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.

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.

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.

Inter-conversion: 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.

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.

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.

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

Pharmacokinetics in target population: Exposure to alogliptin is similar in subjects with T2DM and healthy subjects.

Special populations

Renal impairment: Exposure to alogliptin increased with increasing severity of renal impairment. Peak exposure (C_{max}) 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 ($AUC_{(0\text{-}inf)}$ 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 T_{max} 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 C_{max} 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.

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 MATE 2. 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.

Effect of alogliptin on other drugs: 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.

Effect of other drugs on 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.

Pharmacokinetics of pioglitazone

General pharmacokinetics (ADME)

Pioglitazone is synthesized and used as a racemic mixture. The 2 enantiomers of pioglitazone interconvert *in vivo*; no differences were found in the pharmacologic activity of the 2 enantiomers. Pioglitazone is absorbed rapidly following oral administration, and peak serum concentrations of unchanged pioglitazone are usually reached within 2 hours after administration. Proportional increases in serum concentrations were observed with doses from 2 to 60 mg. Steady state is achieved after 4 to 7 days of dosing. Absorption is not influenced by food intake. The absolute bioavailability of pioglitazone is approximately 83%. Repeated dosing does not result in accumulation of pioglitazone or metabolites. The Vz of pioglitazone is approximately 19 L. *In vitro*

distribution of [^{14}C]pioglitazone into human red blood cells was minimal. Pioglitazone and all active metabolites are extensively bound to plasma protein (>99%).

Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via CYP2C8, although other isoforms may be involved to a lesser degree. Renal elimination is negligible. Three of the 6 identified metabolites are active (M-II, M-III, and M-IV). Pioglitazone metabolites M-III (a keto derivative of pioglitazone) and M-IV (a hydroxyl derivative of pioglitazone) are the major circulating active metabolites in humans and are pharmacologically active. The overall mean recovery of radioactivity in feces + urine was approximately 71% (38.5% excreted in feces [55% of the recovered label] and 32.1% excreted in urine [45% of the recovered label]). The mean serum $T_{1/2}$ of unchanged pioglitazone is 5 to 6 hours, and the mean serum $T_{1/2}$ for its total active metabolites is 16 to 23 hours.

Intrinsic factors

Total exposure $AUC_{(0\ inf)}$ to pioglitazone was approximately 20% higher in elderly (≥65 years of age) subjects than in young subjects (≤50 years of age). Mean AUC and C_{max} values for pioglitazone and its metabolites were 20% to 60% higher in female subjects than in male subjects, and elimination rate constants and oral clearance values of pioglitazone were 25% to 40% lower.

Overall, these small changes in the pharmacokinetics of pioglitazone are not considered clinically relevant, and no dose adjustments based on age or sex are required; however, pioglitazone should be started at the lowest available dose and increased gradually in elderly patients.

Peak exposure (C_{max}) to pioglitazone was 18% and 38% lower in subjects with moderate and severe renal impairment, respectively, than in healthy subjects after 10 days of once daily dosing. Total exposure (AUC) to pioglitazone in subjects with renal impairment decreased with decreases in renal function, and was 12% and 40% lower in subjects with moderate and severe renal impairment, respectively. The AUC of pioglitazone decreases with decreasing renal function. Despite the apparent lower exposure to pioglitazone, no dose adjustment is needed for patients with mild to severe renal impairment (CrCL >4 mL/min); however, pioglitazone was not studied in subjects on hemodialysis, and therefore should not be used in this population.

C_{max} values of pioglitazone in subjects with hepatic impairment were approximately 50% of those of healthy subjects. The volume of distribution in subjects with hepatic impairment was approximately 55% higher and the elimination rate constant was approximately 42% slower in subjects with hepatic impairment. Peak and total exposure to M-III were lower in subjects with hepatic impairment than in healthy subjects. Peak exposure to M-IV was similar in both groups, but total exposure (AUC) was approximately 20% higher in subjects with hepatic impairment than in healthy subjects. The differences in exposure to these metabolites suggests impaired oxidative biotransformation of M-IV to M-III in subjects with hepatic impairment. Peak exposure to the total active compounds (unchanged pioglitazone + M-III + M-IV) was approximately 50% lower in subjects with hepatic impairment than in healthy subjects, but total exposure was similar in both groups. It is recommended that pioglitazone not be used in patients with any degree of hepatic impairment.

Interactions

No clinically meaningful changes in exposure to a number of drugs that are metabolized by CYP isozymes, transported by Pgp or OCT2, or excreted unchanged in urine were observed when these drugs were administered with pioglitazone.

No clinically meaningful changes in exposure to pioglitazone were observed when it was administered with a number of drugs that are CYP, Pgp, or OCT2 substrates; excreted unchanged in the urine; or CYP inhibitors or inducers, except for the following:

Co-administration of pioglitazone with gemfibrozil (an inhibitor of CYP2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycemic control should be considered.

Coadministration of pioglitazone with rifampicin (an inducer of CYP2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered.

2.4.3. Pharmacodynamics

Pharmacodynamics of alogliptin were investigated in 7 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 to 800 mg.

Study CHP-001 was a single dose study including lower dosages of alogliptin (6.25 mg – 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 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.

The applicant, as also being the MAH for Pioglitazone, re-submitted the pharmacodynamics studies of pioglitazone. Additionally, the pharmacodynamics of pioglitazone were derived from the labeling and scientific literature of pioglitazone.

Mechanism of action

Alogliptin and pioglitazone have complementary mechanisms 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.

Pioglitazone is a PPAR-gamma agonist, and decreases both fasting and postprandial glucose, which may improve glucose metabolism and reduce insulin sensitivity in patients with T2DM.

Primary and Secondary pharmacology
Alogliptin

DPP-4 inhibition

Based on current literature, DPP-4 inhibition of ≥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]. E_{max} and T_{max} 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], E_{max} 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). E_{max} and T_{max} 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 (002), E_{max} was >93% for all dose groups (25, 100, and 400 mg), with T_{max} of approximately 1 hour on Day 1 and 1 to 2.5 hours after 14 days of once-daily dosing (Day 14). E_{max} and T_{max} 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.

NONMEM modeling that combined a 2-compartment, first order absorption pharmacokinetic model with an E_{max} pharmacodynamic model confirmed the potency of alogliptin as an inhibitor of DPP-4 activity with a predicted E_{max} value of 96.2% and a predicted EC50 value of 3.73 ng/mL in healthy subjects in *study 001* and a predicted E_{max} 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 (study 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).

Pioglitazone

Once daily doses of pioglitazone reduced both fasting blood glucose and postprandial glucose levels in subjects with T2DM. This hypoglycaemic effect was maintained throughout the day, and was observed as early as 2 weeks after the start of treatment.

Multiple-dose pharmacodynamics of pioglitazone in subjects with T2DM were evaluated in 2 studies. In these studies, the effects of once-daily doses of pioglitazone 15, 30, and 60 mg on fasting insulin, postprandial insulin, and C-peptide were evaluated. For fasting insulin, there were no significant changes from baseline for all 3 doses. Average insulin over the 12-hour postprandial period showed an 18% reduction from baseline with the 30 mg dose and a 20% reduction from baseline with the 60 mg dose, while the 15 mg dose did not produce significant changes.

2.4.4. Discussion on clinical pharmacology

Alogliptin/pioglitazone combination tablets

In study 322OPI-101, the pivotal BE study, the bioequivalence of alogliptin and pioglitazone when dosed orally as the highest proposed dosage strength (A25+P45) formulation and lowest dosage strength that was developed (A12.5+P15) of the proposed commercial FDC product (alogliptin/pioglitazone BL), was shown with individual alogliptin and pioglitazone tablets.

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 scientific advice.

The applicant used as reference tablet in the pivotal bioequivalence study of the FDC the phase 3 formulation of alogliptin, which had been shown in study 027 of the original alogliptin dossier to be bioequivalent to the proposed commercial formulation of alogliptin. The applicant showed sufficiently that the risk of drifting is minimal. In addition, since alogliptin has a bioavailability of near 100% (Study 103), exhibits high solubility, and has very rapid in vitro dissolution characteristics, it may be considered to be a BCS class 1 substance, therefore the approach of the applicant is acceptable.

The applicant included pharmacodynamic studies concerning piogitazone, which already have been assessed by the CHMP in the MAA for pioglitazone (Actos) preceding the authorization in 2000. No specific pharmacodynamic studies were performed with the combination of alogliptin and pioglitazone or the FDC. This is acceptable, since it is not mandatory and phase 3 studies with the combination were included (see efficacy section).

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 reached after 1-2 hours after administration. Bioequivalence between the alogliptin phase 3 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 strengths.

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 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.

In healthy Japanese subjects, the levels of active GLP-1 appear lower than those observed in the healthy volunteers. However, since these differences are observed in the alogliptin groups and the placebo groups, the differences are unlikely to be related to racial differences, but to aspects of the assay, which was conducted with different batches of the kit and in different laboratories.

Subjects with severe hepatic impairment were not evaluated; therefore alogliptin is not recommended for patients with severe hepatic impairment (Class C). The FDC alogliptin/pioglitazone cannot be used in patients with hepatic impairment based on the pioglitazone component, which is contraindicated in patients with hepatic impairment as stated in sections 4.2, 4.3 and 4.4 of the SmPC. Increased exposure to alogliptin is observed in patients with renal impairment, and therefore the applicant proposes dose reduction in these patients. However, the applicant did not apply for an indication for the FDC in patients with severe renal impairment or ESRD.

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 included in section 5.2 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The applicant performed several clinical pharmacology studies to show the pharmacokinetics and pharmacodynamics of alogliptin and pioglitazone, separately and combined. Additionally, specific for the combination product one pivotal bioavailability study and one pivotal food effect studies were submitted. The pharmacodynamic study results of pioglitazone were in line with the already published literature.

Pharmacokinetics and pharmacodynamics were sufficiently investigated in the view of the CHMP.

2.5. Clinical efficacy

An overview of the performed studies is shown in the two tables below. Table 6 shows studies relevant for the Fixed Dose Combination; in table 7 other trials performed with alogliptin are described.

In support of this FDC application, five studies have been submitted (see table 2): study 009 and study 322OPI-004 were main studies: 322OPI-001 and 322OPI-002 were submitted as supportive trials; study 010 is included to show the efficacy and safety of alogliptin as monotherapy.

The total clinical development program for alogliptin (Vipidia) 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 3 studies and 7 supportive phase 3 studies (tables 2 and 6).

Table 6 Overview Studies relevant for Fixed Dose Combination

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
Phase 2 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			
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
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
Main Phase III, Long-Term, Active-Comparator Studies			
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 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.	803	A25+P30 once daily or P45 once daily (titrated from P30) Randomization ratio: 1:1
Supportive Phase III Studies			
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
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

Table 7 Overview other phase 3 alogliptin studies

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
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
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
11 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
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
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 exercise Alone; 6.5% to 8.0% if on oral monotherapy. Change from baseline in HbA1c at Week 52.	441	A25 once daily or Glipizide 5 mg once daily (titrated to 10 mg for inadequate control) 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
Study	**Design, Key Inclusion Criteria, and Primary Endpoint**	**N**	**Treatment**
Other Supportive Phase III Studies (continued)			
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	71	A25 once daily A25+P30 once daily Placebo once daily Randomization ratio: 1:1:1

Study	Design, Key Inclusion Criteria, and Primary Endpoint	N	Treatment
	the plasma concentration-time curve changes for triglycerides at Week 16.		

(a) Studies were, at the time of evaluation of this application, ongoing studies.

2.5.1. Dose response study

No separate dose response studies were performed for the FDC. Dose selection for the FDC was based on alogliptin dose-range studies and approved doses of pioglitazone.

Alogliptin

Results from the phase 1 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 below). HbA1c levels were not significantly reduced with alogliptin 6.25 mg, which is likely due to lack of optimal DPP-4 inhibition.

Table 8 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 3 clinical program. 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.

Pioglitazone

The strengths of the pioglitazone component were mainly based on the approved dose range of pioglitazone (15 to 45 mg). In Europe, the treatment paradigm for antidiabetic therapy requires that a dose of antidiabetic medication be maximized before another antidiabetic medication is added. As such, in the 2 main studies for the alogliptin/pioglitazone FDC, alogliptin was added on to background pioglitazone therapy, which was usually pioglitazone 30 or 45 mg. Therefore, both higher pioglitazone dose strengths (ie, 30 and 45 mg) are being proposed for the FDC, and approval was not being sought for a FDC formulation containing alogliptin in combination with pioglitazone 15 mg. This was found to be acceptable by CHMP.

2.5.2. Main studies

Methods and study design

Study 009 was a 26-week, multicentre, randomised, double-blind, placebo-controlled study in T2DM on pioglitazone or rosiglitazone, with or without metformin or SU. Both 12.5 mg and 25 mg alogliptin was used as active study compounds. 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 TZD with or without metformin or SU. Subjects underwent a 4-week Run-in/Stabilization Phase during which they were stabilized on a dose of 30 or 45 mg pioglitazone (or MTD), ≥1500 mg MET (or maximum tolerated dose [MTD]). The specific indication of add-on treatment to TZD with SU is not being sought in Europe.

Change from baseline in HbA1c was the primary endpoint. 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.

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.

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 uptitration 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 a 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%). Subjects were treated with alogliptin 12.5 or 25 mg or placebo. Change from baseline in HbA1c was the primary endpoint. 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.

Study Participants

Studies 009, 322OPI-004 and 010

Subject demographics and baseline characteristics of studies 009, 010 and 322OPI-004 are shown in the table below.

A total of 1296 subjects were randomized into the 2 main phase 3 studies 009 and study 322OPI-004 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). Mean age in both studies was 55 years. In these 2 studies, 229 (18%) randomized subjects were elderly (≥65 years), with 24 subjects (2%) at least 75 years of age. The majority (67%) of all randomized subjects were White. Mean BMI for all randomized subjects was 32 in Study 322OPI-004 and 33 in study 009. Overall, the characteristics of the study population were consistent with the general T2DM population in the EU. Duration of T2DM was 7.16 years in Study 322OPI-004 and 7.58 years in study 009.

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 9 Subject Demographics and baseline Characteristics (studies 010, 009)

	Study 010 Monotherapy			Study 009 Add-on to TZD, with or without MET or SU		
Category	**Placebo N=65**	**A12.5 N=133**	**A25 N=131**	**Placebo N=97**	**A12.5 N=197**	**A25 N=199**
Sex, n (%)						
Men	33 (50.8)	65 (48.9)	77 (58.8)	53 (54.6)	109 (55.3)	125 (62.8)
Women	32 (49.2)	68 (51.1)	54 (41.2)	44 (45.4)	88 (44.7)	74 (37.2)
Age (years)						
Mean (SD)	53.8 (10.99)	52.6 (12.01)	54.2 (10.16)	55.2 (10.82)	55.5 (9.37)	55.4 (10.16)
Min, Max	35, 80	24, 77	31, 80	24, 80	36, 78	25, 80
BMI						
Mean (SD)	32.17 (5.748)	31.82 (5.166)	32.16 (5.915)	33.23 (6.192)	32.34 (5.698)	33.06 (5.379)
HbA1c						

Mean (SD)	8.03 (0.910)	7.91 (0.810)	7.91 (0.788)	7.97 (0.818)	8.08 (0.910)	8.01 (0.837)
Duration of T2DM (years)						
Mean (SD)	4.32 (5.286)	3.09 (3.825)	2.82 (3.016)	7.76 (6.667)	7.68 (5.585)	7.38 (5.350)
Median	2.67	1.92	1.67	6.50	6.33	6.17

Table 10 Subject Demographics and baseline Characteristics (322OPI-004)

	Study 322OPI-004 Add-on to PIO/MET		
Characteristic	**MET+A25+P30 N=404**	**MET+P45 N=399**	**Total N=803**
Sex, n (%)			
Men	210 (52.0)	204 (51.1)	414 (51.6)
Women	194 (48.0)	195 (48.9)	389 (48.4)
Age			
Mean (SD), yr	54.3 (9.86)	55.9 (9.94)	55.1 (9.93)
<65 years, n (%)	339 (83.9)	320 (80.2)	659 (82.1)
≥65 years, n (%)	65 (16.1)	79 (19.8)	144 (17.9)
≥75 years, n (%)	5 (1.2)	7 (1.8)	12 (1.5)
BMI			
Mean (SD)	31.52 (5.243)	31.58 (5.177)	31.55 (5.210)
HbA1c	n=303 (a)	n=306 (a)	-
Mean (SD)	8.25 (0.820)	8.13 (0.832)	-
T2DM duration, yr			
Mean (SD)	7.47 (5.248)	6.85 (4.611)	7.16 (4.946)
MET dose (mg)			
Mean (SD)	1867.9 (476.71)	1847.6 (494.12)	1857.8 (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.

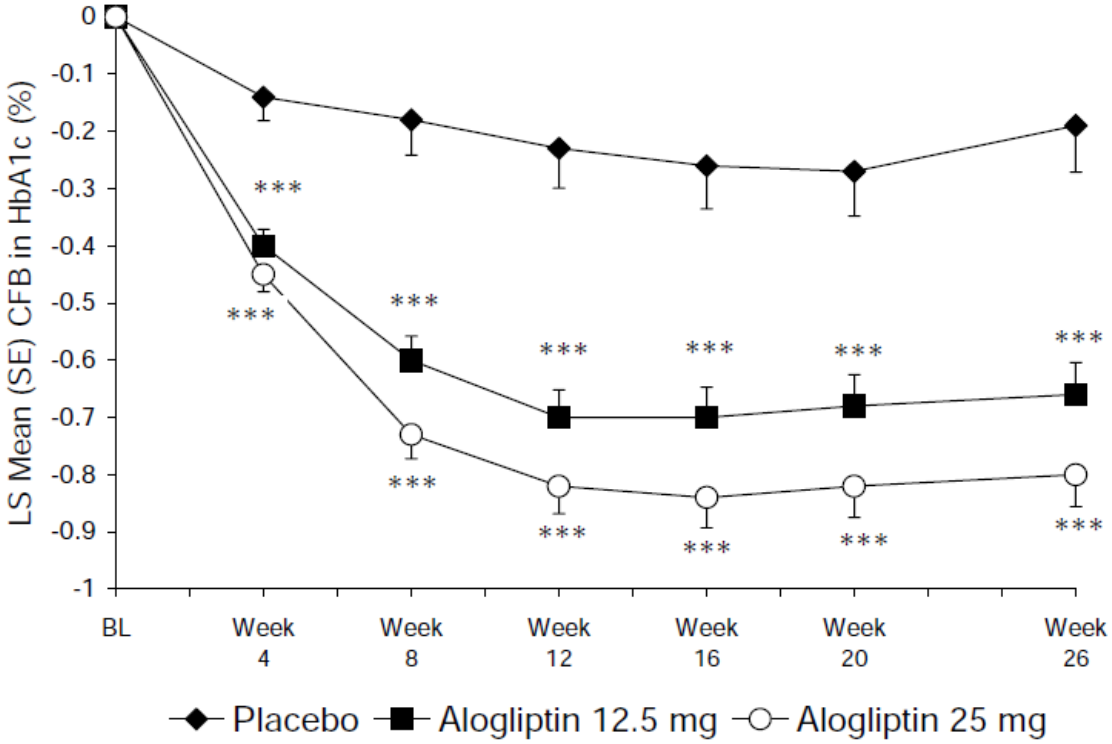
Outcomes and estimation

Primary outcome parameters:

Glycosylated Haemoglobin (HbA1c):

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 (figure below). 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. The positive clinical response of add-on therapy to TZD and MET is confirmed in study 322OPI-004, as described below.

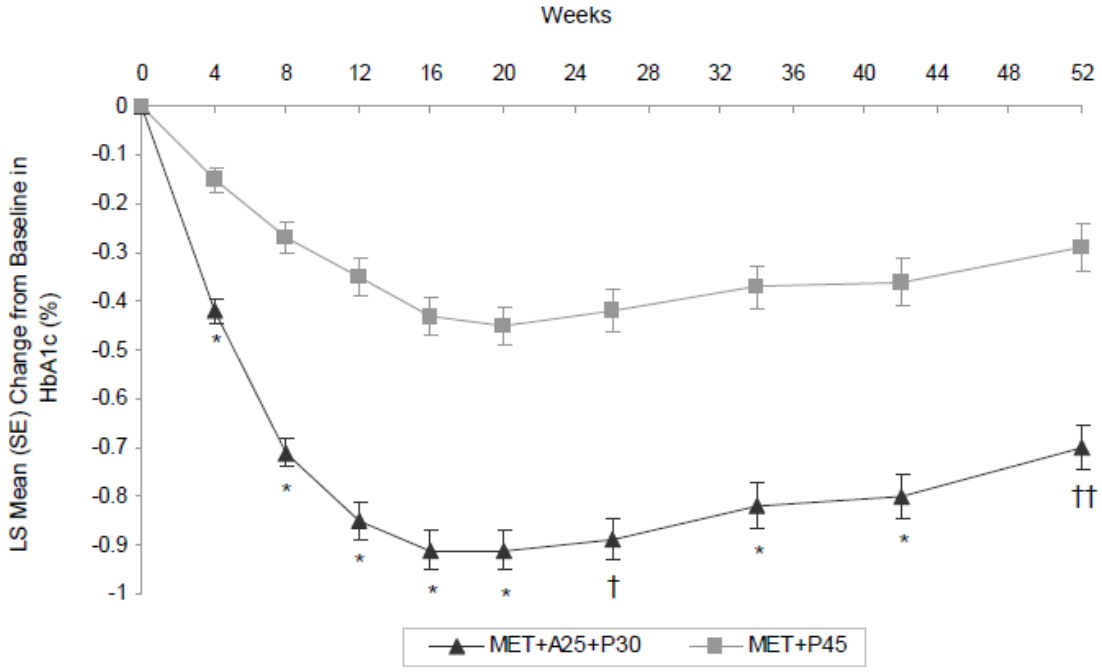
Figure 1 Study 009 (add-on to TZD): Change from baseline in LS Mean of HbA1c (%) by Visit—Full Analysis Set



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

In the long-term, active-controlled **study 322OPI-004**, greater LS mean reductions from baseline in HbA1c were observed in the alogliptin group than in the comparator group at Weeks 26 and 52, and alogliptin efficacy was shown to be sustained for up to 52 weeks. 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 below).

Figure 2 LS Mean (SE) Changes From baseline in HbA1c (%) (LOCF, PPS), study 322OPI-004



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.

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 11 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

Secondary outcome parameters:

Secondary endpoints include clinical response, FPG, changes 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 study 009, a higher percentage of subjects in both alogliptin groups achieved these clinical response endpoints at Week 26 than in the placebo group (44.2%, 49.2% and 34.0% in the A12.5, A25 and placebo groups respectively). Differences from the placebo group were statistically significant ($p \leq 0.016$). 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%; $p<0.001$).

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%).

Change from baseline in FPG

In study 009, LS mean decreases in FPG observed in alogliptin-treated subjects were statistically significant compared with the placebo group for the alogliptin 25 mg group and alogliptin 12.5 mg group (-1.09, -1.10 and -0.32 in the A12.5, A25 and placebo group respectively). 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 ($p<0.01$).

In study 010, at Week 26, subjects in the A12.5 and A25 groups achieved statistically significant LS mean decreases in FPG (-0.57 and -0.91 mmol/L, respectively) compared with subjects in the placebo group (+0.63 mmol/L) ($p<0.001$).

Body weight and serum lipids

In study 009, results suggest that treatment with alogliptin is weight neutral. Following 26 weeks of treatment, there were no meaningful differences in LS mean changes in body weight between the placebo group (1.04 kg) and A12.5 and A25 groups (1.46 and 1.09 kg, respectively). In study 322OPI-004, mean changes in body weight were consistent with the concomitant medication (ie, 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. 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).

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.

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).

Tabular summaries of efficacy for main clinical trials are shown in Table 12, Table 13 and Table 14.

Table 12. Summary of Efficacy for 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

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)			
		p-value	<0.001	<0.001
Notes	None.			

Summary of Efficacy for Study 010 (continued)

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)			
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 13. Summary of Efficacy for Study 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

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)
Notes	None.

Summary of Efficacy for Study 009 (continued)

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)			
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 14. Summary of Efficacy for 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 noninferiority 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

Summary of Efficacy for Study 322OPI-004 (continued)

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)			
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.			

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

No specific subpopulation investigations have been conducted with alogliptin/pioglitazone; 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.

Evaluation of change from baseline in HbA1c was conducted for subgroups defined by sex, age group (<65, ≥65, ≥75 years), race, and baseline BMI (<30 and ≥30). These subgroup analyses were for exploratory purposes and no formal statistical hypothesis testing was performed. The analyses demonstrated that regardless of age, sex, race, and baseline BMI, alogliptin continued to have clinically meaningful reductions in HbA1c compared with placebo in study 009 and study 322OPI-004. This was also seen in the supportive studies 322OPI-001 and 322OPI-002.

Elderly

A total of 559 subjects ≥65 years (16%) were enrolled in the 2 main and 2 supporting studies supporting this application for **alogliptin/pioglitazone**. Of these subjects, 50 were ≥75 years (1%). A total of 326 subjects ≥65 years (17%) and 25 subjects ≥75 years of age (1%) were treated with alogliptin/pioglitazone specifically.

In **study 009**, clinically relevant placebo-adjusted HbA1c mean changes from baseline were observed for both alogliptin doses in both age categories (<65 and ≥65 years), with no clinically meaningful differences observed, although the numbers were small (n=71).

Table 15 Change From baseline in Mean HbA1c (%) at Week 26 by Age (LOCF, FAS) (study 009)

	Study 009 Add-on to TZD, with or without MET or SU		
Subgroup	Placebo N=97	A12.5 N=197	A25 N=199
<65 years	-0.22 (n=81)	-0.66 (n=164)	-0.80 (n=156)
≥65 years	0.11 (n=14)	-0.71 (n=32)	-0.78 (n=39)

Source: 009 Table 15.2.1.8.1.

In a 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 -0.42 % for alogliptin 12.5 mg (n=26) and -0.48% 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 3 studies.

In the long-term **study 322OPI-004**, clinically relevant HbA1c reductions were observed at Week 52 for elderly (≥65 years) subjects who received **alogliptin 25 mg added to pioglitazone + MET**, in keeping with the overall results (-0.97%; n=50).

Subjects with Impaired Renal Function

Dose recommendations for the FDC alogliptin/pioglitazone in patients with *renal impairment* are based on monotherapy alogliptin and pioglitazone data. Pharmacokinetic data generated in subjects with T2DM demonstrated increased systemic exposure with decreasing renal function (see pharmacokinetic section). These results confirm the pharmacokinetic profile observed in phase 1 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.

As stated in the SmPC for pioglitazone, no dose adjustment is required in patients with renal impairment. However, it also states that no information is available from dialyzed patients and, therefore, pioglitazone should not be used in such patients.

Therefore, the FDC alogliptin/pioglitazone is not recommended for patients with severe renal impairment or ESRD, as described in the SmPC sections 4.2 and 4.4.

Subjects with hepatic impairment

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

Longer term studies

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

Supportive studies

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 ($p\leq0.001$) 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.

Study 322OPI-002 was a 26-week initial combination (alogliptin+pioglitazone) study. Subjects were randomized to receive alogliptin 12.5 mg+pioglitazone 30 mg once daily, alogliptin 25 mg+pioglitazone 30 mg once daily, alogliptin 25 mg+placebo once daily, or pioglitazone 30 mg+placebo once daily. A total of 655 subjects were randomized to receive treatment.

Both of the alogliptin 12.5 mg+pioglitazone 30 mg and alogliptin 25 mg+pioglitazone 30 mg groups demonstrated better efficacy with respect to HbA1c reductions vs pioglitazone 30 mg alone.

Overall, the data collected in these supporting studies reflect the conclusions made from the results seen in the main placebo- and active-controlled studies.

Another supportive study is study 402, which is an at the time of the evaluation of this application ongoing 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. 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 3 studies.

2.5.3. Discussion on clinical efficacy

In the total alogliptin program, an extensive number of randomized trials has been performed, including trials with placebo and active comparators, and in combination with several other antidiabetic agents. For this FDC two main studies, two supportive studies and the monotherapy study 010 are relevant.

Dose selection

In dose finding studies, no additional efficacy was observed at alogliptin doses greater than 12.5 mg. However, the inclusion of alogliptin 12.5 mg and 25 mg in the phase 3 trials is reasonable. In most pivotal studies, the 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 25 mg was acceptable.

No specific dose-response studies for pioglitazone were performed. However, the clinical phase 3 studies showed efficacy of both the 30 mg and 45 mg pioglitazone dose. Furthermore, the proposed dose for the pioglitazone component in the FDC is in line with the currently approved dose of pioglitazone and also in line with clinical practice. Therefore, the proposed dose of 30 mg and 45 mg pioglitazone in the FDC tablet was acceptable.

Pivotal trials

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 TZD (with or without metformin)**, pivotal study 009 is submitted. In this study, alogliptin is compared to placebo in patients treated with TZD (with or without

metformin). In addition, 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 is not requested. Nevertheless, a small number of patients treated with alogliptin in combination with TZD and SU were 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 non-inferior compared with increasing the dose of pioglitazone from 30 to 45 mg. 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).

Renal impairment

Renal dose adjustment recommendations of alogliptin 12.5 mg for patients with moderate renal impairment are based on PK data. In the pivotal trials efficacy was not importantly influenced by mild or moderate renal impairment. For the FDC alogliptin/pioglitazone, the applicant did only seek approval of alogliptin/pioglitazone at a dose of alogliptin 12.5 mg in combination with pioglitazone 30 or 45 mg for adults with T2DM in combination with moderate renal impairment. For the FDC alogliptin/pioglitazone the 6.25 mg alogliptin dose was not applied for.

Elderly individuals

Diabetes is a disease that is especially prevalent in elderly individuals.

In study 009, where alogliptin was used as add-on therapy to a thiazolidinedionie, no difference in efficacy between subjects < 65 year and those ≥65 years was observed, although the numbers were small (n=71).

Similarly, in the pivotal trials with alogliptin, 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) which showed non-inferiority of alogliptin 25 mg vs. glipizide, however with a decrease of power due to low baseline HbA1c values. Importantly, results of the large pooled analysis of 2234 subjects from the 5 main phase 3, 26 week, placebo-controlled studies with alogliptin 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 3, active-controlled studies supporting this application for alogliptin/pioglitazone (total of 237 elderly subjects) demonstrated that HbA1c reductions at Week 52 were greater in subjects ≥ 65 years compared with subjects <65 years, although data interpretation in subjects ≥ 75 years is limited by the small numbers of subjects.

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

Secondary endpoints

The results of the analysis of the effects of alogliptin on fasting plasma glucose were in line with the effects on HbA1c. There were no important effects on weight and serum lipids.

Initial combination studies

In patients inadequately controlled with metformin (study 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. The initial combination of alogliptin and pioglitazone (study 322OPI-002) 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.

2.5.4. Conclusions on the clinical efficacy

Efficacy was investigated in 2 pivotal trials for the combined use and in supportive trials. For the combination with a thiazolidinedione (with or without metformin), add-on of alogliptin 25 mg was associated with a clinically relevant reduction in HbA1c of -0.61% after 26 weeks in comparison to placebo.

Since the bioequivalence of alogliptin and pioglitazone at the highest and lowest proposed dosage strength formulations, respectively, was sufficiently demonstrated when compared with individual alogliptin and pioglitazone tablets in the pivotal bioequivalence study, overall efficacy was found to be sufficiently demonstrated; this included also subgroups of elderly patients and patients with mild or moderate renal impairment.

2.6. Clinical safety

Alogliptin + pioglitazone

The safety discussion for the FDC alogliptin/pioglitazone in this safety document will focus on the 2 main phase 3 studies (**009** and **322OPI-004**). As studies 009 and 322OPI-004 utilized different study designs and evaluated unique patient populations, the individual study results were not pooled but are instead summarized individually.

For the assessment of the FDC, an overview of all pooled alogliptin studies is provided. In addition, information regarding pioglitazone is provided.

Alogliptin

Data from all 55 clinical alogliptin 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 2 and 3 Study Group and the main phase 3 studies

Safety data from the 12 completed alogliptin phase 2 and 3 studies (003, 007, 008, 009, 010, 011, 301, 302, 303, 322OPI-004, 322OPI-001, and 322OPI-002) and 1, at the time of evaluation of this application, ongoing phase 3 study (305) were pooled into the Controlled Phase 2 and 3 Study

Group. As the patient populations enrolled into these studies best represent the intended use of alogliptin, results from this Controlled Phase 2 and 3 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 4 of the main phase 3 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 (study 402, ongoing at the time of evaluation of this application) is evaluating a specific subpopulation of patients with T2DM and recent ACS; therefore, these studies are excluded from the pooled data but are discussed separately, as appropriate.

Pioglitazone

The safety profile of pioglitazone has been well established based on pre and postapproval clinical studies conducted in ≥ 27,000 subjects and over 10 years of postmarketing experience. Pioglitazone-containing products have accumulated postmarketing experience in over 25 million patient-years (24th PSUR).

The safety assessment for the FDC alogliptin/pioglitazone involved the 2 main studies (009 and 322OPI-004) and the 2 supporting studies (322OPI-001 and 322OPI-002).

Patient exposure

Alogliptin + pioglitazone

A total of 3504 subjects were randomized in the four alogliptin/pioglitazone studies (009, 322OPI-004, 322OPI-001 and 322OPI-002). Across these 4 studies, 1908 subjects received alogliptin in combination with pioglitazone either as a background medication or as one of the initial-combination treatment assignments. A total of 195 subjects were exposed to alogliptin and pioglitazone for 1 year (≥52 Weeks).

Table 16 Number of Subjects on Combination Therapy – All Phase III Studies

	Main Studies			Supportive Studies			
	009 Add-on to TZD, with/without MET or SU N=494 (a)		322OPI-004 Add-on to PIO/MET N=803	322OPI-001 ALO/PIO Add-on to MET N=1553		322OPI-002 ALO/PIO N=654	
Combination Therapy	A12.5 N=198 (b)	A25 N=199	A25 N=404	A12.5 N=390	A25 N=390	A12.5 N=163	A25 N=164
Number (%) of subjects							
ALO+PIO	48 (24.4)	41 (20.6)	-	-	-	163 (100.0)	164 (100.0)
ALO+MET+PIO	107 (54.3) (a)	114 (57.3)	404 (100.0)	390 (100.0)	390 (100.0)	-	-
ALO+PIO+SU	42 (21.3)	44 (22.1)					

Source: 009 Ad-hoc Table 4; 322OPI-004 Table 15.1.1; 322OPI-001 Table 15.1.1; 322OPI-002 Table 15.1.1.
(a) 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.
(b) Percentages are based on N=197 (randomized set).

Study 009

The median treatment duration was similar in all groups. Mean exposure was similar in the placebo, A12.5, and A25 groups (22.16 weeks, 22.93 weeks, and 23.46 weeks, respectively). The majority of subjects in each of the alogliptin groups were exposed to treatment for at least 26 weeks (≥52.0% in the alogliptin groups and 48.5% in the placebo group).

Overall, 287/493 (58.2%) subjects were men. Mean age for all randomized subjects was 55.4 years. The majority of subjects were <65 years of age (408/493, 82.8%) and White (366/493, 74.2%). Mean BMI for all randomized subjects was 32.81 and mean duration of T2DM was 7.58 years.

Study 322OPI-004

The median treatment duration was similar in both groups. Mean exposure duration was slightly greater in the MET+A25+P30 group (43.14 weeks) compared with the MET+P45 group (39.73 weeks). Less than one-half of subjects in each group were exposed for at least 1 year (48.3% and 42.6% in the MET+A25+P30 and MET+P45 groups, respectively).Overall, 414/803 subjects (51.6%) were men. Mean age for all randomized subjects was 55.1 years. The majority of subjects were <65 years of age (659/803, 82.1%) and White (498/803, 62.0%). Mean BMI for all randomized subjects was 31.55 and mean duration of T2DM was 7.16 years. The median baseline MET dose was 1700 mg for both groups. Overall, no meaningful differences were observed between the groups for any subject demographic or baseline characteristics.

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 2 and 3 studies (the Controlled Phase 2 and 3 Study Group and Studies 012 and 402) are summarized in the table below. In study , 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 3 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 17 Exposure by Dose and Duration – All Alogliptin Phase III Studies

Exposure	Placebo	Active Comparator	A12.5 mg	A25 mg	All Alogliptin (a)
Controlled Phase 2 and 3 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 2 and 3 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 gastroparesis, 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.

Adverse events

Alogliptin + pioglitazone

In **study 009**, alogliptin or placebo was added to TZD therapy (rosiglitazone or pioglitazone), which was given either alone or in combination with MET or an SU. In an ad-hoc analysis of TEAEs by background medication in study 009, there were no clinically important differences in the overall incidence of TEAE or the general safety profile among the pioglitazone only, pioglitazone+MET, and pioglitazone+SU groups. Therefore, the overall safety analysis of the study is presented by alogliptin dose, irrespective of the additional background therapy.

TEAEs reported by ≥3% of subjects in any treatment group during study 009 are summarized by SOC and preferred term in the table below. All treatments were in addition to a pioglitazone with or without MET or an SU.

Table 18 Common TEAEs (≥3% of Subjects in Any Treatment Group) (study 009)

SOC Preferred Term	Number (%) of Subjects Placebo N=97	 A12.5 N=198	 A25 N=199	 Total N=494
Any TEAE	**63 (64.9)**	**138 (69.7)**	**144 (72.4)**	**345 (69.8)**
Blood and lymphatic disorders	**0**	**3 (1.5)**	**7 (3.5)**	**10 (2.0)**
Anemia	0	2 (1.0)	6 (3.0)	8 (1.6)
Gastrointestinal disorders	**13 (13.4)**	**33 (16.7)**	**22 (11.1)**	**68 (13.8)**
Nausea	2 (2.1)	9 (4.5)	6 (3.0)	17 (3.4)
Diarrhea	3 (3.1)	6 (3.0)	1 (0.5)	10 (2.0)
General disorders and administration site conditions	**13 (13.4)**	**22 (11.1)**	**23 (11.6)**	**58 (11.7)**
Edema peripheral	7 (7.2)	12 (6.1)	11 (5.5)	30 (6.1)
Fatigue	3 (3.1)	4 (2.0)	4 (2.0)	11 (2.2)
Infections and infestations	**36 (37.1)**	**69 (34.8)**	**67 (33.7)**	**172 (34.8)**
Nasopharyngitis	6 (6.2)	8 (4.0)	14 (7.0)	28 (5.7)
Upper respiratory tract infection	5 (5.2)	11 (5.6)	10 (5.0)	26 (5.3)
Influenza	4 (4.1)	3 (1.5)	11 (5.5)	18 (3.6)
Sinusitis	6 (6.2)	5 (2.5)	4 (2.0)	15 (3.0)
Urinary tract infection	1 (1.0)	9 (4.5)	4 (2.0)	14 (2.8)
Bronchitis	5 (5.2)	4 (2.0)	3 (1.5)	12 (2.4)
Cellulitis	0	1 (0.5)	6 (3.0)	7 (1.4)
Injury, poisoning and procedural complications	**14 (14.4)**	**13 (6.6)**	**25 (12.6)**	**52 (10.5)**
Joint injury	3 (3.1)	0	1 (0.5)	4 (0.8)
Musculoskeletal and connective tissue disorders	**18 (18.6)**	**28 (14.1)**	**27 (13.6)**	**73 (14.8)**
Arthralgia	2 (2.1)	3 (1.5)	8 (4.0)	13 (2.6)
Back pain	3 (3.1)	5 (2.5)	5 (2.5)	13 (2.6)
Myalgia	2 (2.1)	6 (3.0)	3 (1.5)	11 (2.2)
Muscle spasms	4 (4.1)	2 (1.0)	2 (1.0)	8 (1.6)
Nervous system disorders	**10 (10.3)**	**30 (15.2)**	**33 (16.6)**	**73 (14.8)**
Headache	4 (4.1)	8 (4.0)	10 (5.0)	22 (4.5)
Dizziness	2 (2.1)	7 (3.5)	3 (1.5)	12 (2.4)
Skin and subcutaneous tissue disorders	**15 (15.5)**	**23 (11.6)**	**24 (12.1)**	**62 (12.6)**
Dry skin	3 (3.1)	2 (1.0)	1 (0.5)	6 (1.2)
Vascular disorders	**2 (2.1)**	**8 (4.0)**	**9 (4.5)**	**19 (3.8)**
Hypertension	2 (2.1)	6 (3.0)	8 (4.0)	16 (3.2)

The incidence of TEAEs observed with alogliptin in combination with pioglitazone with or without MET or an SU (69.7% and 72.4% for A12.5 and A25, respectively) was similar to placebo (64.9%). The most commonly reported TEAEs (experienced by ≥5% of subjects in the A25 group) were nasopharyngitis (placebo: 6.2%; A12.5: 4.0%; A25: 7.0%), edema peripheral (placebo: 7.2%; A12.5: 6.1%; A25: 5.5%), influenza (placebo: 4.1%; A12.5: 1.5%; A25: 5.5%), headache (placebo: 4.1%; A12.5: 4.0%; A25: 5.0%), and upper respiratory tract infection (placebo: 5.2%;

A12.5: 5.6%; A25: 5.0%). Of note, the incidence of anemia, which is an ADR for pioglitazone, was higher in the A25 group vs the placebo group (3.0% in the A25 group vs none in the placebo group).

The percentages of subjects who experienced at least 1 TEAE considered by the investigator to be possibly, probably, or definitely related to study drug were comparable across groups (placebo: 18.6%; A12.5: 18.7%; A25: 18.6%). Study drug-related TEAEs that occurred in ≥2% of subjects were edema peripheral, hypokalemia, and headache in the placebo group (2.1% each); no study drug-related TEAEs occurred in >2% of subjects at either alogliptin dose.

The majority of TEAEs were mild or moderate in intensity. The percentage of subjects reporting TEAEs that were severe in intensity was generally similar among the groups (placebo: 6.2%; A12.5: 5.6%; A25: 9.0%). The slightly higher incidence of severe TEAEs in the A25 group was due to 2 subjects each reporting myocardial infarction and cardiac failure congestive. The only other severe event that occurred in more than 1 subject in any group was coronary artery disease (experienced by 2 subjects in the A12.5 group). One of the severe events of cardiac failure congestive was considered by the investigator to be related to study drug.

The TEAEs reported by ≥3% of subjects in either group during **study OPI-004** are summarized in the table below.

Table 19 Common TEAEs (≥3% of Subjects in Any Treatment Group) (322OPI-004)

	Number (%) of Subjects		
SOC Preferred Term	MET+A25+P30 N=404	MET+P45 N=399	Total N=803
Any TEAE	**289 (71.5)**	**275 (68.9)**	**564 (70.2)**
Blood and lymphatic disorders	**31 (7.7)**	**42 (10.5)**	**73 (9.1)**
Neutropenia	12 (3.0)	19 (4.8)	31 (3.9)
Anemia	12 (3.0)	18 (4.5)	30 (3.7)
Gastrointestinal disorders	**66 (16.3)**	**61 (15.3)**	**127 (15.8)**
Diarrhea	11 (2.7)	24 (6.0)	35 (4.4)
General disorders and administration site conditions	**45 (11.1)**	**43 (10.8)**	**88 (11.0)**
Edema peripheral	16 (4.0)	18 (4.5)	34 (4.2)
Infections and infestations	**156 (38.6)**	**130 (32.6)**	**286 (35.6)**
Nasopharyngitis	28 (6.9)	21 (5.3)	49 (6.1)
Upper respiratory tract infection	29 (7.2)	16 (4.0)	45 (5.6)
Influenza	18 (4.5)	23 (5.8)	41 (5.1)
Urinary tract infection	22 (5.4)	13 (3.3)	35 (4.4)
Bronchitis	19 (4.7)	12 (3.0)	31 (3.9)
Metabolism and nutrition disorders	**44 (10.9)**	**44 (11.0)**	**88 (11.0)**
Dyslipidemia	18 (4.5)	18 (4.5)	36 (4.5)
Musculoskeletal and connective tissue disorders	**61 (15.1)**	**55 (13.8)**	**116 (14.4)**
Back pain	15 (3.7)	17 (4.3)	32 (4.0)
Arthralgia	13 (3.2)	13 (3.3)	26 (3.2)
Nervous system disorders	**46 (11.4)**	**36 (9.0)**	**82 (10.2)**
Headache	19 (4.7)	16 (4.0)	35 (4.4)
Vascular disorders	**32 (7.9)**	**28 (7.0)**	**60 (7.5)**
Hypertension	24 (5.9)	22 (5.5)	46 (5.7)

The incidence of TEAEs observed with alogliptin in combination with MET and pioglitazone (71.5%) was similar to that observed for MET and pioglitazone (68.9%). The most commonly reported TEAEs (≥5% in the MET+A25+P30 group) were upper respiratory tract infection (MET+A25+P30: 7.2%; MET+P45: 4.0%), nasopharyngitis (MET+A25+P30: 6.9%; MET+P45: 5.3%), hypertension (MET+A25+P30: 5.9%; MET+P45: 5.5%), and urinary tract infection (MET+A25+P30: 5.4%; MET+P45: 3.3%).

The percentages of subjects who experienced at least 1 TEAE considered by the investigator to be possibly, probably, or definitely related to study drug were comparable between groups (MET+A25+P30: 21.8%; MET+P45: 18.8%). Study drug-related TEAEs that occurred in ≥2% of subjects were edema peripheral (2.0%) in the MET+A25+P30 group and oedema peripheral (3.0%) and diarrhoea (2.0%) in the MET+P45 group.

The majority of TEAEs were mild or moderate in intensity. The percentage of subjects reporting TEAEs that were severe in intensity was similar between groups (MET+A25+P30: 5.9%; MET+P45: 6.8%). Most reported severe TEAEs occurred in only 1 subject, except for muscle spasms (1 MET+A25+P30, 2 MET+P45), neutropenia (2 MET+A25+P30), road traffic accident (2 MET+A25+P30), acute myocardial infarction (2 MET+P45), pneumonia (2 MET+P45), back pain (2 MET+P45), hypertension (2 MET+P45), angina unstable (1 MET+A25+P30, 1 MET+P45), fall (1 MET+A25+P30, 1 MET+P45), osteoarthritis (1 MET+A25+P30, 1 MET+P45), and migraine (1 MET+A25+P30, 1 MET+P45).

Comparison across the main studies for FDC alogliptin/pioglitazone

Specific preferred terms such as anaemia achieve the 3% reporting threshold in alogliptin/pioglitazone studies 009 and 322OPI-004 (3% and 3%, respectively) and oedema peripheral (4% and 5.5%, respectively) versus alogliptin monotherapy sStudy 010 (0% and 3%, respectively). However, both preferred terms are labelled as common ADRs in the pioglitazone SmPC, suggesting an influence of pioglitazone on the reported AE profile, as would be expected.

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 2 and 3 Study Group is summarized by treatment group in the table below.

Table 20 Overview of TEAEs and SAEs - Controlled Phase 2 and 3 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 2 and 3 Study Group are summarized in the table below.

Table 21 Common TEAEs (≥3% of Subjects in any Presented Group) – Controlled Phase 2 and 3 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.

Pioglitazone

The safety profile of pioglitazone has been well established based on clinical and significant marketing experience. In pioglitazone monotherapy studies, the most commonly (>5%) reported AEs were upper respiratory tract infection, headache, sinusitis, myalgia, and pharyngitis. The results from the pioglitazone safety evaluation are consistent with the pioglitazone SmPC.

Across the 4 studies conducted with alogliptin and pioglitazone in combination, no clinically relevant or consistent increased incidence of AEs was noted for the combination vs the comparators.

For pioglitazone, identified ADRs are those presented in the label. Following medical review of AE terms, the ADRs included in the proposed alogliptin/pioglitazone SmPC are identified for each of the single agents and in combination (dual and triple therapies) as listed below:

- headache, diarrhea, pruritus, and myalgia for *alogliptin*;
- upper respiratory tract infection, sinusitis, bladder cancer, hypoesthesia, insomnia, visual disturbance, macular edema, bone fracture, weight increased, and alanine aminotransferase increased for *pioglitazone*;
- upper respiratory tract infection and influenza for *alogliptin/pioglitazone*
- nasopharyngitis, insomnia, abdominal pain, dyspepsia, gastroesophageal reflux disease, nausea, muscle spasms, musculoskeletal pain, hypersensitivity, headache, and rash for *alogliptin/pioglitazone with metformin*.

Comparison across studies

Comparisons of common overall AE rates (>3%) and AE rates by SOC in alogliptin/pioglitazone studies 009 and 322OPI-004, with AE rates reported in alogliptin monotherapy study 010 and against the alogliptin Controlled Phase 2 and 3 Study Group (see section below), showed no clinically relevant or consistent differences in the overall safety profile of the alogliptin/pioglitazone FDC combination versus either dataset. Rate differences in individual preferred terms are subject to multiple different influences such as treatment durations, background medications and random variation.

Serious adverse event/deaths/other significant events
Alogliptin + pioglitazone

In the alogliptin/pioglitazone program there were a total of 3 deaths; one sudden death (**study 009**, A12.5 as add-on to background P30); one myocardial infarction (**study 322OPI-004**, A25+P30); one sudden cardiac death (**study 322OPI-001**, P45).

In **study 009**, the following treatment-emergent SAEs were reported by two subjects each in the A25 (add-on to a TZD with or without MET or an SU) group: cardiac failure congestive, cellulitis, and myocardial infarction. No other individual treatment-emergent SAE was reported by more than 1 subject in any treatment group. Based on the small number of SAEs in each SOC, no clear patterns in the types of SAEs experienced by subjects in the different groups were noted.

In **study 322OPI-004**, two subjects each in the MET+A25+P30 group reported an SAE of non-cardiac chest pain and osteoarthritis. In addition, 2 subjects each in the MET+P45 group reported an SAE of acute myocardial infarction, cataract, fall, and hypotension. No other individual treatment-emergent SAE was reported by more than 1 subject in either treatment group. Based on the small number of SAEs in each SOC, no clear patterns in the types of SAEs experienced by subjects in the different groups were noted.

Alogliptin

Fifteen deaths were reported in the Controlled Phase 2 and 3 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 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 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%). 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 discernible pattern of discontinuations with respect to 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%).

Comparison across studies

Comparisons of overall SAE rates and SAE rates for A25 by SOC in alogliptin/pioglitazone studies 009 and 322OPI-004 with SAE rates reported in Study 010 (alogliptin monotherapy), showed higher overall SAE rates in studies 009 and 322OPI-004 (6.5% and 5%, respectively) compared with Study 010 (0.8%). In study 009, the main contributing SOCs were cardiac disorders and

infections and infestations. In study 322OPI-004, no particular SOC predominated. Such differences can be explained by the progressive nature of the subjects' T2DM in the alogliptin/pioglitazone studies; namely that the requirement for dual or triple therapy contrasts with the alogliptin monotherapy employed in study 010. This suggests that the disease was substantially more advanced, bringing with it higher rates of complications, some of which were serious.

In the alogliptin Controlled Phase 2 and 3 Study Group, the overall SAE rate in the A25 grouping was 4.7%, which is consistent with the rates observed in the 2 main studies (009 and 322OPI-004).

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

Alogliptin + pioglitazone

In the 2 main phase 3 studies, the incidence of TEAEs in the cardiac disorders SOC was slightly higher in A25 mg group (in addition to a TZD with or without MET or an SU) in study 009 (6.5%) and the MET+A25+P30 group in Study 322OPI-004 (6.2%) compared to the A25 mg Grouping in the Controlled Phase 2 and 3 Study Group (4.5%).

For the 2 main phase 3 studies, potential CV events were retrospectively adjudicated. Events adjudicated as MACE (CV death, nonfatal MI, and nonfatal stroke) are presented in the table below.

Table 22 Summary of Adjudicated MACE – Main Phase III Studies (studies 009 and OPI-004)

	Number of Subjects With MACE/Randomized Subjects (%)				
Study	Placebo n/N (%)	Active Comparators n/N (%)	A12.5 n/N (%)	A25 n/N (%)	All Alogliptin n/N (%)
Overall	**0/97**	**3/399 (0.8)**	**2/197 (1.0)**	**4/603 (0.7)**	**6/800 (0.8)**
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)

N/A = not applicable (treatment group not included in study).

The incidence of any MACE in the alogliptin/pioglitazone studies was low and generally similar across treatment groups, although no subjects on placebo reported a MACE.

Alogliptin

In the Controlled Phase 2 and 3 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 2 and 3 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 2 and 3 Study Group, a 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 nonserious. 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 nonserious. The applicant did provide details of the definition of SAEs provided to the investigators, which was applied consistently for 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 nonserious designation has been determined based on that data. The review of the 6 subjects with nonserious AEs of myocardial infarction indicated that these were reported by investigators on the basis of ECG findings, suggestive of myocardial ischaemia rather than hospital admissions with typical chest pain (and confirmatory cardiac enzyme rise). The majority of these AEs were supported with sufficient clinical information indicating that the nonserious 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 2 and 3 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%).

Based on results showing no increase in MACE with alogliptin, no special warning/precaution regarding CV events is included but a warning concerning limited experience with alogliptin in patients with class III/IV congestive heart failure is included in section 4.4 of the SmPC.

Pioglitazone

The CV safety of pioglitazone has been assessed in the PROactive study. This study evaluated CV outcomes in subjects with T2DM and macrovascular disease. Subjects received either pioglitazone titrated from 15 mg to 45 mg (n=2605) or placebo (n=2633) in addition to their glucose-lowering drugs and other medications for approximately 3 years. Overall, the results of this study demonstrated no increase in mortality or total macrovascular events with pioglitazone compared with placebo.

With regard to MACE, which was evaluated as a secondary endpoint, pioglitazone reduced the risk of having an event in the composite of all-cause mortality, non-fatal MI, or stroke compared with placebo (HR: 0.84, 95% CI: 0.72–0.98, p=0.027). Furthermore, results of meta-analyses of all pioglitazone studies were consistent with results of PROactive.

Hypersensitivity Reactions

Alogliptin + pioglitazone

No subjects in the 2 main alogliptin/pioglitazone studies experienced an **SAE** hypersensitivity reaction or a **TEAE leading to discontinuation** within the SMQs. Three subjects from the 2 main phase 3 studies supporting the combination of alogliptin/pioglitazone reported an **AE from the severe cutaneous adverse reaction** SMQ: 1 subject (1/399 [0.3%]) receiving an active comparator (dermatitis exfoliative) and 2 subjects (2/603 [0.3%]) receiving A25 (exfoliative rash and dermatitis exfoliative). Nine subjects from the 2 main phase 3 studies supporting the combination of alogliptin/pioglitazone reported an **AE from the angioedema** SMQ: 1 (1/97 [1.0%]) receiving placebo (urticaria), 4 (4/399 [1.0%]) receiving an active comparator (periorbital edema and swelling face [1 subject] and face edema, lip swelling, and urticaria [1 subject each]), and 4 subjects (4/603 [0.7%]) receiving A25 (angioedema, conjunctival edema, corneal edema, and face edema [1 subject each]). These events were not reported as SAEs and did not lead to study drug discontinuation. No subject in any either of the 2 main phase 3 studies reported an **anaphylaxis reaction** (category A).

Alogliptin

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 non-clinical studies nor have they 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 3 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, such reactions are included as an undesirable effect in section 4.8 of the SmPC, which is consistent with labeling for other DPP-4 inhibitors, and listed as a potential risk in the RMP. 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.

Pioglitazone

Hypersensitivity reactions are known to have occurred following administration of pioglitazone, and hence are noted as an identified risk for pioglitazone in the RMP. A total of 46 serious, medically confirmed cases of anaphylactoid reaction have accumulated in the Takeda global safety database in association with the pioglitazone monoproduct. This equates to a reporting rate of 2.13 per 1 million patient-years, which is very low.

Acute Pancreatitis

Alogliptin + pioglitazone

None of the subjects in the 2 main phase 3 alogliptin/pioglitazone studies reported an AE of pancreatitis.

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 study 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 included as Warning and Precautions in the SmPC, Section 4.4, and acute pancreatitis is listed as an adverse reaction in Post-marketing Reports in the 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.. As additional pharmacovigilance activity the cardiovascular outcome study 402 is further investigating pancreatitis. The final study report is expected to be available in the first quarter of 2014.

Malignancies

Alogliptin + pioglitazone

Two subjects in study 009 in the placebo group reported SAEs within the malignancy SMQ: basal cell carcinoma and colon cancer, and 2 subjects in Study 322OPI-004 reported SAEs within the malignancy SMQ: colon cancer (MET+A25+P30 treatment group) and rectosigmoid cancer (MET+P45 treatment group). Of note, no subject in either of the main phase 3 studies reported bladder neoplasm.

Based on the results in the alogliptin/pioglitazone main studies, there is no evidence to suggest that the combination of alogliptin and pioglitazone is associated with an increase in incidence of malignancy.

Since there is a warning in the pioglitazone SmPC regarding bladder cancer, this is reflected for the FDC product SmPC. Bladder cancer specifically is listed as an identified risk of pioglitazone, and other malignancies are considered a potential risk of pioglitazone in the RMP.

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.

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

Most postmarketing cases reported a time to onset less than 2 months from starting alogliptin 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).

Pioglitazone

Bladder neoplasm was identified as an AE of special interest based on the 2-year carcinogenicity study of pioglitazone that revealed treatment-associated neoplastic changes in the urinary bladder in male rats. A meta-analysis of controlled clinical trials involving over 22,000 patients (12,506 pioglitazone and 10,212 comparator) examined the relationship between pioglitazone and bladder cancer. Results of the analysis revealed 26 total cases (19 pioglitazone, 7 comparator). When subjects that were diagnosed with bladder cancer within the first year of treatment were excluded, there were 9 total cases (7 pioglitazone, 2 comparator). Given the low overall incidence of bladder cancer and biologic implausibility of developing new bladder cancer within 1 year of starting treatment, it is difficult to draw meaningful conclusions from these results. Interim results of an ongoing epidemiological study of the Kaiser Permanente Northern California (KPNC) database showed no statistically significant increase risk of bladder cancer among patients ever treated with pioglitazone. Analyses addressing longer exposure to pioglitazone, however, suggest an increased risk of developing bladder cancer with longer-term therapy. This KPNC study is ongoing, with the final report expected in 2013.

After extensive non-clinical, clinical, and epidemiological investigations, no conclusive evidence has emerged. This may be due partly to the rarity of bladder cancer, the long latency to the development of bladder cancer, confounding of multiple other risk factors (eg, smoking) and treatments in the T2DM population, particularly when pioglitazone is used late in T2DM and following other antidiabetic treatments. Nonetheless, the results from the meta-analysis do not exclude the possibility that there is an association between pioglitazone and bladder cancer.

The CHMP recently reviewed available data on pioglitazone use and the occurrence of bladder cancer and concluded in July 2011 and October 2011 that there is a small increased risk of bladder cancer in subjects taking pioglitazone but that the benefit/risk balance remained positive (referral procedure EMEA/H/C/0285/A-20/0046). The Company Core Safety Information (CCSI) for pioglitazone has subsequently been updated to include active bladder cancer as a listed event and to include warnings in the product information regarding the use of pioglitazone in subjects with active bladder cancer or a history of bladder cancer.

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 + pioglitazone

In the case of alogliptin 25 mg used to form triple therapy with MET and pioglitazone in **study 322OPI-004**, there was an approximate tripling of rate of hypoglycaemic episodes (4.5%) vs dual therapy with MET 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 MET, but with lower incidence rates.

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. There were more hypoglycaemic episodes in the alogliptin 25 mg group (7.0%) compared to the placebo group (5.2%).

Alogliptin

The incidence of hypoglycaemic episodes in the Controlled Phase 2 and 3 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.

From the main individual placebo-controlled studies covering use as add-on to MET (study 008) and add-on to SU (study 007), 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 007 (add-on to SU), fewer subjects in the alogliptin 25 mg group (9.6%) experienced a hypoglycaemic event compared with placebo (11.1%). The noticeably higher rates in the placebo and alogliptin 12.5 mg (15.8%) arms were likely driven by the SU component.

In Study 011 (add-on to insulin, with or without MET), episodes of hypoglycaemia were anticipated due to the insulin background therapy in this study population. 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 was similar for severe cases.

In study 305 (alogliptin vs SU in a general adult T2DM population, on MET monotherapy), hypoglycaemia rates with alogliptin 25 mg vs MET+glipizide were >10-fold lower (1.4% vs 23.8%, respectively). Similarly, the incidence of severe hypoglycaemic episodes was greater in the MET+glipizide group (0.5%) compared with the MET+alogliptin 12.5 mg and MET+alogliptin 25 mg groups (0.1% and 0, respectively). The higher incidence of hypoglycaemia in the MET+glipizide group is consistent with the glipizide label, which states that hypoglycaemia is likely to occur when more than one glucose-lowering drug is used.

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 2 and 3 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.

Cardiac Failure

Alogliptin + pioglitazone

The incidence of cardiac failure and cardiac failure congestive was 0% and 1.5%, respectively, in the alogliptin 25 mg group in **study 009** and 0.5% and 0.2%, respectively, in the MET+A25+P30 group in **study 322OPI-004**. There were no patterns or trends observed for AEs in any of the alogliptin/pioglitazone main studies suggestive of an increased incidence in these types of events when alogliptin is added to pioglitazone treatment.

Pioglitazone

TZDs, including pioglitazone, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of pioglitazone, and after dose increases, patients should be monitored carefully for signs and symptoms of heart failure (e.g. excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Pioglitazone is contraindicated in patients with established NYHA class I to IV heart failure.

Statements in the proposed SmPC are aligned with the approved pioglitazone SmPC.

Oedema

Alogliptin + pioglitazone

The incidence of oedema peripheral was 5.5% in the alogliptin 25 mg group in **study 009** and 4.0% in the MET+A25+P30 group in **study 322OPI-004**. No subject in either of the alogliptin/pioglitazone main phase 3 studies had an SAE of oedema peripheral. One subject in the MET+A25+P30 group reported a TEAE of oedema peripheral that led to study discontinuation.

There were no patterns or trends observed for AEs in any of the alogliptin/pioglitazone main studies suggestive of an increased incidence in these types of events when alogliptin is added to pioglitazone treatment.

Statements in the proposed SmPC are aligned with the approved pioglitazone SmPC.

Pioglitazone

Oedema, a known effect in the TZD drug class, can occur with pioglitazone treatment and is usually mild or moderate. In controlled studies, oedema was reported more frequently in subjects treated with pioglitazone than in placebo-treated subjects and is dose related.

Weight Gain

Alogliptin + pioglitazone

In the main phase 3 studies with the combination, there were no significant treatment differences for the change from baseline in body weight at Week 26 (**study 009**) or Week 52 (**study 322OPI-004**). A similar pattern was observed in supportive phase 3 Study 322OPI-001; however, there was a statistically significant body weight increase for subjects in the A25+P30 group compared with the A25 alone or P30 alone groups in supportive study 322OPI-002.

Statements in the proposed SmPC are aligned with the approved pioglitazone SmPC.

Pioglitazone

Dose-related weight gain, a known effect in the TZD drug class, has been observed with pioglitazone treatment, alone or in combination with other hypoglycaemic agents.

Bone Fracture

Alogliptin + pioglitazone

The incidence of TEAEs in the musculoskeletal and connective tissue disorders SOC was similar in the alogliptin 25 mg group in **study 009** (13.6%) and the MET+A25+P30 group in **study 322OPI-004** (15.1%) compared to the alogliptin 25 mg group (13.9%) and the placebo group (12.1%) in the Controlled Phase 2 and 3 Study Group of the alogliptin clinical program.

Pioglitazone

An increased incidence of bone fracture in women treated with pioglitazone was observed in the PROactive randomized trial. During a mean follow-up of 34.5 months, the incidence of bone fracture in women was 5.1% (44/870) for pioglitazone vs 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in women were nonvertebral fractures, including lower limb and distal upper limb. Results from a recently completed study that evaluated the effect of pioglitazone on bone metabolism in postmenopausal women with impaired fasting glucose, however, do not suggest an altered bone metabolism in pioglitazone-treated subjects that would lead to excessive bone fragility.

Statements in the proposed SmPC are aligned with the approved pioglitazone SmPC.

Hepatic dysfunction

Alogliptin + pioglitazone

There is no evidence to suggest that the combination of alogliptin and pioglitazone is associated with an increased incidence of hepatotoxicity.

Pioglitazone

Specific long-term studies consistently demonstrate that pioglitazone use does not lead to increased hepatotoxicity. The current pioglitazone SmPC provides guidance for use in subjects who exhibit active liver disease, and hepatic dysfunction is listed as an identified risk for pioglitazone in the RMP. Statements in the SmPC are aligned accordingly.

Macular Oedema

Alogliptin + pioglitazone

There is no evidence to suggest that the combination of alogliptin and pioglitazone is associated with an increase in incidence or severity of any of these AEs of special interest.

Pioglitazone

A potential signal for macular edema was observed in a retrospective, postmarketing medical record review in subjects treated with pioglitazone and other TZDs. However, no evidence for increased reporting of this common diabetic complication of retinopathy has been found in the pioglitazone clinical database. Nonetheless, macular edema is included as a potential risk for pioglitazone (RMP).

Comparative safety by dose
Alogliptin + pioglitazone

Only the main study 009 evaluated both alogliptin 12.5 mg and 25 mg for the FDC alogliptin/pioglitazone. In this study, incidence of TEAEs was similar (69.7%, alogliptin 12.5 mg; 72.4%, alogliptin 25 mg) between the dose groups, and there was no clear dose-response relationship. The incidence of SAEs in the alogliptin 12.5 mg group was lower than in the alogliptin 25 mg group (2.5% vs 6.5%, respectively), but both groups were similar to placebo-control (4.1%). The proportion of subjects discontinuing the study due to a TEAE was identical in both alogliptin groups (3.0%)

In study 322OPI-004, TEAE rates were consistent with the data for alogliptin 25 mg described above, but no dose comparison could be performed within this study.

Alogliptin

In most of the phase 3 studies, both alogliptin 12.5 mg and 25 mg were evaluated; however, in some studies, particularly the longer duration studies, only 25 mg was evaluated. Therefore, for the alogliptin 25 mg group, there were more subjects exposed overall and for longer durations 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 2 and 3 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 1 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.

Laboratory findings

Alogliptin + pioglitazone

The incidence of markedly abnormal values for renal function parameters during treatment was low overall and similar across treatment groups. There is no safety signal for an increased incidence of abnormal renal function values when alogliptin is coadministered with pioglitazone.
In **study 009**, 2 subjects in each of the alogliptin groups (1.0% each) had an alanine aminotransferase (ALT) >3× upper limit of normal (ULN) during treatment compared with no subjects in the placebo group. The ALT value exceeded 10×ULN for 2 of the 4 subjects. In both cases, these abnormalities were considered to be unrelated to study drug by the investigator and a possible alternative aetiology was provided (009 Study Report). No subjects had an ALT value >3×ULN in conjunction with elevated bilirubin.
In **study 322OPI-004**, 3 subjects (0.8%) in the MET+A25+P30 group and 2 subjects (0.5%) in the MET+P45 group had an ALT >3×ULN. No subjects had an ALT>10×ULN or an ALT>3×ULN with elevated bilirubin.

Overall, the data indicate the combination of alogliptin and pioglitazone is associated with a low risk of hepatic toxicity.

Alogliptin

For laboratory evaluations of haematology, clinical chemistry, and urinalysis, mean changes from baseline to Endpoint were generally small and consistent across the treatment groups. This was also the case for renal and hepatic function parameters.

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 is associated with a low risk of hepatic toxicity.

Vital signs and electrocardiogram evaluations

No clinically meaningful trends were observed in vital sign measures (pulse, blood pressure, respiratory rate, and temperature) in either the alogliptin studies or the two main studies for the FDC alogliptin/pioglitazone. 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.

Safety in special populations

To determine whether certain factors predispose subgroups of individuals to experience specific TEAEs, analyses were performed using the Controlled Phase 2 and 3 Study Group for a number of intrinsic (sex, age, race, BMI, and renal function) factors. No important differences were noted. The safety of alogliptin/pioglitazone in special groups and situations was not specifically investigated in the clinical program; however, because there is no drug interaction between pioglitazone and alogliptin, the FDC is expected to have a similar profile as the individual components.

Elderly

TEAEs in the Controlled Phase 2 and 3 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 2 and 3 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.

Pioglitazone

No important differences in safety profile in elderly subjects were noted in the pioglitazone studies. However, in the pioglitazone SmPC, age-related risks such as bladder cancer, bone fracture, and heart failure should be taken into account and the balance of benefits and risks should be considered during treatment in the elderly.

Combination treatment with alogliptin and pioglitazone in the elderly population is expected to have a similar safety profile as the individual components. Thus, no dose adjustment is necessary for alogliptin/pioglitazone based on age.

Subjects with Impaired Renal Function

In the phase 1 study 006 with alogliptin (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 ESRD are recommended (SmPC). 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 2 and 3 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 2 and 3 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). As additional pharmacovigilance activity the

cardiovascular outcome study 402 is further investigating effects in patients with renal impairment. The final study report is expected to be in the first quarter of 2014.

The applicant did not apply for an indication of the FDC alogliptin/pioglitazone in T2DM patients with severe renal insufficiency.

Subjects with Impaired Hepatic Function

Results from phase 1 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 in patients with severe hepatic impairment is not recommended in the SmPC.

In line with the SmPC of pioglitazone, the FDC alogliptin/pioglitazone is contraindicated in patients with hepatic impairment. As additional pharmacovigilance activity the cardiovascular outcome study 402 is further investigating effects in patients with renal impairment. The final study report is expected to be in the first quarter of 2014.

Interactions

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.

Post marketing experience

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. The FDC Alogliptin/pioglitazone was approved for use in the treatment of T2DM in Japan in July 2011 and commercially launched (A25+P15 mg and A25+P30 mg) in September 2011.

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

Hepatotoxicity was reported postmarketing 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-tmarketing 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.

During the review period from launch of the **alogliptin/pioglitazone FDC** to the end of the PSUR review period (20 September 2011 to 15 October 2011), patient exposure was estimated to be 7,215 patient-years based on volume of shipment. No spontaneous reports for the alogliptin/pioglitazone FDC were received during the review period.

2.6.1. Discussion on clinical safety

Alogliptine + pioglitazone

The safety profile of the FDC alogliptin/pioglitazone is derived from two main phase 3 clinical studies (009 and 322OPI-004) and from supportive studies. A total of 3504 subjects received at least 1 dose of study drug in the alogliptin/pioglitazone studies. A total of 1908 subjects with T2DM received at least 1 dose of alogliptin with pioglitazone in the phase 3 studies. Treatment duration ranged from 16 to 52 weeks in the phase 3 studies and the majority of subjects in all studies completed treatment. A total of 195 subjects were exposed to alogliptin and pioglitazone in study 322OPI-004 for 1 year.

Alogliptin/pioglitazone was well tolerated in the study population to improve glycaemic control in patients with T2DM. The safety profile of alogliptin in combination with pioglitazone was shown to be consistent with known safety profiles of pioglitazone and the submitted pooled safety data of the alogliptin studies.

Considering the limited number of clinical studies for this FDC, the focus of this assessment is also on the submitted safety data of the single components, which will be discussed below. Importantly, the currently available clinical safety data of the FDC is in line with the available clinical safety data of alogliptin and pioglitazone. This provides sufficient grounds to perform a full assessment for the FDC, even though the studies with co-administration of both medicines is limited.

In the phase 3 studies for the FDC alogliptin/pioglitazone, the most commonly reported TEAEs (≥5% of subjects) in the combination grouping were oedema peripheral, nasopharyngitis, upper respiratory tract infection, influenza, urinary tract infection, headache, and hypertension. The majority or TEAEs were mild or moderate in intensity and considered by the investigator to be not related to study drug. TEAEs tended to occur more often within the SOC of infections and infestations and the incidence was generally similar among treatment groups. Analysis of AE rates on A12.5+pio vs A25+pio groupings revealed small numerical increments in AE rates in the A25+pio grouping, which were not clinically relevant.

In the alogliptin/pioglitazone clinical program, there were three deaths. These deaths occurred in subjects with known pre-existing CV risk factors. The incidences of treatment-emergent SAEs and TEAEs that led to discontinuation from the study were low and similar among the treatment groups, with no meaningful differences observed with respect to the specific types of events reported in the treatment groups.

For alogliptin, special-interest AE assessments were conducted for hypoglycaemia, CV events, hypersensitivity reactions, acute pancreatitis, and malignancies. For pioglitazone, AE assessments

were conducted for CV safety, cardiac failure, oedema, weight gain, bone fracture, and bladder cancer. For the special-interest AE **hypoglycaemia**, alogliptin 25 mg in combination 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 also a small increase in the rate of hypoglycaemic episodes in the alogliptin 25 mg group. This increased rate of hypoglycaemia in combination with TZD is clearly mentioned in the SmPC. There is no evidence to suggest that the combination of alogliptin and pioglitazone is associated with an increase in incidence or severity of any other AE of special interest.

An evaluation of CV risk did not show an increased risk of major adverse CV events for pioglitazone or alogliptin. However, in studies 009 and 322OPI-004, the incidences of TEAEs in the SOC Cardiac disorders was higher in A25 mg (6.5%) and A12.5 (3.0%) vs. placebo (1.0%) in study 009 respectively higher in MET+A25+P30 (6.2%) vs. MET + P45 (4.3%) in study 322OPI-004. The incidence of cardiac failure/ cardiac failure congestive was 1.5% (3 cases) in A25 vs. 0% in placebo in study 009 and 0.7% (3 cases) in MET+A25+P30 vs. 0.3% (1 case) in MET + P45 in study 322OPI-004; although, the incidence of oedema was not increased in the ALO + PIO group compared to the PIO group in either of the studies. The applicant was requested to comment on the increased incidence of cardiac failure/cardiac failure congestive with pioglitazone in combination with alogliptin compared to pioglitazone in study 009 and 322OPI-004 respectively. The applicant has commented on that the incidence of cardiac failure in the subjects taking pioglitazone without alogliptin in study 009 and 322OPI-004 respectively was slightly lower than expected, which could be a plausible explanation. Furthermore, the incidence of cardiac failure in subjects administered alogliptin in combination with pioglitazone was summarized for the 'Pivotal Phase III Alogliptin/ Pioglitazone Controlled Studies'. The incidence of cardiac failure (narrow-scope cardiac failure SMQ) in the A25+PIO group was low (6 subjects [0.5%]) and comparable to the pioglitazone alone grouping (4 subjects [0.4%]), which is considered reassuring although there were a few number of cases wherefore it is difficult to drew any firm conclusions.

For the 2 main phase 3 studies, potential CV events were retrospectively adjudicated. Events adjudicated as MACE (CV death, nonfatal MI, and nonfatal stroke) showed that the incidence was low and generally similar across treatment groups, although no subjects on placebo reported a MACE. A cardiovascular outcome study (study 402), for which the final study report is expected in the first quarter of 2014, will provide additional information.

Specific preferred terms such as anaemia achieve the 3% reporting threshold in alogliptin/pioglitazone Studies 009 and 322OPI-004 (3% and 3%, respectively) and oedema peripheral (4% and 5.5%, respectively) versus alogliptin monotherapy study 010 (0% and 3%, respectively). However, both preferred terms are labelled as common ADRs in the pioglitazone SmPC, suggesting an influence of pioglitazone on the reported AE profile, as would be expected.

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 seems representative of the European population of diabetes patients. Two studies (study 305 and 402) were onging at the time of evaluation of this application.

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. In order to increase the precision of adverse event rates and to achieve a higher validity, the applicant was requested during the procedure to generate a safety data pool containing all 7 pivotal Phase III studies (5 placebo-controlled and 2 active-comparator studies) and to present a table of adverse events to be reflected in the tabulated list of adverse reactions for section 4.8 for the proposed SmPC. The applicant has provided the requested safety data pool containing all pivotal Phase III studies. It is agreed that the pattern of TEAEs in the pool 'Pivotal Phase III Controlled Studies' was similar to the pool 'Controlled Phase 2 and 3 Study 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.

Serious adverse events were higher 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 a more in depth discussion regarding the following 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 is considered that these individual cases (seven classified as possibly related and one as not related) do not strongly 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-containing 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 2 and 3 Study Group, when compared to placebo, alogliptin was associated with a higher cardiovascular event rate (Hazard ratio 1.33). However, in the Controlled Phase 2 and 3 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 during the procedure 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.

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 labelling for other DPP-4 inhibitors such reactions should be mentioned in section 4.4 Special warnings and precautions for use 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 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 Post-marketing Reports in the 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 clearly mentioned 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 were 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 in patients with severe renal impairment for the FDC alogliptin/pioglitazone. For T2DM patients with moderate renal impairment, a lower dose of alogliptin in the FDC tablet (12.5 mg alogliptin/30 mg or 45 mg pioglitazone) is proposed. This is in line with the proposed alogliptin (Vipidia) dose.

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 2 and 3 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 can not be recommended. 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). 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..

Drug interactions

No dose adjustment is required due to drug interactions.

Pioglitazone

The safety profile of pioglitazone has been well established based on pre and post approval clinical studies conducted in ≥27,000 subjects and over 10 years of post- marketing experience. All safety issues are sufficiently addressed in the SmPC and in the Risk Management Plan.

2.6.2. Conclusions on the clinical safety

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

Regarding the pioglitazone component, the safety profile of pioglitazone is well established and includes the risk for bladder cancer, as available epidemiological data suggests a small increase of this risk, and fluid retention, which may exacerbate or precipitate heart failure. Cardiac failure is an identified risk for pioglitazone and is contraindicated in patients with cardiac failure or a history of cardiac failure (NYHA class I-IV) and information is included in section 4.3 and 4.4 of the SmPC for alogliptin/pioglitazone.

For the FDC alogliptin/pioglitazone, the only additional potential safety risk is the higher incidence in hypoglycaemic events, compared to the single components, which is addressed in the product information.

For the FDC alogliptin/pioglitazone, no indication for T2DM patients with severe renal insufficiency was proposed by the applicant. For T2DM patients with moderate renal impairment a dose reduction of 12.5 mg alogliptin was proposed (in line with alogliptin used as monocomponent) in combination with pioglitazone 30 or 45 mg. This is reflected in the SmPC of the FDC alogliptin/pioglitazone.

Hypersensitivity reactions and pancreatitis are mentioned in the SmPC. Because of the cases of hepatotoxicity observed post-marketing in Japan, hepatotoxicity is mentioned in the SmPC. Since pioglitazone is contraindicated in patients with hepatic impairment, the FDC alogliptin/pioglitazone can not be used in these patients.

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/pioglitazone (Incresync) is acceptable.

Proposed indication:

Incresync is indicated as a second or third line treatment in 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 (particularly overweight patients) inadequately controlled on pioglitazone alone, and for whom metformin is inappropriate due to contraindications or intolerance.
- in combination with metformin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients (particularly overweight patients) inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.

In addition, Incresync can be used to replace separate tablets of alogliptin and pioglitazone in those adult patients aged 18 years and older with type 2 diabetes mellitus already being treated with this combination.

After initiation of therapy with Incresync, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, Incresync should be discontinued. In light of potential risks with prolonged pioglitazone therapy, prescribers should confirm at subsequent routine reviews that the benefit of Incresync is maintained (see section 4.4).

Advice on conditions of the marketing authorisation

The PRAC advises that the following should be conditions of the Marketing Authorisation:

Risk management system

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

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

Additional risk minimisation measures:

The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use alogliptin/pioglitazone. Prior to distribution in each Member State, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

- This educational pack is aimed at strengthening awareness of the important identified risks of bladder cancer and heart failure and the overall recommendations intended to optimise the benefit-risk balance at the patient level.
- The physician educational pack should contain: the Summary of Product Characteristics, the Package Leaflet and a Prescriber Guide.

The Prescriber Guide should highlight the following:

- Patient selection criteria including that alogliptin/pioglitazone should not be used as first line therapy and emphasising the need for regular review of treatment benefit.
- The risk of bladder cancer risk and relevant risk minimisation advice.
- The risk of heart failure and relevant risk minimisation advice.
- Caution on using in the elderly due to the age related increased risks (in particular bladder cancer, fractures and heart failure)

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 Hepatotoxicity Pancreatitis Cardiac failure Bladder cancer Peripheral edema and weight gain Bone fractures in women
Important potential risks	Peripheral necrotic skin lesions Gastrointestinal disorders Infections Malignancies (other than bladder cancer) Macular oedema Ischemic heart disease Off-label use

Summary of safety concerns	
Missing information	Patients with concurrent cardiovascular disease Patients with severe renal impairment or ESRD requiring dialysis Patients with severe hepatic impairment Pregnant or lactating women Children and adolescents

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 study	*Evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with type 2 diabetes and ACS*	Investigate hypersensitivity reactions, pancreatitis, skin lesions, hepatotoxicity, GI disorders and infections, effects in patients with concurrent CV disease and effects in patients with renal impairment.	*Ongoing*	*January 2014*

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 a contraindication, data and recommendations*	*None*
Hepatotoxicity	*SmPC Section 4.3, 4.4 and 4.8 provides data and recommendations*	*None*
Pancreatitis	*SmPC section 4.4 and 4.8 provides data and*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	recommendations	
Cardiac failure	*SmPC section 4.3: alogliptin/pioglitazone is contraindicated in patients with cardiac failure* *SmPC sections 4.4 and 4.8 provide further data and warnings*	*Educational pack targeting all physicians expected to prescribe/use alogliptin/pioglitazone. This aims to strengthen awareness of important identified risk of heart failure and the overall recommendations intended to optimise the benefit-risk margin at the patient level. The educational pack contains the SmPC, package leaflet, and a Prescriber Guide.*
Bladder cancer	*SmPC sections 4.3, 4.4,4.8 and 5.3 provides data and warnings*	*Educational pack targeting all physicians expected to prescribe/use alogliptin/pioglitazone. This aims to strengthen awareness of important identified risks of bladder cancer and the overall recommendations intended to optimise the benefit-risk margin at the patient level. The educational pack contains the SmPC, package leaflet, and a Prescriber Guide*
Peripheral edema and weight gain	*SmPC sections 4.4, 4.8, and 5.1 provide data and warnings.*	*None*
Bone fractures in women	*SmPC Sections 4.4 and 4.8 provide data and warnings*	*None*
Malignancies (other than bladder cancer)	*SmPC Section 5.3 provides data*	*None*
Macular oedema	*SmPC Sections 4.4 and 4.8 provide data and warnings.*	*None*
Ischaemic heart disease	*SmPC Sections 4.4 and 5.1 provide data and warnings.*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Off label use	*SmPC Section 4.1.*	*Off-label use is addressed in the Prescriber Guide.*
Patients with concurrent cardiovascular disease	*SmPC Section 4.4 provides a warning concerning limited experience with alogliptin in patients with class III/IV congestive heart failure.*	*None*
Patients with severe renal impairment or ESRD requiring dialysis	*SmPC Section 4.2 and Section 4.4*	*None*
Patients with severe hepatic impairment	*SmPC Sections 4.3 and 4.4.*	*None*
Pregnant or lactating 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*

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

Incresync is a Fixed Dose Combination of a new DPP-4 inhibitor, alogliptin, and the PPAR-γ agonist pioglitazone.

Benefits

Beneficial effects

Pharmacokinetics

The applicant performed several clinical pharmacology studies to show the pharmacokinetics of alogliptin and pioglitazone, separately and combined, demonstrating no significant interaction. For the fixed dose combination (FDC) product one pivotal bioavailability study and one pivotal food effect studies were submitted. In study 322OPI-101, the pivotal BE study, bioequivalence was shown for the commercial FDC product when dosed orally as the highest proposed dosage strength (Alogliptin 25 mg +Pioglitazone 45 mg) formulation and lowest dosage strength (Alogliptin 12.5 mg +Pioglitazone 15 mg), compared with the individual alogliptin and pioglitazone tablets.

The food interaction study (322OPI-006) with highest dosage strength (Alogliptin 25 mg +Pioglitazone 45 mg) of the commercial formulation of the FDC product (alogliptin/pioglitazone BL) did not show any influence of food on the pharmacokinetics of pioglitazone and alogliptin. This was supported by food interaction studies 322-4833/CPH-001 and 322-4833/CPH-002 in Japanese subjects.

Study 017 showed that when alogliptin and pioglitazone (CYP2C8 substrate) were co-administered, no changes in the exposures to alogliptin, pioglitazone, or pioglitazone metabolites were observed.

Clinical

For the FDC four clinical trials were submitted: two pivotal studies (009 and 322OPI-004) and two supportive studies (322OPI-001 and 322OPI-002). In pivotal **study 009**, in which alogliptin was added to 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 both 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 non-inferior compared with increasing the dose of pioglitazone from 30 to 45 mg.

In supportive **study 322OPI-001**, 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 (**study 322OPI-002)** 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 pioglitazone with or without metformin; initial combination therapy was not applied for by the applicant but also cannot be recommended as this is not in line with current diabetes treatment guidelines.

In addition to the specific combination trials of alogliptin with pioglitazone, 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 glucose lowering agents. HbA1c was used as the primary endpoint. In the placebo controlled studies, the treatment effect of alogliptin was modest (0.5-0.6%), but clinically relevant and thus supported the corresponding marketing atuhorisation application of alogliptin.

Uncertainty in the knowledge about the beneficial effects

The number of subjects in the FDC studies was limited.

In study 009, where alogliptin was used as add-on therapy to a thiazolidinedionie, no difference in efficacy between subjects < 65 year and those ≥65 years was observed, although the numbers were small (n=71). Similarly, in the pivotal trials with alogliptin, 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).

A study in elderly individuals showed non-inferiority of alogliptin 25 mg vs. glipizide, however with a decrease of power due to low baseline HbA1c values. Importantly, results of the large pooled analysis of 2234 subjects from the 5 main phase 3, 26 week, placebo-controlled studies with alogliptin 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). However, the study was not performed specifically for the combined use of alogliptin and pioglitazone. Nevertheless, results from the 2 main phase 3, active-controlled studies supporting this application for alogliptin/pioglitazone (total of 237 elderly subjects) demonstrated also that HbA1c reductions at

week 52 were greater in subjects ≥ 65 years compared with subjects <65 years, although data interpretation in subjects ≥ 75 years is limited by the small numbers of subjects.

Risks

Unfavourable effects

For the FDC alogliptin/pioglitazone two main studies were submitted. In these phase 3 studies, the most commonly reported TEAEs (≥5% of subjects) in the combination grouping were oedema peripheral, nasopharyngitis, upper respiratory tract infection, influenza, urinary tract infection, headache, and hypertension. The majority or TEAEs were mild or moderate in intensity and considered by the investigator to be not related to study drug. TEAEs tended to occur more often within the SOC of infections and infestations and the incidence was generally similar among treatment groups. Analysis of AE rates on alogliptin 12.5 mg + pioglitazone vs alogliptin 25 mg + pioglitazone groupings revealed small numerical increments in AE rates in the alogliptin 25 mg + pioglitazone grouping, which were not clinically relevant.

In **study 322OPI-004**, there was an approximate tripling of rate of hypoglycaemic episodes (4.5%) for patients on alogliptin + pioglitazone + MET treatment vs dual therapy with MET 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 MET, but with lower incidence rates. In **study 009** (add-on to TZD), there were more hypoglycaemic episodes in the alogliptin 25 mg group (7.0%) compared to the placebo group (5.2%).

Regarding the mono components, the safety profile of pioglitazone is well established and includes the risk for bladder cancer, as cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone, and available epidemiological data suggests a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. Pioglitazone can also cause fluid retention, which may exacerbate or precipitate heart failure and is therefore contraindicated in heart failure (NYHA classes I-IV).

Regarding alogliptin, the following unfavouralbe effects associated with the use of alogliptin:

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 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 postmarketing 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.

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 Study 009 (add-on to TZD), there was a small increase in the rate of hypoglycaemic episodes in the alogliptin 25 mg group. 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.

Subgroups

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.

Uncertainty in the knowledge about the unfavourable effects

The number of subjects in the FDC studies was limited leaving some uncertainty regarding the exact safety profile of the combination therapy alogliptin plus pioglitazone, which was further addressed during the procedure. In the two main FDC trials, there was a numerically higher incidence in CV outcome. However, the numbers were very low. The same was true for all alogliptin studies together. Alogliptin, when compared to placebo, was associated with a higher cardiovascular event rate (Hazard ratio 1.33). However, in the Controlled Phase 2 and 3 Study Group, cardiovascular event rate was lower compared to active comparators (Hazard ratio 0.8). In addition, interim analyses of the cardiovascular outcome study (study 402) demonstrated that alogliptin was associated with a lower cardiovascular risk (Hazard ratio 0.81).

Pioglitazone use is associtated with the following uncertainties:

Cardiac failure is an identified risk for pioglitazone and pioglitazone is contraindicated in patients with cardiac failure or a history of cardiac failure (I-IV) and information is included in section 4.4 of the proposed SmPC for Incresync. Furthermore, cardiovascular ischaemic disease is considered as a potential risk for pioglitazone and is included in the proposed RMP.

With regards to alogliptin the following uncertainties were observed.

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 negligible. 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%).

Patients with hepatic disease

Patients with hepatic disease were excluded in the phase 2 and 3 studies. In a pharmacokinetic study in patients with moderate hepatic impairment, there were no adverse events and no clinically meaningful changes in laboratory tests reported. Patients with severe hepatic impairment were not investigated. In addition, five cases of hepatotoxicity, including one case of hepatic failure, were reported postmarketing in Japan. 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, 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.

Balance

Importance of favourable and unfavourable effects

Overall, alogliptin demonstrates a clinically and statistically significant treatment effect as dual and triple combination therapy with pioglitazone ±MET and as monotherapy. The treatment effect is generally consistent for primary and secondary efficacy variables, and appears maintained over time. The combination was not associated with weight gain, and there were no detrimental effects on blood pressure and serum lipids. The selected doses for the fixed-dose combination studies are in line with the doses evaluated in the clinical studies and in accordance with clinical practice.

The main goal of treatment of diabetes is the prevention of cardiovascular events. HbA1c is only a surrogate endpoint. The effect of alogliptin on cardiovascular events is not clear. Nevertheless, interim analyses of the cardiovascular outcome study (study 402) 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 first quarter of 2014.

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. Similar to other DPP-4 inhibitors, alogliptin is associated

with pancreatitis. However, these events were rare, and consistent with labeling for other DPP-4 inhibitors these risks can be mentioned in the SmPC (4.4 Special warnings and precautions for use).

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. Pancreatitis is included as an identified risk in the Risk Management Plan, into which new pancreatitis data has been integrated during the procedure.

The risk of hypoglycaemia for alogliptin in combination with metformin and SU is only slightly increased.

There is insufficient knowledge about efficacy and safety in patients with severe hepatic disease. The use of alogliptin in patients with severe hepatic impairment can not be recommended. This is stated in the SmPC. In addition, hepatotoxicity was reported postmarketing in Japan. A relation with treatment with alogliptin cannot be ruled out but the hepatic safety database for the controlled clinical trials is considered reassuring.

Benefit-risk balance

Considering the consistent clinically and statistically significant treatment effect observed with alogliptin in the monotherapy study, the add-on to oral therapy study and the long-term active comparator study, the benefit risk balance of the alogliptin/pioglitazone FDC is considered postive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Incresync is favourable in the "second or third line 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 (particularly overweight patients) inadequately controlled on pioglitazone alone, and for whom metformin is inappropriate due to contraindications or intolerance.
- in combination with metformin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients (particularly overweight patients) inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.

In addition, Incresync can be used to replace separate tablets of alogliptin and pioglitazone in those adult patients aged 18 years and older with type 2 diabetes mellitus already being treated with this combination.

After initiation of therapy with Incresync, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, Incresync should be discontinued. In light of potential risks with prolonged pioglitazone therapy, prescribers should confirm at subsequent routine reviews that the benefit of Incresync is maintained (see section 4.4)."

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

Conditions or restrictions regarding supply and use

Medicinal products 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.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use alogliptin/pioglitazone. Prior to distribution of the prescriber guide in each Member State, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

- This educational pack is aimed at strengthening awareness of the important identified risks of bladder cancer and heart failure and the overall recommendations intended to optimise the benefit-risk balance at the patient level.
- The physician educational pack should contain: the Summary of Product Characteristics, the package leaflet and a prescriber Guide.

The Prescriber Guide should highlight the following:

- Patient selection criteria including that alogliptin/pioglitazone should not be used as first line therapy and emphasising the need for regular review of treatment benefit.
- The risk of bladder cancer and relevant risk minimisation advice.
- The risk of heart failure and relevant risk minimisation advice.
- Caution on using in the elderly due to the age related increased risks (in particular bladder cancer, fractures and heart failure).

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.

APPENDIX

DIVERGENT POSITION

Divergent Position

We have a divergent opinion on the above mentioned Marketing Authorisation from that which has been adopted by the CHMP during its July 2013 session:

We consider that pioglitazone being of a negative benefit-risk ratio, any combination containing this same drug has necessarily a negative benefit-risk ratio as well.

This is due to the increased risk of bladder cancer in addition to the other well known adverse effects (especially heart failure and bone fracture) of this medicine, its questionable long term benefit in terms of cardiovascular protection and the available alternative treatments in type 2 diabetic patients.

Regarding bladder cancer, it was concluded by the CHMP in July 2011 that the small increased risk of bladder cancer could be reduced by appropriate patient selection and exclusion, including a requirement for periodic review of the efficacy and safety of the individual patient's treatment.

However, we observe that there is still a very substantial increase in the number of bladder cancer cases reported worldwide during the last 6-month period (01 /08/2012 to 31/01/2013) covering by PSUR 76: 1780 medically confirmed cases (3000 cumulatively) and 3162 non-medically confirmed cases (cumulatively 4925) mostly from US, despite risk minimization measures. Furthermore results of the Drug Utilisation Study are inconclusive in terms of adherence to minimisation activities and to the performance of a benefit monitoring under treatment.

This increased number of bladder cancer is one among a range of factors to be considered in the negative benefit-risk of pioglitazone:

- The sole beneficial effect of pioglitazone is its glucose reducing effect (a recognized marker of microvascular complications), which is similar to other oral antidiabetic drugs, such as sulphonylureas. Pioglitazone has not demonstrated a cardiovascular benefit, it is considered as neutral on cardiovascular complications, despite an increase of congestive heart failure associated with its use.
- According to PROactive long term follow up and utilisation studies, a large proportion of patients stop pioglitazone treatment within the first years of treatment precluding potential long term benefit on prevention of cardiovascular events. The identified increased bladder cancer risk is likely to reduce adherence to pioglitazone long-term treatment.
- Several other serious risks have already been identified, as cardiac failure, weight increase, bone fractures and macular oedema.

Thus, it appears impossible to define a subpopulation of diabetic patients that could benefit of pioglitazone or any combination containing this same drug.

London, 25 July 2013

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Pierre Demolis (France)