European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Janumet

International Nonproprietary Name: sitagliptin / metformin hydrochloride

Procedure No. EMEA/H/C/000861

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 30 April 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Janumet, 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 EMEA/CHMP on 21 September 2007.

The legal basis for this application refers to Article 10(b) of Directive 2001/83/EC, as amended – relating to applications new fixed combination products.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication:

For patients with type 2 diabetes mellitus:
Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on metformin alone or those already being treated with the combination of sitagliptin and metformin.
Janumet is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulphonylurea.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 21 January 2005. The Scientific Advice pertained to pre-clinical and clinical aspects of the dossier.

Licensing status:
A new application was filed in the following countries:

Brazil	6 November 2006	Colombia	28 February 2007
Egypt	10 October 2006	Korea	22 December 2006
Malaysia	15 September 2006	Mexico	16 August 2006
New Zealand	22 June 2006	Peru	4 January 2007
United Arab Emirates	4 October 2006	USA	31 May 2006

The product was licensed in the United States at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Harald Enzmann**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 30 April 2007.
- The procedure started on 23 May 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2007.
- During the meeting on 17-20 September 2007, 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 20 September 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 5 February 2008.
- During the CHMP meeting on 18-21 February 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted written explanations to the CHMP List of Outstanding Issues on 17 March 2008.
- The Rapporteurs circulated the Joint Assessment Report on the CHMP List of Outstanding Issues to all CHMP members on 11 April 2008.
- During the meeting on 21-24 April 2008, 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 Janumet on 24 April 2008.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 16 July 2008.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetes. This disorder afflicts an estimated 6% of the adult population in Western society and over 2% worldwide. The worldwide prevalence of T2DM is increasing and expected to grow by 3% per annum, reaching a total of 220 million cases by 2010. Although the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that intensive treatment of hyperglycaemia leads to a lower incidence of diabetes complications (e.g., retinopathy and nephropathy), many patients remain inadequately treated using diet/exercise regimens and existing therapies. Furthermore, over time, there is a progressive loss of β-cell function that has been best characterized in the UKPDS study, but has also been observed in other studies of patients with T2DM. This gradual loss of β-cell function underlies the progressive deterioration in glycaemic control in T2DM and the corresponding need for more intensive therapies to treat patients with the disease.

Currently available therapies are:

- Sulphonylureas (SU), which increase insulin secretion. Their main adverse effects are hypoglycaemia and weight gain.
- Metformin (Met), which increases intestinal glucose utilisation, decreases hepatic glucose production and increases insulin sensitivity. Metformin may also improve dyslipidaemia. Gastrointestinal undesirable effects and lactic acidosis represent the main adverse effects.
- Thiazolidinediones (TZDs), such as pioglitazone, which increase insulin sensitivity and enhance glucose uptake in skeletal muscle. Undesirable effects are fluid retention or weight gain, possibility of increased fracture rate in female patients and possibly increased risk of heart failure.
- Alpha-glucosidase inhibitors, which have shown limited efficacy but with no risk of hypoglycaemia. Gastrointestinal undesirable effects limit compliance.
- Insulin, which is used in type 2 diabetes when oral agents have failed to achieve glycaemic control or in case of complications. Insulin may cause hypoglycaemia and weight gain.
- Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), such as sitagliptin, which enhance active incretin levels leading to increases in insulin release and decreases in glucagon levels in a glucose-dependant manner. Common adverse events are upper respiratory tract infection, nasopharyngitis, and headache.

A fixed dose combination (FDC) tablet (Janumet (MK-0431A)) containing 2 antihyperglycaemic agents (AHAs)—one novel (sitagliptin phosphate [MK-0431]) and one commonly used (metformin hydrochloride)—with complementary mechanisms of action for lowering glucose has the potential to provide a new treatment option for patients with T2DM.

The application concerns a centralised procedure in accordance with article 10b of Directive 2001/83/EC as amended – relating to applications new fixed combination products.

Relevant Guidelines for this product are:

- Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00).
- Note for guidance on fixed combination medicinal products (CPMP/EWP/240/95).

The claimed indication was:
For patients with type 2 diabetes mellitus:

Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on metformin alone or those already being treated with the combination of sitagliptin and metformin.
Janumet is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as

an adjunct to diet and exercise in patients inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulphonylurea.

The approved indications are:
For patients with type 2 diabetes mellitus:

Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Janumet is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

The proposed dose recommendations are:
For patients not adequately controlled on metformin alone, the usual starting dose of Janumet should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

For patients switching from co-administration of sitagliptin and metformin, Janumet may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea the dose of Janumet should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Janumet is used in combination with a sulphonylurea a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia.

Sitagliptin (Januvia) is a DPP-4 inhibitor that has been approved for marketing in the EU in March 2007. The indication is:
For patients with type 2 diabetes mellitus, Januvia is indicated:

- to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- to improve glycaemic control in combination with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Januvia is indicated:
- in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

Metformin is a biguanide that has been used widespread for T2DM. It has become the most commonly selected first-line agent in the treatment of patients with T2DM. It was originally granted national authorisations in the EU between 1959 and 1997. Following a referral to the CPMP under Article 11 of Council Directive 75/319, as amended, a decision on a harmonised SPC for metformin was issued in February 2001. Metformin is authorized for the indications:

"*Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.*
- In adults, metformin may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, metformin may be used as monotherapy or in combination with insulin."

The recommended starting dose of metformin is two or three times daily 500 or 850 mg taken with or after meals. Due to frequent gastrointestinal (GI) side effects, uptitration is recommended at 10-15 day intervals. The recommended maximum daily dose is 3000 mg but most patients do not tolerate such high doses and the additional effect achieved with daily doses beyond 2000 mg is usually minor.

2.2 Quality aspects

Introduction

Janumet is presented as film-coated tablets containing sitagliptin and metformin hydrochloride as active substances in the strength combinations 50 mg/850 mg and 50 mg/1000mg. The other ingredients are microcrystalline cellulose, povidone, sodium stearyl fumarate, sodium lauryl sulfate and purified water. The film consists of polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide red, iron oxide black and purified water.

The film-coated tablets are marketed in opaque blisters (outside PVC/PE/PVDC coated blister foil, inside heat seal laquered with aluminum foil).

Drug Substance

Two active substances are used in this fixed combination product, sitagliptin and metformin hydrochloride.

Sitagliptin

The drug substance is sitagliptin as monohydrate phosphate salt and its chemical name is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate according to the IUPAC nomenclature.
Sitagliptin is a white to off-white powder and exhibits pH dependent aqueous solubility. It is soluble in water and *N*,*N*-dimethyl formamide, slightly soluble in methanol, very slightly soluble in ethanol, acetone and acetonotrile and insoluble in isopropanol and isopropyl acetate. The above-mentioned active substance contains a chiral centre and is used as a single enantiomer (R).

- **Manufacture**

Sitagliptin is synthesised in two reactions steps, hydrogenation, in order to obtain the stereospecific free base, followed by the preparation of the phosphate monohydrate salt. Finally the active substance is purified by crystallisation.
The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included.

Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented.

Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy and the molecular weight as determined by mass spectroscopy is in agreement with the expected molecular weight. The results of the X-ray crystallography are consistent with the proposed molecular structure.

- **Specification**

The active substance specifications include tests for colour (white to off-white powder), identification (IR), assay (98.5-101.5 % w/w HPLC), impurities (HPLC), residue on ignition and water content (Karl Fisher).
The specifications reflect all relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were described and their validations are in accordance with the ICH Guidelines.

Impurities have been described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance. All limits are in accordance with ICH requirements. The chiral purity was also tested. Certificates of analyses for the active substances issued by the finished product manufacturer were provide and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines and demonstrated adequate stability of the active substance. The active substance is not susceptible to degradation under the influence of light. The results of the long-term and accelerated studies support the retest period.

Metformin hydrochloride

Metformin hydrochloride's chemical name is 1,1-Dimethylbiguanide monohydrochloride according to the IUPAC nomenclature. This active substance is described in the Ph.Eur. It is a white, hygroscopic crystalline powder that is odourless and has a bitter taste. The compound is freely soluble in water, slightly soluble in ethanol and practically insoluble in chloroform, acetone, ether and in ethylene chloride. It has a specific crystalline form and has not demonstrated polymorphism or solvates. Particle size does not significantly influence dissolution of metformin hydrochloride, because it is freely soluble in water.

The chemistry, manufacturing and control information on metformin hydrochloride has been evaluated by the EDQM and a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) has been issued.

Metformin hydrochloride which was used in all of the formulation development meets the specifications of Ph.Eur. Monograph.

The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance.

Batch analysis data of the three batches of metformin hydrochloride drug substances are provided. The three lots are within the specifications and consistent from batch to batch.

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines and demonstrated adequate stability of the metformin hydrochloride. The re-test period proposed was considered acceptable according to the stability data submitted.

Drug Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified.
Janumet film-coated tablets were developed 3 tablet strengths of sitagliptin / metformin hydrochloride (50 mg/500 mg, 50 mg/850, 50 mg/1000 mg) which were used either in clinical trials or in stability program. However, only two tablet strengths (50 mg/850 and 50 mg/1000 mg) will be marketed in the EU.
The main aim of the applicant was to develop a formulation which would be bioequivalent to individual sitagliptin phosphate and metformin hydrochloride tablets co-administered. The formulation was optimized to provide rapid release of the both active substances. In this context, the excipients have been chosen in order to take into account the following objectives: facilitate rapid dissolution of the drug substances as expected with an immediate release dosage form; provide satisfactory chemical stability and provide appropriate process robustness.
A fluid bed granulation process was selected based on the poor compatibility of metformin hydrochloride and its high drug load in the fixed dose combination (FDC) tablet.

It was noticed that the formulation development activities were driven by both product quality and process robustness considerations. The key points examined during formulation development were: the effect of binder level on granule and tablet properties, the effect of surfactant on tablet dissolution, and the effect of lubricant on stability, tablet compression performance and tablet dissolution. Furthermore, it was verified that the excipient levels were optimized to provide high quality tablets for film-coating as well as maintain rapid dissolution of both active substances. Additionally, the composition optimization sought to minimize the excipient quantities consistent with achieving the desired quality attributes, and to minimize the tablet sizes.
Results of formulation and process development studies demonstrate that the tablet formulation and the manufacturing process are robust and under control.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as fluid bed granulation, drying, granulation milling, blending and lubrication, compression, and film-coating unit operations. Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps in the manufacturing process.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The drug product specifications were established according to the ICH guidelines and include the following tests: appearance, identification (IR and HPLC), assay (95.0%-105.0%) of both drug substances, degradates (sitagliptin) and related substances (metformin) by HPLC-testing, dose uniformity, dissolution, and microbial limits (Ph Eur).
All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the CHMP and ICH guidelines.
Batch analysis data on three clinical and pilot scale batches scale batches confirm satisfactory uniformity of the product at release

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guideline. Three production scale batches of 50/500 mg and 50 mg /1000 mg have been stored at long term and accelerated conditions in the proposed market packaging. The bracketing of the 50/850 mg tablets by testing only 50/500 mg tablets and 50/1000 mg tablets was considered acceptable.
Two production batches per strength were stored under photostability stress testing under ICH conditions. The photostability results show that the tablets are not sensitive to light.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the Summary of Product Characteristics (SPC) are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.
At the time of the CHMP opinion, there were not unresolved quality issues.

2.3 Non-clinical aspects

Introduction

Janumet is a fixed dose combination product containing two approved drugs, sitagliptin (Januvia) and metformin.
The non-clinical primary and secondary pharmacodynamics (PD) of sitagliptin have been previously fully evaluated and approved. Preclinical animal models that accurately mimic the human pharmacology of metformin, however, are not available. Hence, there are no primary and secondary pharmacodynamic reports for the FDC.
The preclinical safety of the individual drugs has been fully evaluated and approved by regulatory agencies. As the known pharmacological properties of sitagliptin and metformin do not suggest undesirable combination effects, no additional safety pharmacology studies were performed.
Pharmacodynamic drug interactions in preclinical species are of limited relevance to human physiology, as such, and with support of the clinical data no pharmacodynamic drug interaction studies with the FDC have been reported.

The applicant provided minimal data on the toxicology of metformin, based on the package inserts and NDA of the products Fortamet and Glucophage. However, metformin is a well-known substance and there is an extensive amount of clinical experience. Therefore, from a preclinical point of view, it was not considered necessary to request more safety data regarding metformin.

The applicant received Scientific Advice pertaining to the toxico-pharmacological development of the FDC from the CHMP on 21 January 2005. This scientific advice was followed, and as such a series of toxicity studies in dogs were conducted to assess the potential for both toxicological and toxicokinetic interactions with co-administration of both compounds.

Pivotal studies regarding sitagliptin, and the combination of metformin and sitagliptin, were performed in compliance with GLP. However, the exploratory single dose oral toxicokinetic study TT05-1150 and the repeated-dose toxicology study with metformin alone (TT06-6018) were non-GLP studies.

Metformin is a well-established substance. It is not known whether published studies with metformin were performed in compliance with GLP.

Pharmacology

- Primary pharmacodynamics

Sitagliptin is an orally-active DPP-4 inhibitor that acts as an incretin enhancer. The main mechanism of action of sitagliptin is inhibition of the activity of the DPP-4 enzyme, which hydrolyzes active incretin hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), to produce inactive degradation products. These hormones are released after a meal (by specialized endothelial cells in the intestine) and play an important role in the glucose homeostasis (glucose-dependent insulin biosynthesis and secretion). As such, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells when glucose concentration is elevated, but not during hypoglycaemia. In turn, higher insulin levels result in enhanced uptake of glucose in tissues. GLP-1 also lowers glucagon secretion from pancreatic alpha cells which, along with higher insulin levels, leads to reduced hepatic glucose production. Efficacy of sitagliptin in lowering blood glucose levels after a dextrose challenge was shown in lean mice, in diet-induced obese mice and in diabetic db/db mice. With respect to the pharmacology of the metabolites of sitagliptin, M1, M2, and M5 were shown to be ~300-, 1000-, and 1000-fold less active, respectively, than sitagliptin as DPP-4 inhibitors. The DPP-4 inhibitor activity of M3, M4, and M6 was not determined. The levels of these metabolites in human plasma are low and they are not expected to have a meaningful impact on the pharmacological activity of sitagliptin.
Metformin is a well-established treatment for type 2 diabetes. The efficacy of metformin is believed to be mediated primarily via inhibition of hepatic glucose production.

- Secondary pharmacodynamics

The selectivity of sitagliptin was assessed in a number of assays, including several proline-specific enzymes, proteases, ion channels and 5-HT_2 receptors. Sitagliptin appeared to have little affinity for

these biological biomolecules (generally IC50 >100 μM). Only a weak activity was demonstrated in assays for some ion channels (IKr, L-type Ca channel, and Na channel Site II) and 5-HT_2 receptors. Considering safety pharmacology data, together with the safe clinical use of 5-HT_2 receptor antagonists, these observations are not considered to be a major concern for sitagliptin in T2DM. Sitagliptin is not expected to inhibit DPP-4 related proteins DPP-8, DPP-9, FAP and PEP, with IC50s exceeding 50 μM. DPP-6 and DPP-10 are homologues of DPP-4 that lack a catalytic serine residue and are therefore inactive as peptidases. Both proteins appear to modulate cellular trafficking, membrane targeting, and functional properties of neuronal Kv4-mediated A-type potassium channels. Though it is not known whether sitagliptin can bind to the hydrolase domain of DPP-6/10, such binding even if it occurred would not be expected to influence potassium channel function.
No secondary pharmacodynamic assays were performed with metformin; these studies were not considered necessary in view of the extensive clinical experience accumulated over the many years on the market.
No secondary pharmacodynamic assays were performed with the fixed dose combination.

- Safety pharmacology programme

Sitagliptin caused no effect on respiratory system, renal function, platelet function, the gastrointestinal system, and behavioural and other CNS effects. Minor cardiovascular effects were observed in dogs (decreased blood pressure and heart rate). Sitagliptin inhibited hERG current in a hERG channel assay at high concentrations (IC50 > 100x human C_{max} at maximally recommended dose of 100 mg/day sitagliptin). No effects were observed on ECG or QT-interval in dogs.
No formal safety pharmacology studies have been performed on metformin. These studies were not considered necessary in view of the extensive clinical experience accumulated over the many years on the market.
No specific safety pharmacology studies were conducted with the FDC. It is accepted that the known pharmacological properties of sitagliptin and metformin do not suggest undesirable combination effects that would require further safety pharmacology studies. ECG recordings were however performed during the repeated-dose toxicology studies in order to investigate potential interactions and how any PD or pharmacokinetic (PK) interactions might affect the QT_c. These measurements did not reveal any treatment-related effects.

- Pharmacodynamic drug interactions

No preclinical PD drug interaction studies were performed on the combination of sitagliptin and metformin. This is endorsed as sitagliptin and metformin act through different mechanisms of action, hence adverse PD interactions are not expected. Furthermore, the combination of sitagliptin and metformin is a clinically approved combination.
No non-clinical data were provided on possible PD interactions of sitagliptin/metformin in combination with a sulphonylurea (SU). However, clinically, no relevant concerns were discovered regarding the safety of the combination of sitagliptin/metformin with glimepiride.

Pharmacokinetics

Sitagliptin is a moderate to high clearance drug, with a relatively short plasma half-life. Sitagliptin was rapidly absorbed, bioavailable, and exhibited fairly linear oral pharmacokinetics in rat and dog. *In vitro* plasma protein binding is low in mouse, rat, rabbit, dog, and human. [^{14}C]Sitagliptin-related radioactivity is distributed widely throughout the body following intravenous (IV) administration to rats, but is cleared efficiently from all tissues. However, cecum, intestine, liver and kidneys contained still relatively high concentrations of sitagliptin related material after 24 hours. Enterohepatic circulation can therefore not be ruled out. Sitagliptin was shown to cross the rat and rabbit placenta readily. The sitagliptin metabolites, which are present at low to trace levels in plasma, are formed by N-sulfation, N-carbamoyl glucuronidation, hydroxylation of the triazolopiperazine ring, and by oxidative desaturation of the piperazine ring followed by cyclization via the primary amine. All the metabolites detected in human plasma are observed in rat and dog; however, not all observed metabolites are present in the same matrix as observed in humans. Due to the minor metabolism of sitagliptin, consequences of the differences in metabolism between human, rat and dog on the

observed PK are not expected. *In vitro* studies indicated that CYP3A4 is primarily involved in the metabolism of sitagliptin, with a minor contribution of CYP2C8. In dogs and humans, sitagliptin is cleared primarily by renal excretion of parent drug, while in rats it is cleared by both renal and biliary excretion. Sitagliptin is shown to be a substrate of the mouse and human P-glycoprotein (Pgp), and the human renal organic anion transporter hOAT3. Sitagliptin is secreted into rat milk (milk-to-plasma ratio ~ 4). Sitagliptin has no inhibitor capacity for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 at concentrations up to 100 μM. Furthermore, sitagliptin is not an inducer of CYP3A4 *in vitro*. *In vitro*, sitagliptin has no inhibitory effect on the MDR1 Pgp-mediated transport of digoxin, verapamil, ritonavir, and vinblastine. Sitagliptin weakly inhibited MDR1 Pgp-mediated transport of quinidine, but only at very high concentrations. Cyclosporin A (potent Pgp inhibitor) significantly inhibited MDR1 Pgp-mediated transport of sitagliptin. Sitagliptin is a weak inhibitor of hOAT3-mediated cimetidine uptake; however not at clinically relevant concentrations. The effect of various commonly prescribed drugs (cimetidine, enalapril, enalaprilat, fenofibrate, fenofibric acid, furosemide, gabapentin, ibuprofen, indapamide, probenecid and quinapril) on hOAT3-mediated uptake of sitagliptin is evaluated *in vitro*. For the major half of these drugs, the IC50 is higher than their maximum total or unbound concentration in plasma. Some of these drugs (probenecid, fenofibric acid, furosemide and ibuprofen) have plasma C_{max} concentrations of free and bound fraction above the observed IC50 levels. Sitagliptin is eliminated by renal and non-renal mechanisms. Assuming that tubular reabsorption of sitagliptin is minimal, approximately 50% of the total plasma clearance of sitagliptin is due to active renal secretion. Therefore, even in the unlikely event that active renal secretion is completely inhibited; the change in plasma exposure of sitagliptin would be only approximately 2-fold. Given the apparently wide therapeutic index of sitagliptin, clinically relevant increases in plasma concentrations would not be expected in the presence of hOAT3 inhibitors.

The pharmacokinetics of metformin in rats after oral and IV administration are dose proportional. Oral bioavailability in rats was 29 – 34%. *In vitro* studies indicate that transepithelial transfer of metformin in the intestine is at least partly by passive permeation.
After oral administration of [^{14}C]metformin to normal and diabetic mice, the highest concentrations of radioactivity are found in the small intestine, stomach, colon, salivary gland, kidney and liver. The mean binding value of metformin to rat plasma protein is 15%. The equilibrium plasma-to-blood cells partition ratios of metformin in rat plasma are 1.37, 1.25, and 1.33 at initial blood concentrations of 1, 5, and 20 mg/mL, respectively.
Metformin is the major radioactive component in plasma and urine from mice, rats, dogs and humans dosed with [^{14}C]metformin. A metabolite, 1-methyl biguanide, is identified in rabbit plasma and urine. Studies with various inducers and inhibitors of cytochrome P450 enzymes indicated that metformin is metabolized via CYP2C11, 2D1, and 3A1/2 in rats.
Metformin is excreted primarily in urine in rats and dogs. The estimated renal clearance value of metformin is considerably faster than the reported glomerular filtration rate in rats, indicating that, like sitagliptin, metformin is subject to active renal secretion in rat renal tubules. However, unlike sitagliptin, metformin has been shown to be a substrate of the cationic organic transporters hOCT1 and hOCT2, but not hOAT1, hOAT3 or hOCT2-A.

Possible PK interactions of sitagliptin and metformin with other drugs have been studied in previous submissions or are known from clinical experience. Interactions between sitagliptin and metformin based on cytochrome P450 metabolism are not likely since neither substance is metabolised to a great extent. Furthermore, different enzymes are involved in the metabolism of these substances and sitagliptin is shown not to be an inducer or inhibitor of cytochrome P450 enzymes. Interactions at the level of renal transporters are not likely either, since different transporters are involved. Toxicokinetic results of a combination study in dogs also indicate that no relevant PK interactions occur between sitagliptin and metformin.
Pharmacokinetic interactions of sitagliptin/metformin in combination with a SU were not investigated non-clinically. However, clinically, there was no cause for concern regarding the combination of sitagliptin/metformin with glimepiride.

Toxicology

- Single dose toxicity

Single dose studies with sitagliptin were performed in mice and rats. The highest non-lethal dose in mice is 1000 mg/kg (122 times the human exposure based on AUC). In rats the highest non-lethal dose was 2000 mg/kg for females and 3000 mg/kg for males (271 and 182 times the human exposure based on AUC respectively).

The LD_{50} values for metformin in mice, rats, rabbits, and dogs are 2400, 1770, 552, and 375 mg/kg, respectively.

- Repeat dose toxicity (with toxicokinetics)

Sitagliptin repeat-dose toxicity studies were performed in mice (up to 93 days), rats (up to 184 days) and dogs (up to 365 days). The maximum non-lethal dose was 750 mg/kg/day for mice (approximately 80 times the human exposure based on AUC), 500 mg/kg/day for rats (48 times the human exposure based on AUC), and ≥ 50 mg/kg/day for dogs (≥ 22 times the human exposure based on AUC).

In both mice and rats renal toxicity is observed at systemic exposure values above 58 times the human exposure levels, while the no-effect level is found at 19 times the human exposure level. In mice it consisted of dilatation of the renal pelvis (associated with variable loss of papillary, medullary, and cortical tissue) and increases in relative kidney weights. In rats, renal toxicity consisted of renal tubular necrosis (accompanied by tubular degeneration and dilatation) and treatment related urinary changes (consistent with renal tubular necrosis). The mortality seen in rats is due to renal tubular necrosis. It is likely that renal toxicity is specific for rodents, due to the very high and rapid renal elimination of sitagliptin in rodents. This is supported by the lack of any renal toxicity in dogs.

Liver toxicity was seen in both mice and rats and consisted of liver weight increases, centrilobular hepatocellular hypertrophy, inflammation, degeneration, and necrosis (at higher doses) in the 14-week range-finding study at doses ≥500 mg/kg/day; and cystic degeneration and focal hepatocellular alteration in the 106-week carcinogenicity study at 500 mg/kg/day. Even though the mechanism for sitagliptin-induced liver toxicity is not completely clear, the safety margins for these effects are sufficient. In addition, no hepatotoxicity is found in dogs treated with maximum-tolerated doses of sitagliptin for up to 1 year.

Sitagliptin caused teeth abnormalities in rats at exposures similar to the human exposure, based on AUC. These effects were only observed on the continuously growing teeth in rats; they were not observed on the continuously growing teeth in mice. Janumet is not indicated for use in children below 18 years of age thereby excluding patients with ongoing tooth development, indicating that in the current indication, these effects are of little relevance.

Other treatment-related findings in the rat were myocardial degeneration, mammary gland necrosis, uterine atrophy, tremors, lymphoid and some haematological changes, alopecia, increased organ weights (thyroid (F), adrenal, prostate) and decreased organ weights (pituitary gland (F) and spleen (M)). These findings are observed at doses equal to or above the LOAEL for liver and renal toxicity. The safety margins for these effects are sufficient.

Intermittent tremors of a transient nature are observed in rats receiving high doses of sitagliptin (≥1500 mg/kg/day). The NOEL for neurological signs in dogs is 10 mg/kg. In dogs, the safety margin for these effects is approximately 6 (based on AUC as well as on C_{max}). This is rather low, however no signs of neural toxicity are observed in the clinical trials with sitagliptin at doses sufficiently above the maximum recommended clinical dose. The neurological findings in rats and dogs are not considered relevant for humans receiving therapeutic doses of sitagliptin. However, as a precautionary measure potential neurotoxicity is addressed in the Risk Management Plans of Januvia and Janumet.

The clinical relevance of the muscle fibre degeneration found in dogs is limited. This is based on the severity of muscle degeneration found in dogs (slight degeneration of isolated fibers which was only observed microscopically), the relative low incidence of muscle degeneration in the two studies (2/8

and 1/8 dogs for 14-week and 27-week study, respectively), and the lack of adverse muscle findings for the high-dose in the 1-year dog study as well as in the phase 3 trials. However, in view of a safety margin of ≥6, this finding is monitored in the Risk Management Plans of Januvia and Janumet.

Necrotic skin lesions in monkeys are reported by the FDA as potential risk of DPP-4 inhibitors. A 14-week repeated-dose study in monkeys (TT #06-1005) showed a no-effect level for skin lesions of ≥100 mg/kg/day, corresponding with a 22-28 times higher exposure as compared to the maximum recommended dose in human (100 mg/day).

A study in which metformin was administered at 50 mg/kg/day to dogs showed increased mortality, increased serum lactate levels and emesis.

Sitagliptin + metformin
The applicant performed three repeated-dose toxicity studies in dogs to rule out unexpected toxicologic effects of the combination (two studies with the combination sitagliptin + metformin, and one study with metformin alone to establish the effects of metformin alone in the dog strain used). The dog was chosen as the most sensitive species since in rats very high doses of sitagliptin were required to produce toxicity. The dog proved also rather sensitive towards metformin; repeated application of 50 mg/kg/day of metformin, alone or in combination with different doses of sitagliptin, caused salivation, emesis, increased serum lactate and unscheduled deaths (probably due to lactic acidosis). In a few early-death animals in the combination study TT06-6000 (10 mg/kg sitagliptin + 50 mg/kg metformin or 50 mg/kg sitagliptin + 50 mg/kg metformin), vacuolation and/or neuronal necrosis was observed in the brain. These histological findings were accompanied by severe physical signs pre-death and therefore are most likely signs of agony. Spontaneous deaths also occurred in study TT06-6018 (metformin 50 mg/kg/day alone) but in this study no histological examination was performed. The brain effects as observed in study TT06-6000 were most likely caused by metformin and not by the combination of metformin and sitagliptin, because it was shown that degenerative effects in the brain have also been observed in studies where dogs had been administered metformin alone. Also in these studies, these effects were observed at doses from 50 mg/kg/day. The combination studies with sitagliptin and metformin in dogs thus indicated no evidence of toxicokinetic or toxicologic interactions.
No non-clinical studies were performed for the combination of sitagliptin/metformin with a SU, however, sitagliptin, metformin and SU have different toxicity profiles, and therefore interactions seem unlikely. Furthermore, clinically, no relevant concerns were discovered regarding the safety of the combination of sitagliptin/metformin with glimepiride.

- Genotoxicity

Sitagliptin was not seen to be genotoxic in an *in vitro* assay on gene mutations in bacteria (Ames test), in an *in vitro* assay on gene mutations in mammalian cells (rat hepatocytes), in an *in vitro* chromosome aberration assay (Chinese hamster ovary cells) or in an *in vivo* mouse micronucleus test.

Metformin is not mutagenic or clastogenic in the Ames bacterial mutagenicity assay, chromosomal aberration assay, cytogenetic assay, or *in vivo* micronucleus assay.

- Carcinogenicity

In a 2-year mouse study performed with sitagliptin no treatment-related increase in tumour incidence is observed. In a 2-year rat study, there is an increased incidence in hepatic tumours which is likely related to chronic hepatic toxicity. The safety margin for these tumours is 19, which is considered sufficient.

No increased tumour incidence is observed in a 2-year study in mice with metformin. No tumourigenic potential is observed in rats except for an increase in benign stromal uterine polyps in females. Extensive clinical experience does not indicate an increased tumourigenic potential.

- Reproduction Toxicity

Sitagliptin did not affect male or female fertility in rats up to 1000 mg/kg/day (approximately 100-fold the human exposure at 100 mg/day). In combined embryo-foetal/pre- and postnatal studies in rats, a slight increased incidence of foetal rib malformations (absent, hypoplastic, and wavy ribs) was observed at 1000 mg/kg/day as well as decreased body weight gain in the pups. The NOEL for this effect was 250 mg/kg/day (approximately 32-fold the human exposure at 100 mg/day). An embryo-foetal study in rabbits showed no developmental effects. Sitagliptin is excreted in rat milk.

Metformin did not affect fertility and is not teratogenic in rats and rabbits. Metformin is excreted in rat milk.

The FDC of sitagliptin/metformin should not be used in women who are breast-feeding; this is reflected in the SPC.

- Local tolerance

Sitagliptin was not seen to be a dermal irritant in rabbits and in an *in vitro* human epidermal skin culture system. Sitagliptin is a mild ocular irritant in the *in vitro* bovine corneal opacity assay and a moderate ocular irritant *in vivo* in rabbits. Sitagliptin is not a dermal sensitizer in a local lymph node assay in mice.

No local tolerance studies were performed with metformin.

- Other toxicity studies

Immunotoxicity: Inhibition of DPP-4 by sitagliptin does not seem to play a major role in T-cell dependent immune responses. Animal data on the role of DPP-4 in T-cell immune response showed no consistent changes after inhibition/knock out of DPP-4. *In vitro* studies showed that the concentrations of sitagliptin needed to evoke noticeable effects on T-cells are sufficiently far above the maximal plasma concentration which is reached after a therapeutic dose of 100 mg in humans. In the repeated-dose toxicity studies, there is no suggestion of an immunosuppressive effect of sitagliptin.

Ecotoxicity/environmental risk assessment

Environmental risk regarding sitagliptin has been evaluated during the registration procedure of Januvia. It is concluded that sitagliptin is neither vPvB nor PBT and that the risk to the aquatic environment is acceptable.

No ERA is provided for metformin. However, metformin is a well-established substance, and therefore submission of complete new studies is regarded not necessary.

2.4 Clinical aspects

Introduction

The clinical pharmacology programme consisted of 4 pharmaceutical/pharmacokinetic studies which served to bridge the FDC tablet to the clinical pharmacologic, pharmacokinetic, safety and efficacy data for sitagliptin and metformin combination use presented in the original sitagliptin MAA.

Dose selection for the sitagliptin component of Janumet was based upon dose-range finding studies (P010 and P014). Dose selection of the metformin component of Janumet was based upon the usual prescribed doses of metformin in the treatment of patients with T2DM.

Initial data supporting the efficacy of the combination of sitagliptin and metformin emerged from a Phase II study (P015). The Phase III clinical development program was designed to evaluate 3 treatment modes:

- sitagliptin as add-on therapy to ongoing metformin monotherapy dosed at ≥1500 mg/day (P015, P020, and P024)
- sitagliptin as add-on therapy to the ongoing combination of metformin and a sulfonylurea (P035, Stratum 2)
- initial treatment with the combination of sitagliptin and metformin (P036).

Summary of Phase II and Phase III Clinical Research Studies Contributing to the Efficacy Profile of Janumet

Protocol No./Ref	Study Title	Randomization Ratio (total randomized N) and Treatment Arms (Exposed N/arm)	Efficacy Endpoints	Total Study Duration (Phase A/Phase B)
Phase II Studies				
P015	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Crossover Study With MK-0431 in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin	Randomization ratio: 1:1(N=28) • Placebo/Sitagliptin 50 mg b.i.d. (N=13) • Sitagliptin 50 mg b.i.d./Placebo (N=15)	• Primary: 24-hour WMG • Secondary: • FPG, fructosamine, mean daily SBGM (7-point fingerstick daily glucose average concentration and 2-hour post-meal average)	8 weeks: Two 4-week double-blind placebo-controlled cross-over periods
Phase III Studies				
P020 (Phase B ongoing)	A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin Therapy	Randomization ratio: 1:2 (N=701) • Placebo (N=237)* • Sitagliptin 100 mg q.d. (N=464) *Note: Placebo patients were switched (after the 24-week Phase A portion of the study) to glipizide uptitrated to 15 mg as tolerated	• Primary: HbA_{1c} • Secondary: FPG, 2-hour PMG, lipid panel *In subset:* Frequently sampled meal-tolerance test (MTT) to assess indices of insulin secretion • Other Endpoints: Proinsulin-to-insulin ratio	104 weeks: (24-week double-blind placebo-controlled/80-week double-blind active-controlled)
P024	A Multicenter, Double-Blind, Randomized Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 Compared With Sulfonylurea Therapy in Patients With Type 2 Diabetes With Inadequate Glycemic Control on Metformin Monotherapy	Randomization ratio: 1:1 (N=1172) • Glipizide (N=584) • Sitagliptin 100 mg q.d. (N=588)	• Primary: HbA_{1c} • Secondary: FPG, lipid panel; in subset: frequently sampled MTT to assess indices of insulin secretion (based upon measurements of PMG, insulin, C-peptide) • Other endpoints: Appetite changes, HOMA-IR, QUICKI, HOMA-β, Proinsulin-to-insulin ratio	104 weeks: (104-week double-blind active- control; primary efficacy hypothesis after 52 weeks)
P035	A Multicenter, Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Glimepiride alone or in Combination with Metformin	Randomization ratio: 1:1 (N= 441) Entire Cohort • Placebo (N=219) • Sitagliptin 100 mg q.d. (N=222) Stratum 1 • Placebo (N=106) • Sitagliptin 100 mg q.d. (N=106) Stratum 2 • Placebo (N=113) • Sitagliptin 100 mg q.d. (N=116)	• Primary: HbA_{1c} • Secondary: FPG, time to rescue, lipid panel; in subset: frequently sampled MTT to assess indices of insulin secretion (based upon measurements of PMG, insulin, C-peptide) • Other endpoints: HOMA-IR, QUICKI, HOMA-β, Proinsulin-to-insulin ratio	54 weeks: (24-week double-blind placebo-controlled/30-week double-blind active-controlled)

Protocol No./Ref	Study Title	Randomization Ratio (total randomized N) and Treatment Arms (Exposed N/arm)	Efficacy Endpoints	Total Study Duration (Phase A/Phase B)
P036	A Multicenter, Randomized, Double-Blind Factorial Study of the Co-administration of MK-0431 and Metformin in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control	Randomization ratio: 1:1:1:1:1:1 (N=1091) • Sitagliptin 50 mg b.i.d. plus metformin 500 mg b.i.d. (N=190) • Sitagliptin 50 mg b.i.d. plus metformin 1000 mg b.i.d. (N=182) • Metformin 500 mg b.i.d. (N=182) • Metformin 1000 mg b.i.d. (N=182) • Sitagliptin 100 mg q.d. (N=179) • Placebo (N=176)* • Open-label Cohort (N=117) *Note: Placebo patients are switched (after the 24-week Phase A portion of the study) to metformin	• Primary: HbA_{1c} • Secondary: FPG, 2-hour PMG, proportion of patients achieving glycemic goals, proportion of patients receiving glycemic rescue, 3-point MTT to assess indices of insulin secretion (based upon measurements of PMG, insulin, C-peptide, fructosamine), lipid levels in subset: 10-point MTT to assess indices of β-cell function • Other endpoints: HOMA-IR, QUICKI, HOMA-β, Proinsulin-to-insulin ratio	54 Weeks: 24-week double-blind placebo-controlled /30-week double-blind active-controlled

b.i.d. = twice daily; q.d. = once daily; WMG = weighted mean glucose; FPG = fasting plasma glucose; SBGM = self-blood glucose monitoring; HbA_{1c} = haemoglobin A_{1c}; PMG = post-meal glucose; MTT = meal tolerance test.; HOMA-β= homeostasis model assessment-β; HOMA-IR = homeostasis model assessment of insulin resistance; QUICKI = quantitative insulin-sensitivity check index.

The claimed indication and approved indication are very similar; for details on the indication and posology see section 3.1 of this report.

The applicant received Scientific Advice from the CHMP on 21 January 2005 pertaining to the clinical development programme of the fixed dose combination.

Janumet is not recommended for use in children below 18 years of age. Limited safety data is available in patients > 75 years of age; therefore Janumet should be used with caution as age increases. Further special populations such as patients with renal insufficiency and hepatic impairment have also been studied, leading to contraindications in both.

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.

Pharmacokinetics

In support of the current MAA for the proposed FDC, the Applicant submitted a single dose pilot study (P038), a single dose bioequivalence study (P048), a double blind cross-over study assessing incretin levels (P050), and a single dose bioequivalence study (P095) as well as a single dose sitagliptin/metformin interaction study (P012). The latter study had already been submitted and evaluated during the initial MAA for sitagliptin and suggests the absence of relevant pharmacokinetic (PK) interactions between sitagliptin and metformin. The submitted pharmacology studies are listed below, and a summary is presented in the introduction section 3.4.

Study PN012: Sitagliptin (1000 mg) and metformin (50 mg) drug interaction study in patients; N=13

Study PN038: Three way, two part, single dose biocomparison study with 2 probe formulations of sitagliptin/metformin 50/500 mg and 50/1000 mg FDC tablets and coadministration of corresponding doses of sitagliptin and metformin as individual tablets; N=24

Study PN048: Two way, two part, single dose bioequivalence study with the final formulations sitagliptin/metformin 50/500 mg and 50/1000 mg FDC tablets and coadministration of corresponding doses of sitagliptin and metformin as individual tablets; N=48

Study PN095: Two way, three part, single dose bioequivalence study with the final formulations of sitagliptin/metformin 50/500 mg, 50/850 and 50/1000 mg FDC tablets and coadministration of corresponding doses of sitagliptin and metformin (Glucophage®) as individual tablets; N= 82

Study PN050 Double blind, four period crossover study to evaluate effect of sitagliptin and metformin alone or in combination on post-meal active GLP-1 concentrations; N=18

- Absorption

Following oral administration of a 100 mg dose, maximal plasma concentrations of sitagliptin were reached within 1 to 4 hours. The absolute bioavailability (BA) of sitagliptin is high i.e. 87%. A high-fat meal had no effect on the rate or extent of absorption; therefore, sitagliptin can be administered with or without food.

After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute BA of a 500 mg or 850 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the PK of metformin absorption is non-linear.
At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Demonstration of bioequivalence (BE) of the sitagliptin/metformin FDC tablets and their active components given as individual tablets is important to extrapolate the efficacy and safety results obtained with the sitagliptin and metformin co-administration studies to the FDC (no phase II/III studies have been performed using the FDC) and to ensure that T2DM patients already taking metformin (and sitagliptin) can be safely and effectively switched to the FDC tablets.
These BE studies are also of prime importance as the applicant did not submit a full PK dossier with all required studies but instead referred to the results of the individual dossiers of sitagliptin and metformin.

The rationale for not submitting specific pharmacology/pharmacokinetic study reports with regard to the PK properties of the FDC tablet was that at the time of the submission, information regarding the PK properties was known for the individual components. Since, no drug interaction between sitagliptin and metformin was identified in study P012 and as also no clinically meaningful food-effect on either sitagliptin or metformin absorption was identified, no additional PK studies with the FDC tablets were considered necessary.

The submitted BE studies P038 (exploratory) and P048 (pivotal) demonstrated bioequivalence between the higher (50/1000 mg/mg) or lower (50/500 mg/mg) dose strengths of the FDC and the respective dose strengths of the components given as individual tablets. The 90% CI of the corresponding treatment differences for the $AUC_{0-\infty}$ and C_{max} of sitagliptin and metformin were all within the prespecified bounds of (0.80, 1.25).
Study P048 presented several shortcomings, making it impossible to claim bioequivalence for the individual components and therefore impossible to refer to the corresponding dossier. The issues identified were:

1) The reference product for metformin used in both P048 and P038 is a generic product from the American/Canadian market, while, according to the "*NfG on the investigation of bioavailability and bioequivalence",* it should have been an innovator product from the European market. Only the sitagliptin tablets used in study P048 are valid as reference product, therefore reference could be made to the sitagliptin dossier only. Consequently, the CHMP requested a new BE study using the European innovator product (Glucophage). Since metformin has a non-linear saturation kinetics and the sensitivity to detect differences, if present, is higher for lower doses, such a study was requested at minimum for the dose strength containing 500 mg metformin.

2) The use of a bracketing strategy for the intermediate dose strength of 50/850 mg/mg which includes BE studies for the higher (50/1000 mg/mg) and lower (50/500 mg/mg) dose strengths and demonstration of similar dissolution profiles of the 3 dose strengths of the FDC. In principle, this strategy is acceptable. However, the submitted comparative dissolution studies either lacked the intermediate dose strength or were not performed with biobatch. Therefore, in accordance with the "*NfG on the investigation of bioavailability and bioequivalence",* the CHMP requested a dissolution study comparing dissolution profiles of the biobatches of all 3 dose strengths under the same conditions.
Furthermore, CHMP requested the submission of dissolution tests comparing metformin release for each dose strength of the FDC with the respective dose strengths of the EU reference product Glucophage.

In response to these comments results from a new BE study (P095) were submitted, together with results from additional dissolution studies. The reference product for metformin was Glucophage as requested. The results of study P095 clearly demonstrate that with respect to metformin all strengths of Janumet are bioequivalent with Glucophage. The half-lives and t_{max} values were also comparable.

The comparative dissolution testing with the bio-batches used in the BE study P095 showed that the two Janumet biobatches (50/500 mg and 50/1000 mg) as well as Janumet 50/850 mg batches release metformin considerably faster in the media pH 1.2 and pH 4.5 than the Glucophage originator batches; and at pH 6.8 the Janumet batches release metformin slightly faster than the Glucophage originator batches.
Oral BA of metformin in humans is 50-60% of an administered dose and it is categorized as a BCS Class III compound, i.e. fast dissolution and low permeability. In other words, for BA of metformin the speed of dissolution from the tablet formulation is not the critical step in the process. Therefore it is concluded that the faster dissolution performance of metformin from Janumet in comparison to Glucophage, is not critical and not unfavourable for the bioavailability performance of the product.

- Distribution

Following 100 mg IV dose, the steady state volume of distribution (V_d) was estimated to be approximately 198 liters, indicating that sitagliptin distributes to the tissues. Plasma protein binding is low (38 % bound) thus the potential for clinically relevant drug-drug interactions by plasma protein binding displacement is low. The equilibrium blood-to-plasma concentration ratio of sitagliptin is 1.21.

Plasma protein binding in metformin is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63-276 L.

- Elimination

For sitagliptin metabolism is a minor pathway of elimination. Following a [14C]-labelled oral dose, approximately 16% of the radiolabeled sitagliptin was recovered as metabolites. *In vitro* studies suggested that the primary enzymes responsible for the metabolism were CYP3A4 and, to a lesser extent CYP2C8. Since the metabolites were present at low concentrations in plasma relative to parent

compound, sitagliptin, and not its metabolites, was considered mainly responsible for DPP-4 inhibitory activity.
Plasma clearance following a 100 mg IV dose of sitagliptin was 417 ml/min. Renal clearance and plasma elimination half-life were similar after IV and oral dosing. The apparent terminal plasma half-life is approximately 10-12 hours. Renal excretion of unchanged sitagliptin is the primary mechanism of elimination. In patients and subjects with normal renal function (CrCl >80 mL/min), approximately 75 to 80 % of an oral dose is excreted unchanged in urine with a renal clearance of approximately 350 mL/min. Since renal clearance exceeds the typical glomerular filtration rate in humans, it appears to involve active tubular secretion mechanisms. The results of *in vitro* studies indicted that sitagliptin is a substrate for hOAT3 and Pgp, but not a substrate of human organic cation transporter-2 (hOCT2), or hOAT1. As cyclosporine A did not affect the renal elimination of sitagliptin, Pgp appears not to be involved in the renal excretion. The role of hOAT3 and/or other transporters in the active renal secretion is unknown.

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. Renal clearance of metformin is > 400 ml/min, indicating that it is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

- Dose proportionality and time dependencies

No specific studies were conducted with regard to dose proportionality and time dependency with the FDC tablet. As BE between the FDC tablet and co-administration of corresponding doses of the individual doses was demonstrated, no drug interaction between sitagliptin and metformin was identified and no clinically meaningful food-effect of either sitagliptin and metformin was identified; no additional PK studies were considered necessary.

- Special populations

As metformin and sitagliptin are both excreted by the kidney, Janumet should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly. Limited safety data on sitagliptin is available in patients > 75 years of age and care should be exercised.

Janumet should not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 ml/min) (see sections 4.3 and 4.4 of the SPC).

Janumet is not recommended for use in children below 18 years of age due to a lack of data on its safety and efficacy in this population.

- Pharmacokinetic interaction studies

PK interactions between metformin and sitagliptin were investigated in a placebo-controlled, 3-period, cross-over study (P012) in 13 patients with T2DM on stable monotherapy with metformin. Metformin had no effect on the PK of sitagliptin or *vice versa*.
In the original Januvia dossier an interaction study of sitagliptin with glyburide was included in which no interactions were identified. The applicant also provided a comprehensive overview on possible interactions of SU drugs. In view of these data it can be concluded that the use of the sitagliptin/metformin combination tablet within a triple combination therapy with a SU is possible.

Sitagliptin and metformin are mainly excreted by the kidney and do not interact in clinical significant way with CYP450 co-enzymes. Also, protein binding of these components of Janumet is low, and therefore any displacement from proteins will not relevantly influence their pharmacokinetics.

- Pharmacokinetics using human biomaterials

No reports of studies pertinent to PK using human biomaterial were conducted in support of this marketing application. At the time of submission, information regarding the protein binding and effects on CYP enzymes and/or transporters was previously known for the individual components of the FDC tablet. Because BE between the FDC tablet and coadministration of corresponding doses of the individual tablets was demonstrated and no drug interaction between sitagliptin and metformin was identified, such data were considered applicable to the FDC.

Pharmacodynamics

Pharmacodynamics of sitagliptin was studied in 9 previous trials, including 252 healthy volunteers and 58 T2DM patients. In these studies the effects of sitagliptin on DPP-4 activity, incretins, glucose, insulin, C-peptide and glucagon levels were investigated. These trials were included in the initial MAA of Januvia. The PD of metformin is well-known (see metformin section below). Therefore no additional studies investigating PD of sitagliptin or metformin *per se* are required for the present MAA. One new study (P050) investigating the effect of concomitant administration of sitagliptin and metformin on post-meal plasma incretin hormone concentrations has been submitted with this MAA.

- Mechanism of action

Sitagliptin is a DPP-4 inhibitor. Although several actions potentially contribute to the glucose-lowering effect of DPP-4 inhibitors, the most likely mechanism is through elevated incretin concentrations that lead to enhancement of glucose-dependent insulin secretion and a reduction in glucagon release. Increases in incretin concentrations occur because DPP-4 inhibition reduces the cleavage and inactivation of the active (intact) form of the incretin hormones, including GLP-1 and GIP.

Metformin improves glycaemic control in patients with T2DM by lowering both basal and postprandial plasma glucose concentrations. These effects result from: 1) a decrease in hepatic glucose production, 2) a decrease in intestinal absorption of glucose and, 3) an improvement in insulin sensitivity by increasing peripheral glucose uptake and utilisation.

- Primary and Secondary pharmacology

Primary pharmacology
Single dose PD for sitagliptin was investigated in a total of 90 healthy male volunteers, healthy elderly male and female subjects, young female subjects, obese males and 18 Japanese subjects. Single dose PD in patients with mild to moderate T2DM was also investigated, including 58 drug naïve. Multiple dose PD was investigated in a total of 162 healthy male volunteers, middle-aged, obese male and female subjects, and 60 healthy young male Japanese subjects.

In both normoglycaemic healthy subjects and patients with T2DM, sitagliptin inhibited plasma DPP-4 activity in a dose and concentration-dependent manner. Race, gender and age did not have meaningful effects on the relationship between sitagliptin plasma concentrations and DPP-4 activity.
Compared to placebo, sitagliptin increased post-meal (in healthy subjects and T2DM patients) active GLP-1 levels by approximately 2-3-fold. Active GIP levels were similarly increased following an oral glucose tolerance test (OGTT) in patients with T2DM. Sitagliptin did not increase total GLP-1 or GIP plasma levels.

GLP-1 has been demonstrated to slow gastric emptying; it was thought that this effect might also be seen with sitagliptin; this relationship has not been confirmed.

Secondary pharmacology
In a study performed in patients with mild-to-moderate hypertension on stable treatment with one or more antihypertensive agents sitagliptin compared to placebo showed small but statistically significant

or nearly significant decreases in mean 24-hour blood pressure between both 100 mg b.i.d. and 50 mg for systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

In a thorough QTc study, following a dose of 800 mg, QTc interval was slightly increased, but not to a clinically significant extent. However, considering the data separately by gender, a borderline effect was seen in females at the high dose (800mg) (mean value 5.85 msec with an upper limit of the 95% CI of 9.96 (~10 msec), which is the threshold according to ICH guideline E14). However, sitagliptin was shown to inhibit HERG current at concentrations (IC50 117 μM, worst case scenario) that were far beyond therapeutic free plasma levels. The safety margin calculated from non-clinical studies was 38, which was considered sufficient, even if women were slightly more sensitive to an effect of sitagliptin on QTc. No change in QTc interval was measured after a single dose of 100 mg.

The potential effectiveness of the combination of sitagliptin and metformin is based on several considerations: 1) recent data demonstrate that metformin increases GLP-1 concentrations—hence potentially increasing the efficacy of a medication that inhibits GLP-1 metabolism; 2) differences in the primary glucose-lowering effects, with metformin predominantly lowering fasting plasma glucose and sitagliptin lowering both postprandial and fasting plasma glucose concentrations; and 3) the complementary mechanisms of action, with metformin enhancing insulin sensitivity and lowering hepatic glucose production and sitagliptin enhancing insulin release. Thus, co-administration of sitagliptin and metformin may be a useful option in managing patients with T2DM.

The newly submitted study P050 was a randomised, placebo-controlled, double-blind, four-period crossover study in 18 healthy adult subjects. The objective of this study was to explore the mechanisms of action of sitagliptin and metformin on the incretin axis. The effects of administration of sitagliptin alone, metformin alone, the combination of sitagliptin and metformin or placebo on incremental changes in post-meal incretin hormones (active and total glucagon-like peptide [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) and glucose concentrations were also determined. The primary endpoint was the 4-hour post-meal (meal consumed at 2 hours postdose; at the approximate T_{max} for sitagliptin and metformin) weighted average active GLP-1 concentrations after concomitant administration of sitagliptin and metformin compared with administration of sitagliptin alone.
Compared with placebo, both sitagliptin alone and metformin alone increased the 4-hour incremental weighted average active GLP-1 concentrations by approximately 80 to 95% (1.8- to 1.95-times) whereas the increase for the combination of sitagliptin and metformin was approximately 310% (4.1-times). Metformin, but not sitagliptin, increased active and total GLP-1 concentrations to similar extents. Sitagliptin, but not metformin, increased active GIP concentrations. The reduction in the post-meal incremental glucose AUC_{0-4hr} after concomitant administration of sitagliptin and metformin compared with administration of either sitagliptin alone or metformin alone was similar in these healthy subjects. It is unclear how these findings relate to changes in glycaemic control in patients with type 2 diabetes.

Clinical efficacy

- Dose response studies

Initial data supporting the efficacy of the combination of sitagliptin and metformin emerged from Phase II study P015 that showed sitagliptin provided improvement in 24-hour glucose concentration profiles in patients with inadequate glycaemic control on metformin monotherapy.

Dose selection for the sitagliptin component of Janumet was based upon dose-range finding studies P010 and P014. Results of these studies showed that sitagliptin provided improvements in glucose control, as reflected by reductions across glycaemic endpoints examined (including HbA_{1c}, FPG, and fructosamine). Of the doses examined, 100 mg per day, either given as 100 mg q.d. or 50 mg b.i.d., provided maximum glucose-lowering effect; there was no meaningful difference in efficacy with sitagliptin 100 mg administered as 100 mg once-daily or as 50 mg twice-daily.
When determining the doses of sitagliptin and metformin to be included in the FDC development program, the registered doses of metformin and the common prescribing practices for metformin

(twice daily dosing), as well as the tolerability and efficacy of metformin, were considered. For the FDC a twice-daily dosing regimen compatible with the twice daily dosing regimen of immediate release metformin has been developed. The choice of the dose and dose frequency of the 50/850 mg/mg and 50/1000 mg/mg are acceptable.
The lowest proposed strength, i.e. 50mg/500mg, however was not considered acceptable. The minimal metformin dose assessed in studies P020 and P024 was 1500 mg per day; the efficacy of metformin in reducing T2DM complications was demonstrated in UKPDS 34, in which a great majority of the patients were treated with metformin doses >1700 mg per day. Although there might be a minority of patients who cannot tolerate metformin at doses higher than 1000 mg, it is unlikely that the FDC tablet offers a meaningful benefit compared to the administration of the separate components. In addition, the low dose FDC tablet could promote initial combination therapy which is not approved and not covered by current diabetes treatment guidelines. Therefore, the approval of the 50/500 mg tablet is not recommended. The Applicant has withdrawn this strength.

- Main studies

As well as two new studies P035 and P036; studies P020 and P024, previously submitted in the MAA for Januvia, were resubmitted in support of the present application. These studies are presented as an abbreviated version.
The final study reports of study P035 and study P036, presenting the complete 54-week data were submitted by the Applicant with their Day120 response document.

Study P020: A multicenter, randomised, double-blind study to evaluate the safety and efficacy of the addition of sitagliptin to patients with type 2 diabetes mellitus who have inadequate glycaemic control on metformin therapy.

This combination study suggested that sitagliptin was more effective than placebo in reducing HbA_{1c} at 24 weeks.

Study P024: A multicenter, double-blind, randomised, active controlled study to evaluate the safety and efficacy of the addition of MK-0431 compared with sulfonylurea therapy in patients with Type 2 Diabetes with inadequate glycaemic control on metformin monotherapy.

The assessment of the CHMP concluded that sitagliptin 100 mg per day as add-on therapy to metformin was shown to have a significant and clinically relevant effect on glycaemic control but non-inferior efficacy compared to sulfonylureas was not unequivocally proven. However, results were sufficient to approve the add-on indication.

Study P035: A double-blind, randomised, placebo-controlled study of sitagliptin as add-on therapy in patients with inadequate glycaemic control on glimepiride alone or in combination with metformin

This study was also submitted in support of a Type II Variation to support the use of sitagliptin in dual combination with a sulfonylurea (SU) or in triple combination with a SU and metformin which was approved on the 19 December 2007.

Study P036: A randomised, double-blind, factorial, parallel-group study in T2DM patients to assess the efficacy and safety of an initial combination therapy with sitagliptin 50 mg b.i.d. and metformin 500 mg b.i.d. or 1000 mg b.i.d. compared to either agent alone when diet and exercise did not provide adequate glycaemic control.

METHODS

Study Participants
Main inclusion criteria
Adult patients with T2DM either on previous or no previous antihyperglycaemic medication (AHA) and pre-defined HbA_{1c} values at screening and at the end of the wash-out/run-in period (7-10% in study P020, 6.5-10% in study P024, 7.5-10.5% in study P035, 7.5-11% in study P036) indicating

insufficient glycaemic control on metformin monotherapy of at least 1500 mg per day (studies P020, P024) or on SU monotherapy or on combination therapy of SU and metformin (study P035) or on diet and exercise alone (study P036) were eligible. Upper age limit for participation was 78 y in studies P020, P024 P036 and 75 y in study P035.

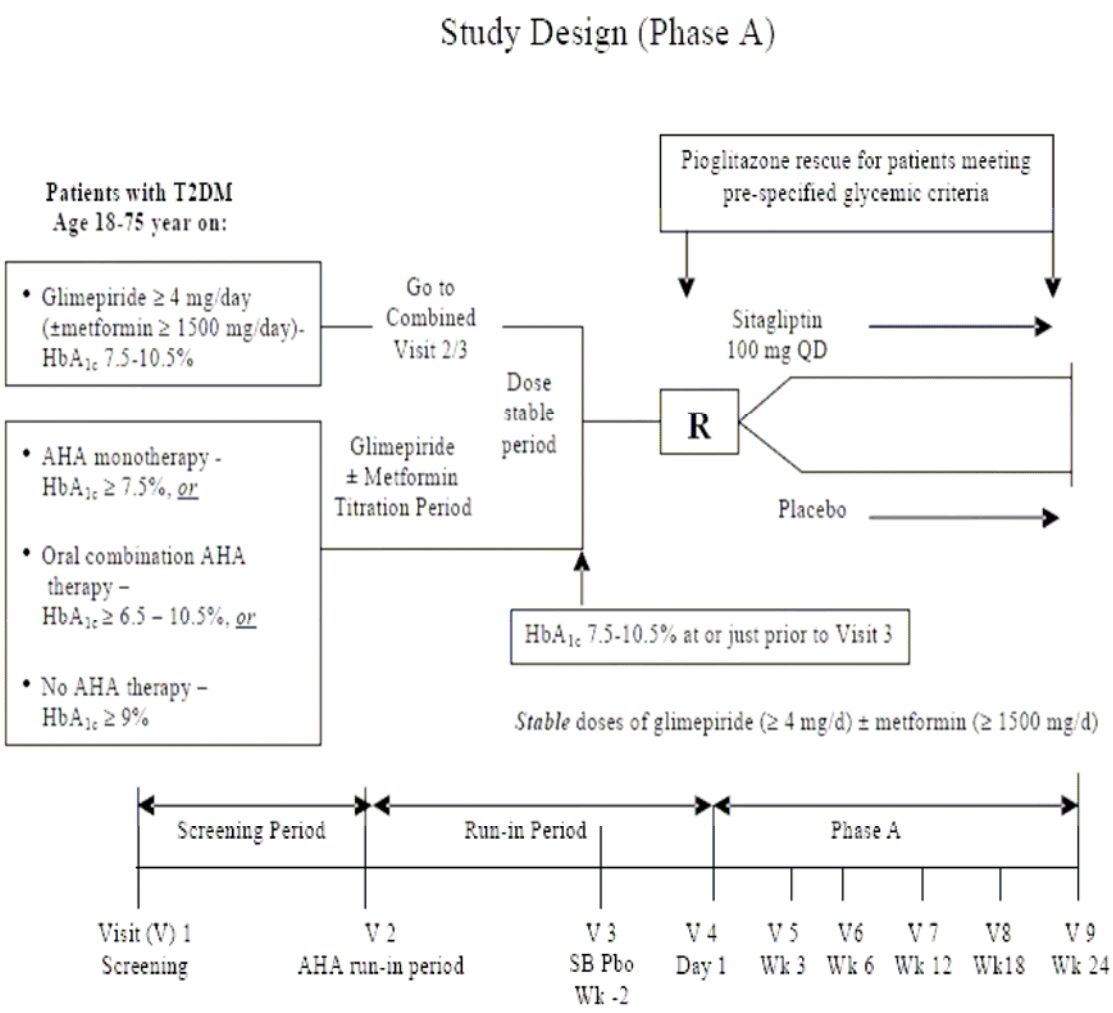
Main exclusion criteria
- Patient required insulin within the prior 8 weeks
- Patients with contraindications or not tolerating the run-in or co-medication (if applicable)
- Moderate to severe renal insufficiency, active hepatic disease or cirrhosis, chronic myopathy, progressive neurological or neuromuscular disorder, major haematological disease, poorly controlled hypertension, NYHA class III or IV congestive heart failure; myocardial infarction, unstable angina or stroke within the past 6 months

Treatments
In all studies, patients had to discontinue any previously used AHAs that were not allowed to be used during the study. During the subsequent dose titration/stable dose run-in phase the desired baseline medication (metformin in studies P020, P024 and glimepiride [+/- metformin] in study P035) was introduced and uptitrated. The final dose achieved during the run-in phase (at least 1500 mg metformin and 4-8 mg glimepiride) had to be maintained during the double-blind treatment period. However, glimepiride could be down-titrated if necessary because of the occurrence of hypoglycaemia.
Subsequently, patients meeting pre-defined HbA_{1c} criteria entered a 2-week single blind placebo run-in phase, and if ≥75% compliant with study medication, were subsequently randomized to one of the treatment groups.
Concurrent lipid-lowering or antihypertensive medications were expected to remain on a stable regimen during the run-in phase and the double-blind treatment period.

Rescue therapy
To ensure that patients did not have prolonged periods of inadequate glycaemic control, open-label, sponsor-supplied rescue therapy was implemented in patients meeting pre-specified criteria for HbA_{1c} and/or fasting plasma glucose (FPG) in studies P020, P035 and P036.
Patients on rescue medication continued the double-blind study medication.

Discontinuation criteria (regarding glycaemic control)
- Hypoglycaemia (repeated) without a reasonable explanation
- Patient meets glycaemic rescue criteria but is not eligible for rescue therapy (if applicable).
- Hyperglycaemia (persistent) as measured by FPG or HbA_{1c} (predefined limits depending on study duration) and despite completion of uptitration of rescue medication (if applicable).

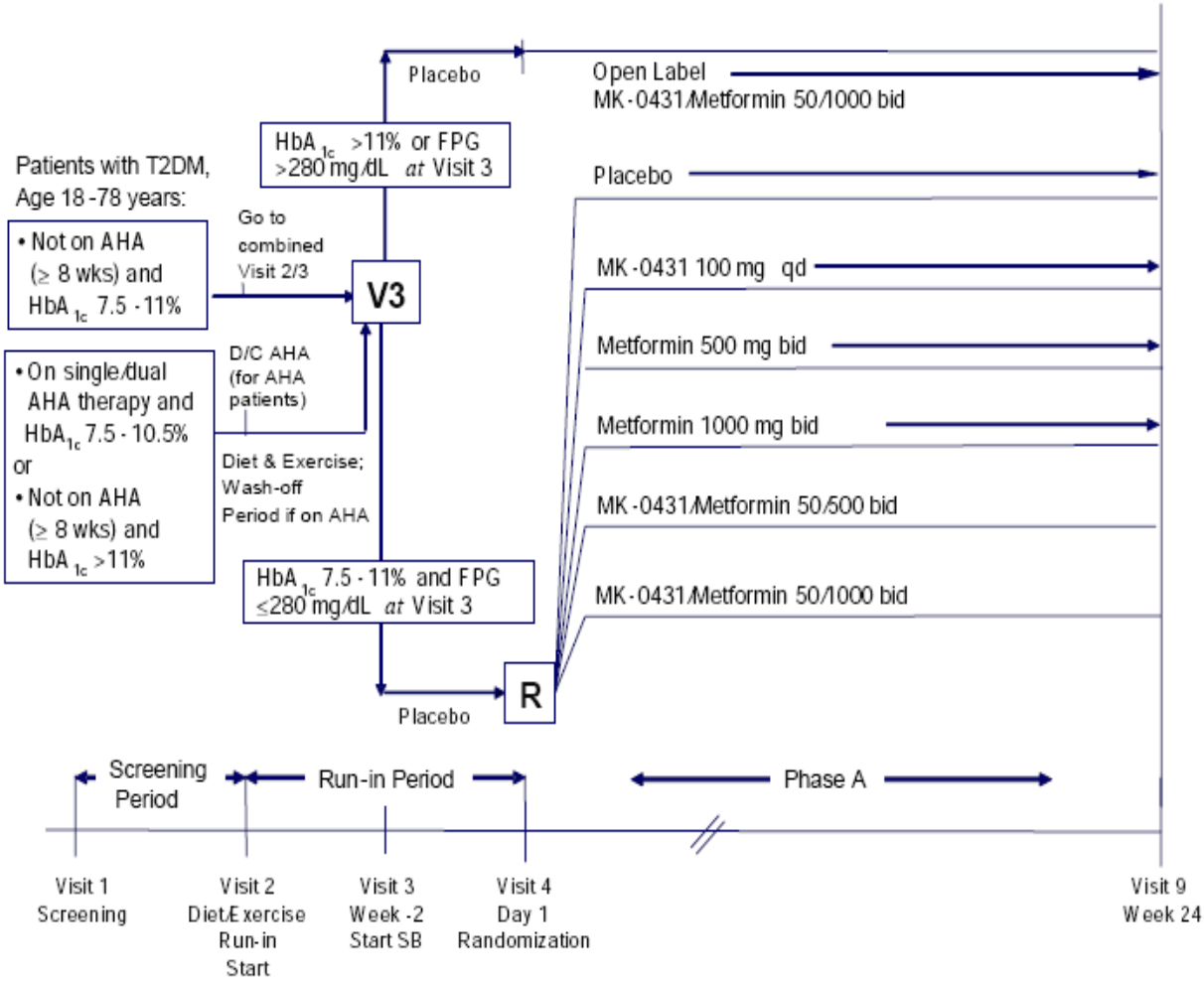
The following figure provides a description of P035 study design. The study had a 24-week double-blind placebo-controlled phase (Phase A) followed by a 30-week active comparator (pioglitazone) phase (Phase B).



SB PBO: SINGLE BLIND PLACEBO

Study P036 had a 24-week, placebo-controlled, Phase A, and an ongoing 30-week, active-controlled Phase B. Patients were randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment groups (see figure below).

Phase A Study Design



Objectives
The primary objectives of the combination and active comparator studies were:

P020: In patients with type 2 diabetes mellitus who have inadequate glycaemic control on metformin at a dose of ≥1500 mg/day: (1) After 24 weeks, to assess the effect of the addition of treatment with sitagliptin compared with the addition of placebo on HbA_{1c}; (2) To assess the safety and the tolerability of sitagliptin.
P024: In patients with type 2 diabetes mellitus who have inadequate glycaemic control on metformin at a dose of ≥1500 mg/day: (1) After 52 weeks, to assess the effect of the addition of sitagliptin compared with the additon of glipizide on HbA_{1c} (2) To assess the safety and the tolerability of sitagliptin compared with glipizide.
P035: In patients with type 2 diabetes mellitus who have inadequate glycaemic control on glimepiride at a dose of ≥4 mg/day, alone or in combination with metformin at a dose of ≥1500 mg/day: (1) After 24 weeks, to assess the effect of the addition of treatment with sitagliptin compared with the addition of placebo on HbA_{1c}; (2) To assess the safety and the tolerability of sitagliptin.
P036: In patients with type 2 diabetes mellitus with inadequate glycaemic control on diet and exercise: Primary: After 24 weeks: (1) To assess the effect of co-administration of sitagliptin and metformin compared with the effect of metformin monotherapy on HbA_{1c}; (2) To assess the effect of co-administration of sitagliptin and metformin compared with the effect of sitagliptin monotherapy on HbA_{1c}; (3) To assess the safety and tolerability of co-administration of sitagliptin and metformin,

sitagliptin monotherapy, and metformin monotherapy, including the incidence of selected gastrointestinal adverse events (i.e., abdominal pain, nausea, vomiting, and diarrhoea).

Outcomes/endpoints
Primary endpoint in all Phase III studies was change from baseline in HbA_{1c} (at Week 24 in P020, P035, and P036 and at Week 52 in P024). Key secondary endpoints included FPG and PMG (post-meal glucose).
Additional glycaemic efficacy endpoints included fasting measures of β-cell function (HOMA-β and proinsulin-to-insulin ratio), measures of insulin resistance (HOMA-IR and QUICKI), and endpoints assessed using 9- or 10-point frequently sampled meal tolerance tests (MTT), including model-based analysis and the insulinogenic index.

Sample size
In the superiority trials (P020, P035 and P036) sample size was calculated to have clearly over 90% power to detect a true difference of 0.5% in the mean change from baseline in HbA_{1c} between any sitagliptin group and placebo for a two-tailed test at α=0.05. In trial P024, the non-inferiority margin was set at 0.3%.

Randomisation
Allocation numbers were randomly assigned (in a blinded manner) to the possible treatment groups.

Blinding (masking)
Investigator site personnel and patients were blinded to the patient treatment assignment until all patients had completed the study. Applicant research personnel remained blinded to the individual patient treatment assignment until the initial 24-week (P020, P035, and P036) and 52-week (P024) portions of studies were completed, the in-house review of the patient-level data was finished, and the data file frozen for analysis.

Statistical methods
An ANCOVA model with treatment, baseline HbA_{1c} and prior AHA therapy as covariates was used to compare the treatment groups in the continuous efficacy parameters focusing on change from baseline at study endpoint. Due to the large number of study centers and the small numbers of patients at each center, study center was not included as a factor in the analysis model. However, as local influences were deemed a concern, the applicant was requested to provide additional analyses regarding the consistency of the treatment effect, taking in to account that if the number of patients per centre is too small for such an analysis, grouping per region could be an acceptable alternative.

Hierarchical testing procedures were used in studies P020, P035 and P036.

To avoid the confounding influence of rescue therapy on efficacy comparisons, the efficacy analyses treated data as missing after the initiation of rescue therapy. The primary approach to handling missing data was the last observation carried forward (LOCF) method. As a sensitivity analysis, a maximum likelihood approach for repeated measurements was used as the secondary approach for handling missing data. Where appropriate, a time-to-rescue analysis was performed using the Kaplan-Meier estimator and the log-rank test.

The primary analysis in the superiority trials (P020, P035 and P036) was the all-patient-treated (APT) analysis, which included patients with a baseline measurement, consumption of at least one dose of double-blind study medication and the presence of a post-randomization measurement. In addition, a completer analysis was performed for the primary endpoint HbA_{1c} and, if applicable, for FPG. No per protocol (PP) analysis excluding patients with major protocol violations was planned.

The primary analysis in the non-inferiority trial P024 was the per protocol (PP) population, the secondary analysis the APT population.

An analysis of the proportion of individuals meeting the HbA_{1c} goal of <7.0% or <6.5% at end of study was conducted using a logistic regression model which included terms for baseline HbA_{1c}, prior antihyperglycemic therapy status, and treatment group.

No interim analyses were performed in the phase 3 trials.

RESULTS

Participant flow

In **P020** a total of 1464 patients were screened and 701 were randomized. The most common reasons for patients not being randomized were failure to meet HbA_{1c} inclusion criteria (43.4%) and an elevated creatinine or decreased creatinine clearance (12.7%).
In **P024** a total of 2141 patients were screened and 969 patients were excluded during screening. The most common reason for patients not being randomised was for patient not meeting HbA_{1c} inclusion criteria based at Visit 1 or Visit 3 (34.3%).

In study **P035** a total of 1098 patients were screened, 441 of whom were randomized. The most common reason for patients not being randomised was HbA_{1c} outside inclusion criteria at Visit 1 (39.8%) or at Visit 3 (18.7%). Of note, the final number of patients randomized into the study exceeded the protocol-specified target number of patients (n=360).

The percentage of patients completing Phase A was similar in the sitagliptin (83.3%) and placebo (81.7%) groups. However, among sitagliptin treated patients, more patients on glimepiride and metformin (stratum 2) completed Phase A (87.9 %) compared to patients on glimepiride alone (stratum 1; 78.3%).
Discontinuation due to lack of efficacy was more frequent in the placebo than the sitagliptin group.

In **P036** a total of 3544 patients were screened and 1091 were randomized. Another 117 patients entered the open-label cohort. The most common reasons for patients being excluded from the study were failure to meet HbA_{1c} inclusion criteria (52.6%) and an elevated serum creatinine or decreased creatinine clearance (10.3%).

The overall disposition of patients who entered the study through Week 24 is shown in the diagram below. Amongst the randomized patients, the overall discontinuation rate was highest in the placebo group (27.8%), followed by the sitagliptin monotherapy group (20.7%), and was lowest in the “high dose” combination sitagliptin 50 mg b.i.d. / metformin 1000 mg b.i.d. group (10%).
The discontinuation rate due to lack of efficacy was highest in the placebo group (6.8%), followed by the metformin 500 mg b.i.d. group (2.7%) and was lowest in the “high dose” and “low dose” combination therapy groups (1.1 and 1.05%, respectively).

Overall disposition of patients including data after initiation of glycaemic rescue therapy.

Screened	**3544**						
Excluded	**2336**						
Randomised	**1091**						**117**
	Sita 100 mg q.d. N (%)	**Met 500 mg b.i.d.** N (%)	**Met 1000 mg b.i.d.** N (%)	**Sita 50 mg b.i.d. + Met 500 mg b.i.d.** N (%)	**Sita 50 mg b.i.d. + Met 1000 mg b.i.d.** N (%)	**Placebo** N (%)	**Sita 50 mg b.i.d. + Met 1000 mg b.i.d. OLC** N (%)
Randomised	n=179 (100)	n=182 (100)	n=182 (100)	n=190 (100)	n=182 (100)	n=176 (100)	n=117 (100)
Completed	142 (79.3)	153 (84.1)	156 (85.7)	164 (86.3)	164 (90.1)	127 (72.2)	79 (67.5)
Discontinued	37 (20.7)	29 (15.9)	26 (14.3)	26 (13.7)	18 (9.9)	49 (27.8)	38 (32.5)
Clinical AE	6	4	5	4	1	7	3
Laboratory AE	2	0	0	0	0	2	0
Lack efficacy	3	5	3	2	2	12	19
Lost to follow-up	3	2	4	3	8	8	3
Pat. discont. for other	2	1	0	0	1	2	1
Pat. withdrew consent	12	11	12	9	3	12	4
Prot-spec discon criteria	3	3	0	5	3	3	5
Protocol dev	6	3	2	3	0	3	3
Patients are counted within a Time Frame based on the latest discontinuation reason for that patient							

Recruitment

The periods of recruitment for the phase 3 pivotal trials were the following:
- P020 13-Jul-2004 through 20-Jul-2005
- P024 26-Oct-2004 to 14-May-2005
- P035 27-Apr-2005 through 9-Jan-2007
- P036 01-Apr-2005 to 01-Mar-2007

Conduct of the study

There were no study amendments in P020, P024, P035 or P036 that would likely affect the results of the study.

Baseline data

Baseline characteristics in study P020 and P024 were generally balanced across the treatment groups.

In **Study P035**, baseline characteristics were generally balanced between the treatment groups in the entire cohort, and also in each stratum. However, patients in stratum 2 (on dual combination therapy with glimepiride and metformin) had slightly lower baseline HbA_{1c} values, a longer duration of T2DM, and were more likely to be on combination therapy at screening compared with patients in stratum 1 (on glimepiride monotherapy). The proportion of patients on previous AHA therapy was very similar among sitagliptin and placebo-treated patients.

In **Study P036** the **Randomized Cohort**, mean age (range) was 53.5 y (20-78), BMI 32.1 kg/m^2 (18.0-59.7), HbA_{1c} 8.8% (6.3-11.9), FPG 200 mg/dL (95-373), and mean duration of diabetes 4.5 years (0-35); 49.4% of patients were male, 51.7% were White and 27.2% Hispanic. 49.6% of patients were taking AHAs at screening. With the exceptions of a slight difference in the proportion of male

patients (lowest 42.3%, highest 55.3%) there were no relevant baseline differences between treatment groups.
Compared to patients in the Randomized Cohort, patients in the **Open-label Cohort** exhibited generally poorer baseline glycaemic control (mean HbA_{1c} 11.2%), a longer mean duration of T2DM (6.1 y), and were more likely to be taking AHAs at screening (62.4%) and also had a larger proportion of Hispanics (46.2%) and a lower proportion of Whites (37.6%).

Numbers analysed

For study P035, in all treatment groups, at least 95% of patients were included in the primary APT analysis. The number of patients included in the secondary completers' analysis was markedly lower, being lowest in the placebo group (65.8%), largely due to the requirement for rescue therapy.
Compliance rate was similar between the sitagliptin and placebo groups (98.5% vs. 98.6%). Only a small number of randomized patients (approx. 1.5%) were assessed as having potentially important protocol violations, which was considered unlikely to meaningfully alter the study's conclusion.

For study P036, in all treatment groups, more than 96% of patients were included in the primary APT analysis. The number of patients included in the secondary completers' analysis was markedly lower, being lowest in the placebo group (50.6%) and in the sitagliptin 100 mg q.d. group (63.1%), being largely due to the requirement for rescue therapy. Compliance with study drug was > 97% in all treatment groups. Only 23 of the randomized patients (2.1%) were assessed as having potentially important protocol violations, which was considered unlikely to meaningfully alter the study's conclusion. One patient was prematurely unblinded due to a SAE (ketoacidosis).

Outcomes and estimation

The main study results (Phase A) for study **P020** were the following:

Glycaemic control
The addition of 100 mg q.d. sitagliptin to metformin was superior to placebo in lowering HbA_{1c} (see table below). The completers analysis confirmed this conclusion, although the placebo adjusted treatment effect was smaller, which was explained by the removal of a larger number of rescued/discontinued patients (with a poorer HbA_{1c}) from the placebo group than the sitagliptin group.

Endpoints of the Primary and Secondary Hypotheses:
Least Squares Means for Change from Baseline at Week 24 with 95% Confidence Interval
All-Patients-Treated Population

Treatment Group	HbA_{1c} (%)	Fasting Plasma Glucose (mg/dL)	2-Hour Post-Meal Glucose (mg/dL)
MK-0431 100 mg	-0.67 (-0.77, -0.57)	-16.9 (-21.5, -12.3)	-62.0 (-70.2, -53.8)
Placebo	-0.02 (-0.15, 0.10)	8.5 (2.9, 14.1)	-11.4 (-21.7, -1.0)
Difference from Placebo †			
MK-0431 100 mg vs. Placebo	-0.65 (-0.77, -0.53)	-25.4 (-31.0, -19.8)	-50.6 (-60.5, -40.8)
† All comparisons vs. placebo had $p < 0.001$.			

The results of the primary endpoint were supported by secondary glycaemic parameters such as FPG, proportion of patients achieving HbA_{1c} <7% or <6.5%, glucose-lowering effect after administration of a standard meal challenge or proportion of patients requiring rescue therapy. Initiation of rescue therapy was substantially later in the sitagliptin treatment group compared to the placebo group.

In this study sitagliptin add-on at a dose of 100 mg q.d. provided statistically significant and clinically relevant improvement in glycaemic control compared to placebo add-on in patients with T2DM not

sufficiently controlled on metformin alone. This superiority was reflected in all glycaemic parameters evaluated. The study was powered to detect a true between-group difference of 0.5% in HbA_{1c}.

The main study results for study **P024** were the following:

Glycaemic control

The addition of 100 mg q.d. sitagliptin was non-inferior to glipizide in lowering HbA_{1c} at the end of the 52-week treatment period (see table below). The APT analysis showed similar results.

Analysis of change from baseline in HbA_{1c} (%) at week 52, PP and APT population

Per-Protocol Population							
		Mean (SD)		Change from Baseline			
Treatment	N	Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
MK-0431 100 mg	382	7.48 (0.76)	6.84 (0.66)	-0.64 (0.04)	-0.67 (0.04)	(-0.75, -0.59)	<0.001
Glipizide	411	7.52 (0.85)	6.86 (0.69)	-0.66 (0.04)	-0.67 (0.04)	(-0.75, -0.59)	<0.001
Between Treatment Difference		Difference in LS Means (95% CI)					
MK-0431 100 mg vs. Glipizide		-0.01 (-0.09, 0.08)					
Root Mean Square Error of Change =0.58							
All-Patients-Treated Population							
		Mean (SD)		Change from Baseline			
Treatment	N	Baseline	Week 52	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	
MK-0431 100 mg	576	7.69 (0.89)	7.15 (0.99)	-0.54 (0.03)	-0.51 (0.04)	(-0.60, -0.43)	
Glipizide	559	7.65 (0.90)	7.08 (0.87)	-0.57 (0.03)	-0.56 (0.04)	(-0.64, -0.47)	
Between Treatment Difference		Difference in LS Means (95% CI)					
MK-0431 100 mg vs. Glipizide		0.04 (-0.04, 0.13)					
Root Mean Square Error of Change =0.73							
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							

The results of the primary endpoint were supported by secondary glycaemic parameters such as FPG, proportion of patients achieving HbA_{1c} <7% or <6.5% and glucose-lowering effect after administration of a standard meal challenge.

In this study more patients in the sitagliptin arm discontinued due to lack of efficacy as compared to glipizide treated patients (86 [15%] vs 58 [10%]). Sitagliptin patients discontinued primarily at the beginning of the study, while glipizide patients discontinued at the end. If the glipizide dose could have been increased beyond the initial titration phase, better results might have been obtained with glipizide. There was a difference between the APT and PP results, but the difference was not substantial, as would have been expected if early discontinuing patients were to be meaningfully impact the study results.

Similar results were obtained for FPG data. Proportions of patients reaching target HbA_{1c} were consistent with HbA_{1c} data.

At Week 52, a modest, statistically significant ($p<0.001$), decrease from baseline in body weight of 1.5 kg was observed in the sitagliptin treatment group, while the glipizide treatment group had a modest, statistically significant ($p<0.001$), increase of 1.1 kg from baseline in body weight, resulting in a significant between-group difference of -2.5 kg ($p<0.001$).

Although the Applicant claimed non-inferiority, the CHMP concluded that sitagliptin 100 mg per day as add-on therapy to metformin was shown to have a significant and clinically relevant effect on glycaemic control but non-inferior efficacy compared to SU was not unequivocally proven. However, results were sufficient to approve the add-on indication.

In study **P035** a significant reduction in HbA_{1c} was obtained in patients when sitagliptin was added to glimepiride and metformin, while the addition of placebo had no effect. After **24 weeks** the mean

change from baseline was –0.59% (95% CI -0.74, -0.44) for sitagliptin versus +0.30% (95% CI 0.14, 0.45) for placebo. The mean between group difference was –0.89% (-1.10, -0.68) in favour of sitagliptin. In the sitagliptin group, a nadir in HbA_{1c} reduction from baseline was observed at Week 12, with a rise observed from Week 12 to Week 24; a similar rise was observed in the placebo group.

Efficacy Results on HbA_{1c} (%) at Week 24
Least Squares Means for Change from Baseline with 95% CI
All-Patients-Treated Populations

Treatment Group	Entire Cohort	Subset of Patients on Glimepiride Alone (Stratum 1)	Subset of Patients on Glimepiride and Metformin (Stratum 2)
Sitagliptin 100 mg	-0.45 (-0.57, -0.34)	-0.30 (-0.48, -0.12)	-0.59 (-0.74, -0.44)
Placebo	0.28 (0.17, 0.40)	0.27 (0.09, 0.45)	0.30 (0.14, 0.45)
Difference from Placebo †			
Sitagliptin 100 mg vs. Placebo	-0.74 (-0.90, -0.57)	-0.57 (-0.82, -0.32)	-0.89 (-1.10, -0.68)
† All comparisons against placebo had $p < 0.001$.			

In this study, a total of 160 patients in the sitagliptin group and 122 patients in the placebo group, respectively, had completed Phase A and continued in Phase B. A similar proportion of these patients, i.e. 57% and 56% in the sitagliptin and pioglitazone group, respectively, completed Phase B. Overall; the most common reason for discontinuation was lack of efficacy. Due to the study design (switching patients from placebo to pioglitazone but maintaining patients on sitagliptin on unchanged medication) and the small remaining sample size, possible conclusions from this follow-up study are very limited.

The main **54-week** efficacy results of study **P035** are presented in the table below.

Efficacy Results on HbA_{1c} (%) at Week 54
Least Squares Means for Change from Baseline with 95% Confidence Interval
All-Patients-Treated Populations

Treatment Group	Entire Cohort	Subset of Patients on Glimepiride Alone (Stratum 1)	Subset of Patients on Glimepiride and Metformin (Stratum 2)
Sitagliptin 100 mg	-0.46 (-0.62, -0.31)	-0.47 (-0.72, -0.21)	-0.44 (-0.64, -0.25)
Placebo/Pioglitazone	-0.62 (-0.80, -0.44)	-0.89 (-1.16, -0.61)	-0.35 (-0.60, -0.11)

Efficacy Results on Fasting Plasma Glucose (mg/dL) at Week 54
Least Squares Means for Change from Baseline with 95% Confidence Interval
All-Patients-Treated Populations

Treatment Group	Entire Cohort	Subset of Patients on Glimepiride Alone (Stratum 1)	Subset of Patients on Glimepiride and Metformin (Stratum 2)
Sitagliptin 100 mg	0.36 (-6.14, 6.87)	4.32 (-5.94, 14.58)	-2.22 (-10.50, 6.05)
Placebo/Pioglitazone	-18.61 (-26.05, -11.18)	-25.85 (-36.88, -14.82)	-11.80 (-21.88, -1.71)

The results show that, after 54 weeks, sitagliptin continued to provide limited but clinically meaningful reductions in HbA_{1c} in the entire study population, when added to ongoing therapy with glimepiride alone (Stratum 1) or glimepiride and metformin (Stratum 2).

In study **P036** co-administration treatment resulted in larger decreases in HbA_{1c} than sitagliptin monotherapy and metformin monotherapy (see table below, analysis of change from baseline in HbA_{1c}(%) at W**eek 24** all-patients-treated population). The Applicant does not claim a first-line

treatment. This study does not demonstrate that starting with combination treatment is superior to sequential treatment.

Results of patients reaching their goal HbA_{1c}, data on FPG and other secondary parameters were in line with HbA_{1c} results.

		Mean (SD)		Change from Baseline			
Treatment Group	N	Baseline	Week 24	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-Value
Sita 100 mg q.d.	175	8.87 (0.99)	8.18 (1.45)	-0.69 (0.10)	-0.66 (0.08)	(-0.83, -0.50)	<0.001
Met 500 mg b.i.d.	178	8.90 (1.00)	8.04 (1.36)	-0.85 (0.09)	-0.82 (0.08)	(-0.98, -0.66)	<0.001
Met 1000 mg b.i.d.	177	8.68 (0.91)	7.58 (1.27)	-1.09 (0.08)	-1.13 (0.08)	(-1.29, -0.97)	<0.001
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	183	8.79 (1.00)	7.37 (1.20)	-1.42 (0.09)	-1.40 (0.08)	(-1.56, -1.24)	<0.001
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	178	8.76 (0.95)	6.87 (1.09)	-1.89 (0.08)	-1.90 (0.08)	(-2.06, -1.74)	<0.001
Placebo	165	8.68 (1.00)	8.88 (1.47)	0.20 (0.09)	0.17 (0.09)	(0.00, 0.33)	0.049

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)	p-Value
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.58 (-0.81, -0.36)	<0.001
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.73 (-0.96, -0.51)	<0.001
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.77 (-1.00, -0.55)	<0.001
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-1.24 (-1.47, -1.01)	<0.001

Comparing Active Treatment Groups with Placebo	Difference in LS Means (95% CI)	p-Value
Sita 100 mg q.d. vs. Placebo	-0.83 (-1.06, -0.60)	<0.001
Met 500 mg b.i.d. vs. Placebo	-0.99 (-1.22, -0.75)	<0.001
Met 1000 mg b.i.d. vs. Placebo	-1.30 (-1.53, -1.06)	<0.001
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Placebo	-1.57 (-1.80, -1.34)	<0.001
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Placebo	-2.07 (-2.30, -1.84)	<0.001

Other Comparisons	Difference in LS Means (95% CI)	p-Value
Average of Differences†: Sita + Met vs. Met	-0.68 (-0.84, -0.52)	<0.001
Average of Differences†: Sita + Met vs. Placebo	-1.82 (-2.02, -1.62)	<0.001
Average of Differences†: Met vs. Placebo	-1.14 (-1.34, -0.94)	<0.001
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.27 (-0.50, -0.04)	0.019

p-Value for ANCOVA Effects	
Baseline Value	<0.001
Treatment	<0.001
Prior Anti-hyperglycemic Medication	<0.001

Root Mean Square Error of Change = 1.09

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

In this study, only 1 to 6 patients of each randomised group completed Phase A and did not enter Phase B. Among patients treated with active drug in both treatment phases (A and B), the proportion of patients completing both phases was highest in the co-administration groups (77-78%), followed by the metformin 1000 mg BID group (75%) and was lowest in the sitagliptin 100 mg QD (68%) and metformin 500 mg BID (69%) groups. In line with this finding, discontinuation due to lack of efficacy occurred more often in the latter monotherapy groups than in the high-dose metformin monotherapy or the co-administration groups.

The main **54-week** efficacy results of study **P036** are presented in the table below.

Least Squares Means for Change from Baseline at Week 54 with 95% CI
All-Patients-Treated Population

	HbA_{1c} (%)		FPG (mg/dL)	
Treatment Group	LS mean (SE)	95% CI for LS mean	LS mean (SE)	95% CI for LS mean
Sita 100 mg q.d.	-0.82 (0.10)	(-1.00, -0.63)	-16.0 (3.7)	(-23.2, -8.7)
Met 500 mg b.i.d.	-1.01 (0.09)	(-1.18, -0.83)	-29.0 (3.5)	(-35.9, -22.2)
Met 1000 mg b.i.d.	-1.34 (0.08)	(-1.50, -1.17)	-39.6 (3.3)	(-46.0, -33.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	-1.41 (0.08)	(-1.57, -1.25)	-42.5 (3.1)	(-48.6, -36.3)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	-1.80 (0.08)	(-1.96, -1.65)	-55.6 (3.1)	(-61.6, -49.6)
Placebo/Met 1000 mg b.i.d.	-1.10 (0.11)	(-1.32, -0.88)	-43.9 (4.3)	(-52.3, -35.5)

HbA_{1c} Comparing Co-administration with Individual Components	Difference in LS means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.41 (-0.64, -0.17)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.60 (-0.84, -0.35)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.47 (-0.69, -0.24)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-0.99 (-1.23, -0.74)

FPG Comparing Co-administration with Individual Components	Difference in LS means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-13.4 (-22.6, -4.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-26.5 (-36.0, -17.0)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-16.0 (-24.8, -7.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-39.6 (-49.1, -30.2)

HbA_{1c} and FPG reductions from baseline at week 54 were significantly and clinically relevantly higher in the co-administration groups compared to the respective monotherapy groups confirming the benefit of adding sitagliptin to a metformin regimen in terms of glycaemic control. Small and similar increases in HbA_{1c} after Week 30 were observed for all treatment groups (except for the placebo/metformin group). Maintenance of the FPG effect was observed for the co-administration and metformin monotherapy groups, with the FPG profile remaining relatively flat during Phase B for these groups, whereas the sitagliptin monotherapy group showed a slight but continuous increase in FPG after week 18. Numerically, HbA_{1c} and FPG reductions from baseline at week 54 were lowest in the sitagliptin monotherapy group. In the secondary completers analysis, however, HbA_{1c} reduction was slightly higher in the sitagliptin 100 mg (-1.4%) than the metformin 500 mg BID (-1.2%) monotherapy group. Overall, given as monotherapy, sitagliptin 100 mg QD appears to have a antihyperglycaemic potency similar to that of metformin 500 mg BID. The Applicant has not applied for monotherapy use of sitagliptin.

Taken together, the previously submitted studies P015, P020 and P024 as well as the new studies P035 and P036 support the already approved use of sitagliptin in combination with metformin. The newly submitted 54-week results on studies P036 and P036 show a continued clinically relevant improvement of glycaemic control when sitagliptin is added to a SU agent and/or metformin.

Additional analyses, requested by the CHMP, revealed that in both studies P035 and P036 there is strong indication that the effects in Europe are systematically smaller than in other regions of the world. However, the Applicant has made it plausible that these differences are due to a spuriously large estimate for one treatment group (sitagliptin 100mg), which affected all comparisons involving that group. This is considered acceptable.

Data on another DPP-4 inhibitor suggest that, when given in combination with a SU, a daily dose of 100 mg is no more effective than a 50 mg dose. The Applicant was requested to discuss whether the same is true for sitagliptin. The Applicant does not expect that the dose-response will be meaningfully different when sitagliptin is added to SU. Although both SU agents and sitagliptin raise insulin levels,

the mechanisms by which this occurs are distinct. This answer is not completely satisfying, as a different mechanism of action does not necessarily mean that the effects are additive. Nevertheless, tolerability of the 100 mg dose is good, and therefore this dose is acceptable.

Ancillary analyses

In study P035 a notable difference was observed between the two strata in HbA_{1c} -lowering effect by baseline HbA_{1c} category. In stratum 2, stepwise and greater placebo-subtracted HbA_{1c} lowering was observed from lower to higher baseline HbA_{1c} categories: -0.55% in patients with baseline HbA_{1c} of < 8% to -1.34% in patients with baseline $HbA_{1c} \geq 9\%$. In contrast, in stratum 1 no discernable trend in placebo-subtracted HbA_{1c} -lowering was observed with higher baseline HbA_{1c} categories.

For treatment effects on HbA_{1c} by other baseline characteristics, the responses were generally consistent across subgroups in the entire cohort and in the two strata, although in stratum 2, there were few patients who were treatment naive or who were on AHA monotherapy.

In general, in study P036, the treatment effects were consistent and demonstrated effective HbA_{1c} lowering for the co-administration and monotherapy treatments in all subgroups defined by baseline demographic and anthropometric factors, and disease history. The treatment effect was generally higher in patients with higher baseline HbA_{1c} levels compared to those with lower HbA_{1c} levels. On the other hand, the HbA_{1c} -lowering effects of the co-administration regimens were higher than those of the single components for both HbA_{1c} subgroups.

- Clinical studies in special populations

No clinical studies were performed in special populations.

Clinical safety

The safety assessment during the initial MAA of sitagliptin led to the conclusion that sitagliptin treatment is associated with an increased incidence in infections and infestations, gastrointestinal disorders, musculoskeletal disorders, and nervous system AEs and that event rate was increased for skin and subcutaneous tissue disorders. These AEs had been included in the SPC, and in the RMP of sitagliptin.

The second component of Janumet, metformin, has a well-established safety profile that includes several common events (primarily gastrointestinal AEs such as nausea or diarrhoea) and a rare event (lactic acidosis) occurring in predisposed patients (particularly those with renal insufficiency).

The previously submitted safety data on the sitagliptin/metformin combination therapy showed that, compared to metformin monotherapy, the combination therapy was associated with an increase in the adverse drug reactions (ADRs) somnolence, nausea, upper abdominal pain, diarrhoea, blood glucose decreased, anorexia and weight decreased.

Since there is no meaningful PK interaction between sitagliptin and metformin, as seen in Study P012, the safety and tolerability profile of co-administered metformin and sitagliptin is expected to be similar to those of the individual agents.

- Patient exposure

Overall, 1685 patients were exposed to sitagliptin and metformin in Phase II and Phase III combination studies, of which 116 received metformin plus glimepiride.

The "safety summary" for this MAA contains the previously submitted studies (P015, P020, and P024) and the new studies P035 and P036, and an additional study (P053) which was completed after submission of the original marketing application. The tabulated safety summary includes the following categories:

- metformin + sitagliptin,
- metformin + placebo,
- metformin + SU + sitagliptin,
- metformin + SU (with or without additional placebo).

The Applicant has also provided other updated safety comparisons:

- Comparison I: metformin plus sitagliptin-exposed vs. metformin plus sitagliptin non-exposed patients
- Comparison II: metformin plus sitagliptin vs. metformin plus placebo (add-on and initial therapy) – a subpopulation of comparison I only including studies with parallel "metformin + sitagliptin" and "metformin + placebo" treatment arms.

The treatment groups compared within Comparisons I and II were generally similar with regard to age, gender, race, duration of diabetes, secondary diagnoses, baseline HbA_{1c} and duration of exposure. For the tabulated safety summary no major differences were present with regard to mean age, gender distribution and BMI. However, mean baseline HbA_{1c} and FPG were highest in the metformin + placebo group (8.6% and 190 mg/dL, respectively) and lowest in the metformin + SU group (7.7% and 165 mg/dL, respectively). Based on the data (number of patients and patient years), the mean duration of exposure was calculated at 0.84 y, 0.61 y, 0.85 y and 0.77 y for the 4 groups (metformin + sitagliptin, metformin + placebo, metformin + SU + sitagliptin, metformin + SU), respectively. As expected, mean duration of diabetes was highest in the triple combination group (9.3 y) and lowest in the metformin + placebo group (5.6 y). Because of imbalances in baseline characteristics between treatment groups, results should be interpreted with caution. However, possible conclusions from Comparison I are also limited due to the fact that populations with very different treatment regimens are compared (patients on dual or triple combination therapy with metformin + sitagliptin (+ SU) are compared to patients on either metformin monotherapy or dual or triple combination therapy of metformin + SU (+pioglitazone).

- Adverse events

The results from Comparison I (metformin plus sitagliptin-exposed vs. metformin plus sitagliptin non-exposed patients) suggest that the combination therapy metformin + sitagliptin has an acceptable safety profile compared to other antidiabetic drug regimens including metformin but not sitagliptin. The safety assessment during the initial MAA of sitagliptin led to the conclusion that sitagliptin treatment is associated with an increased incidence in:

- infections and infestations (including nasopharyngitis and upper respiratory tract infections)
- gastrointestinal disorders (including nausea, constipation, diarrhoea, abdominal pain and flatulence)

and may be associated with:

- musculoskeletal disorders (including myalgia, myopathy and muscle weakness)
- neurotoxicity and
- skin and subcutaneous tissue disorders (including urticaria).

These AEs had been included in the SPC and/or in the RMP of sitagliptin. The new safety summary (Comparison I) does not suggest such increased risks, which is reassuring, but it should be kept in mind that the populations and their antidiabetic regimens are different in the current analysis (focus on metformin + sitagliptin combination therapy in comparison to other treatment options) than in the previous analysis. The observed slight decrease in haemoglobin (Hb) during sitagliptin treatment has been identified previously but is not considered clinically relevant.

The results from Comparison II suggest a favourable safety profile of the combination therapy metformin + sitagliptin. The previously submitted safety data on sitagliptin/metformin combination therapy showed that, compared to metformin monotherapy, the combination therapy was associated with an increase in the adverse drug reactions:

- somnolence
- nausea
- upper abdominal pain
- diarrhoea
- blood glucose decreased
- anorexia and weight decreased.

However, according to the newly submitted updated safety summary, such associations cannot be confirmed; particularly hypoglycaemia and GI AEs appear not to be increased when sitagliptin is added to metformin. The observed slight decrease in Hb during sitagliptin treatment has been identified previously but is not considered clinically relevant. Whether the observed differences in discontinuation due to pre-defined kidney criteria are due to differences in adherence to these discontinuation criteria cannot be clarified. The effect of sitagliptin on the remaining kidney function was previously assessed in patients with moderate to severe chronic renal failure (P028). From previously submitted studies there is no indication that sitagliptin has a deleterious effect on kidney function. Events in the SOC 'skin and subcutaneous tissue disorders' occurred at an increased frequency when sitagliptin was added to metformin. Because skin lesions have been identified as a potential safety concern, monitoring of such events are already included in the risk management plan.

The results from the tabulated safety summary suggest an acceptable safety profile for the triple combination therapy of metformin + SU + sitagliptin compared to the dual combination metformin + SU. The only trial (P035) that has directly compared these treatment regimens found small but significantly increased incidences in the AEs of:

- gastroenteritis
- pneumonia
- arthralgia
- osteoarthritis
- pain in extremity
- dizziness
- headache and
- hypoaesthesia

and a markedly increased incidence (16.4 vs. 0.9%) in hypoglycaemia with the triple combination. In the new comparison, which is acknowledged to have relevant limitations, some AEs such as infections and headache are also found at an increased rate. On the other hand, hypoglycaemia occurred at a lower rate which clearly contrasts previous findings. This difference may be explained by the relevantly lower baseline HbA_{1c} in the dual therapy vs. the triple therapy group in the tabulated safety summary.
The dual combination therapy with metformin + sitagliptin was associated with a markedly lower frequency of hypoglycaemia than the combination metformin + SU. This is not unexpected since sitagliptin itself does not lead to hypoglycaemia. However, it should be noted that the, on average, lower baseline HbA_{1c} levels in patients on metformin + SU may have added to the large difference in hypoglycaemia rates. Overall, this tabulated safety summary does not elicit new safety concerns.

- Serious adverse event/deaths/other significant events

In addition to the above comparisons, the new safety summary also presents an update on reported deaths that occurred until the cut-off date of 30-September-2007. Until then, a total of 26 deaths (2 reported prior to randomization) had been reported in studies of sitagliptin in combination with metformin. Of the 24 post-randomization deaths, 9 occurred in the sitagliptin group and 15 in a non-sitagliptin group. Causes of death reported for more than 1 patient included:

- carcinomas (3 on glipizide, 1 on metformin)
- myocardial infarctions (3 on glipizide)
- sudden cardiac death (1 on glipizide, 1 on placebo)
- accidental death (3 on sitagliptin, bicycle accident, fall/drowning and electrocution while mowing lawn)

- suicide (1 on pioglitazone, 1 on glipizide).

No death was considered by the investigator to be drug-related.

The observation that the hypoglycaemia rate is increased when sitagliptin is added to a SU agent was addressed by the Applicant. It is accepted that a similar observation of increased hypoglycaemia incidence is made when other AHA agents that themselves are not associated with hypoglycaemia (e.g., metformin or PPARγ agents) are used in combination with a SU agent. In addition, this increased hypoglycaemia incidence and rate may partly be due to the improved glycaemic control in sitagliptin compared to placebo treated patients. Most events were mild, i.e. did not require medical or non-medical assistance and no hypoglycaemic event of marked severity, as defined in the studies, occurred which is reassuring. The increased incidence of hypoglycaemia is adequately addressed in section 4.8 of the proposed SPC.

There was a concern that the limited efficacy of sitagliptin in combination with glimepiride could be due to the combination-induced hypoglycaemia that led to a reduction in the SU dose and thus to a decrease in efficacy. In other words, the combination may not have reached/sustained its full potency due to dose-limiting side effects. The Applicant answered that down-titration occurred in only approximately 2% of patients, and ranged from day 14 to day 99. Thus, down-titration of glimepiride due to hypoglycaemia was not commonly required. This is consistent with the observation that the hypoglycaemia events in the sitagliptin group were generally neither recurrent nor severe. Hypoglycaemia with concomitant SU use will be further evaluated in a 3-4 year clinical trial committed to during the initial MA procedure of sitagliptin.

In agreement with previous findings from the sitagliptin development program, there was no discernable increase in the incidence of death or overall or specific non-fatal SAEs when sitagliptin was added to metformin or to a dual combination therapy of metformin and a SU agent. In addition, the overall rates of discontinuation due to clinical or laboratory AEs were low and similar between sitagliptin and placebo or SU treated patients. There were no clear treatment differences for discontinuations due to specific AEs except for hypoglycaemia, which occurred only in glipizide-treated patients in Study P024.

- Laboratory findings

Laboratory data from the new studies P035 and P036 are also in line with findings from previously submitted sitagliptin/metformin combination studies.
Taken together, sitagliptin/ metformin dual combination therapy compared to metformin monotherapy was associated with small increases in uric acid and white blood cell count, WBC (ANC), and with small decreases in AP and possibly in ALT, AST, Hb and bilirubin.
Sitagliptin/metformin/SU triple combination therapy compared to metformin/SU dual combination therapy (P035) was associated with small increases in WBC (ANC) but not uric acid, and with small decreases in ALT, AST, AP and Hb.
Of note, neither of these changes is considered clinically relevant. In addition, there are indications that the observed changes in these parameters may be largely due to the glycaemic effects of antihyperglycaemic medications rather than a direct effect of the study drugs.

At the therapeutic dose of 100 mg per day, sitagliptin either alone or in combination with metformin does not appear to have a relevant effect on blood pressure or the conduction system of the heart.

- Safety in special populations

No subgroup analyses of safety were performed for patients taking the combination of sitagliptin and metformin. However, subgroup analyses by age, gender and race for the previously submitted overall Pooled Phase II/III Studies were presented. No clinically meaningful differences in the incidence of specific AEs by age, gender or race were observed

Metformin is contraindicated and sitagliptin is currently not recommended in patients with moderate to severe renal failure. Metformin but not sitagliptin is licensed for use in paediatric patients with T2DM. Therefore, no data can be expected for the fixed combination sitagliptin/metformin in these populations.

- Discontinuation due to adverse events

Overall, the rates of discontinuation due to a clinical or laboratory AE were low and similar between sitagliptin and placebo or SU treated patients. There were few AEs that led to discontinuation in more than one patient, i.e. gastrointestinal AEs, hypoglycaemia, urticaria, increased blood creatinine, or decreased creatinine clearance. There were no clear treatment differences for discontinuations due to specific AEs except for hypoglycaemia: all 6 cases occurred in a glipizide group.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Lactic acidosis	Routine Pharmacovigilance Clinical Trials: 1. Ongoing Trials: P024-01, and P036-10 2. Completed Trials - Study Report Pending: P020-04, P035-01, and P036-04 3. Planned Trial: A planned 3-4 year study to monitor safety in patients with type 2 diabetes mellitus inadequately controlled on maximum tolerated doses of metformin or a PPARγ agonist	Labeling-SPC Section 4.4 Special warnings and precautions for use: Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.
Hypoglycaemia with concomitant sulfonylurea	Routine Pharmacovigilance Clinical Trials: 1. Ongoing Trials: P024-01, and P036-10 2. Completed Trials - Study Report Pending: P020-04, P035-01, and P036-04 3. Planned Trial: A planned 3-4 year study to monitor safety in patients with type 2 diabetes mellitus inadequately controlled on maximum	Labeling-SPC Section 4.4 Special warnings and precautions for use: <u>Hypoglycaemia</u> Patients receiving Janumet in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea may be necessary.

	tolerated doses of metformin or a PPARγ agonist	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
There are no unresolved quality issues, which may affect the Benefit/Risk balance.

Non-clinical pharmacology and toxicology

The pharmacology of sitagliptin and metformin has been investigated for each drug separately. No primary or secondary pharmacology studies of the combination were conducted, which was found to be acceptable by the CHMP. Specific safety pharmacology studies were not performed either, however, ECG recording were performed during the repeated-dose toxicology studies of the combination, not revealing any treatment-related effects. Overall, the general pharmacology studies corroborate the information previously available for the individual components and support the combined use.

From the pharmacokinetic standpoint, specific studies on the combination were not performed. Interaction studies for the triple combination with a sulphonylurea were not considered necessary as clinically no relevant concerns were discovered regarding the safety of the combination of sitagliptin/metformin with glimepiride.

The combination studies with sitagliptin and metformin in dogs indicated no evidence of toxicokinetic or toxicologic interactions. No non-clinical studies were performed for the combination of sitagliptin / metformin with a sulphonylurea, however, sitagliptin, metformin and sulphonylurea have different toxicity profiles, and therefore interactions do not seem likely. Furthermore, clinically, no relevant concerns were discovered regarding the safety of the combination of sitagliptin/metformin with glimepiride.

Efficacy

Demonstration of bioequivalence (BE) of the sitagliptin/metformin FDC tablets and its active components given as individual tablets is important to extrapolate the efficacy and safety results obtained with the sitagliptin and metformin co-administration studies to the FDC (no phase II/II studies have been performed using the FDC) and to ensure that T2DM patients already taking metformin (and sitagliptin) can be safely and effectively switched to the FDC tablets.
Demonstration of BE is also of prime importance as the applicant did not submit a full PK dossier with all required studies but instead referred to the results of the individual dossiers of sitagliptin and metformin.

The Applicant submitted two BE studies, particularly study P048 and study P095. Study P095 established bioequivalence between the sitagliptin component of Janumet and sitagliptin given as individual tablet. Bioequivalence study P095, performed with the European reference product Glucophage for metformin was submitted later upon CHMP request together with additional dissolution studies. The results of this study clearly demonstrate that with respect to metformin all strengths of Janumet are bioequivalent with Glucophage. The half-lives and t_{max} values were also comparable.

The previously submitted studies P020 and P024 as well as the new studies P035 and P036 support the already approved uses of sitagliptin in combination with metformin and triple combination of sitagliptin + metformin + SU.

The significant and clinically relevant effect of sitagliptin added to the regimen of patients with inadequate glycaemic control on metformin monotherapy (as observed in P020 and P024) was numerically smaller than the effect of sitagliptin on glycaemic control in patients insufficiently controlled on the combination of SU and metformin (P035). This effect was also numerically larger than that observed with the addition of sitagliptin in patients insufficiently controlled on SU monotherapy. The combination therapy of sitagliptin with a SU is already approved, hence, the triple therapy of sitagliptin, metformin and a SU, applied for in the current application for the FDC, is considered acceptable based on the presented efficacy data.

Although the current dose recommendation for sitagliptin is 100 mg taken as a single daily dose (QD), the previous study P014 (submitted with the initial MAA for sitagliptin) showed that efficacy and safety of a daily dose of 100 mg is similar when given either as a single dose or divided into two daily doses. Therefore, the content of 50 mg sitagliptin in the proposed FDC tablets resulting in a 50 mg twice daily (BID) dosing is acceptable.

The lowest proposed strength, i.e. 50mg/500mg, was not considered acceptable. The minimal metformin dose assessed in studies P020 and P024 was 1500 mg per day; the efficacy of metformin in reducing T2DM complications was demonstrated in UKPDS 34, in which a great majority of the patients were treated with metformin doses >1700 mg per day. Although there might be a minority of patients who cannot tolerate metformin at doses higher than 1000 mg, it is unlikely that the FDC tablet offers a meaningful benefit compared to the administration of the separate components. In addition, the low dose FDC tablet could promote initial combination therapy which is not approved and not covered by current diabetes treatment guidelines. Therefore, the approval of the 50/500 mg tablet is not recommended and the Applicant has withdrawn the application for this strength.

Safety

Overall, it can be concluded that, based on the submitted data, sitagliptin in combination with metformin and/or SU agent has an acceptable safety profile. Based on previous safety assessment it was concluded that sitagliptin treatment is associated with an increased incidence in infections and infestations, gastrointestinal disorders, musculoskeletal disorders, and nervous system AEs. Event rate was increased for skin and subcutaneous tissue disorders. These AEs have been included in the SPC and the RMP.

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

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The results from the readability testing were submitted at the time of the response package at Day 121. The test included sufficient questions about the critical sections and the results were satisfactory, i.e. 90% of the participants were able to find the information and of those 90% were able to adequately express the information in their own words.

Risk-benefit assessment

Benefits

The submitted Phase II/III studies, the previously submitted studies P015, P020 and P024 as well as the new studies P035 and P036, support the use of sitagliptin in combination with metformin, either as dual combination therapy or as triple combination therapy with a sulfonylurea agent (both already approved for sitagliptin). The results also suggest that the glucose-lowering potential of sitagliptin *per se* is lower than that of high-dose metformin but nevertheless clinically moderate and relevant.

Given the observation that the efficacy of sitagliptin appears optimal in combination with metformin, the lack of relevant PK interactions of these two drugs, and the fact that combination therapy with metformin (add-on to metformin) is already approved, the development of a FDC combination is acceptable. The FDC tablets may improve compliance due to the reduced daily tablet load in patients with T2DM usually taking a variety of medicinal products.

Although the current dose recommendation for sitagliptin is 100 mg taken as a single daily dose, the previous study P014 (submitted with the initial MAA for sitagliptin) showed that efficacy and safety of a daily dose of 100 mg is similar when given either as a single dose or divided into two daily doses. Therefore, the content of 50 mg sitagliptin in the proposed FDC tablets resulting in a 50 mg twice daily dosing is acceptable.

Metformin causes GI side effects such as nausea, diarrhoea and abdominal pain in a substantial number of patients. Consequently, the tolerated maximum daily dose varies among patients. Therefore, the proposed dose strengths of Janumet including 50/850 (mg/mg) and 50/1000 (mg/mg) of sitagliptin/metformin, respectively, are reasonable and acceptable.

The results of the pivotal bioequivalence studies (P048 and P095) clearly demonstrate that, with respect to the sitagliptin and metformin component, all three strengths of Janumet are bioequivalent with Januvia and Glucophage, respectively.

Risks

When combining sitagliptin with metformin and/or SU, the only remarkable issue was that the incidence of hypoglycaemia was increased compared to placebo when sitagliptin was added to a SU. No such increase was seen with the combination of sitagliptin with metformin. However, none of the hypoglycaemia episodes met criteria for marked severity or required medical attention, and no patients were discontinued due to hypoglycaemia. The updated safety summaries do not elicit new safety concerns.

Balance

The overall risk benefit ratio of Janumet 50 mg/850 mg and 50 mg/1000mg is considered positive.
The proposed indications are considered acceptable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Janumet in the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin; or in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea, was favourable and therefore recommended the granting of the marketing authorisation.