# SCIENTIFIC DISCUSSION

## 1. Introduction

Type 2 diabetes mellitus (T2DM) afflicts an estimated 6% of the adult population in Western society. Three key defects underlie the pathogenesis of the disease: insulin resistance, reduced insulin secretion, and hepatic glucose overproduction. Limitations of current therapies include a range of safety and tolerability issues, limited extent and/or durability of efficacy, and inconvenience in dosing. The most common adverse events associated with current agents are hypoglycaemia (with sulfonylureas, meglitinides, insulin), weight gain (with sulfonylureas, meglitinides, insulin, thiazolidinediones [TZDs]), and gastrointestinal intolerance (with metformin, alpha-glucosidase inhibitors). Thus, the sitagliptin development program was based upon the need for new medical therapies that have distinct mechanisms of action and that offer an improved safety and tolerability profile with good efficacy and durability.

This is a complete stand-alone application.

The originally proposed indication was "For treatment of patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ agonist (e.g. thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycaemic control". The approved indication is "Xelevia is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise plus metformin 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, Xelevia is indicated in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control." The dose is 100 mg sitagliptin once daily. The dosage of metformin or PPARγ agonist should be maintained, and Xelevia administered concomitantly.

## 2. Quality aspects

**Introduction**
Januvia is presented as film-coated tablets containing 25 mg, 50 mg and 100 mg of Sitagliptin (as monohydrate Phosphate salt) as active substance. The other ingredients are microcrystalline cellulose, dibasic calcium phosphate, croscamellose sodium, magnesium stearate and sodium stearyl fumarate. The film coat consists of polyvinyl alcohol, titanium dioxide, macrogol, talc, purified water and colorants.

The film-coated tablets are marketed in PVDC/PE/PVC-foil, which are heat-seal lacquered to an aluminium foil.

**Active Substance**

The active 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-powder and exhibits pH dependent aqueous solubility. It is soluble in water and *N,N*-dimethyl formamide, slightly soluble in methanol, 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, and 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 (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. Certificates of analyses for the active substances issued by the finished product manufacturer were provided 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 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.

**Medicinal Product**

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
Sitagliptin tablets were developed in four tablet strengths (25 mg, 50 mg, 100 mg and 200 mg).
The main aim of the applicant was to develop a formulation that would rapidly release the active substance, that would behave as much as possible as an oral solution upon dosing and would provide a consistent bioavailability. In this context, the excipients have been chosen not only to achieve these aims but also to ensure the chemical stability. A direct compression manufacturing process was selected based on its inherent simplicity and demonstrated ability to produce high quality tablets reproducibly.
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 blending, lubrication, direct 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 medicinal product specifications were established according the ICH guidelines and include the following tests: appearance, identification (NIR), assay, impurities/degradants (HPLC), uniformity of dosage units, disintegration, microbial limits (Ph Eur).
All analytical procedures that were used for testing the medicinal product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the CHMP and ICH guidelines.
Batch analysis data on five commercial 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 each strength have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch per strength was 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 two minor unresolved quality issues, which do not have any impact on the benefit/risk ratio of the medicinal product. The applicant gave a letter of undertaking and committed to resolve these as follow up measures after the opinion, within an agreed timeframe.

## 3. Non-clinical aspects

**Introduction**

To support the clinical evaluation of sitagliptin an extensive number of non-clinical toxicity studies were conducted prior to and in parallel with the clinical program. These studies included a battery of *both in vitro* and *in vivo* genotoxicity studies, safety pharmacology studies, acute and repeated dose oral studies, rodent carcinogenicity studies, developmental and reproductive toxicity studies

All pivotal non-clinical toxicity studies were conducted consistent with ICH Non-clinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations. In addition, also non-GLP studies were conducted (in-vitro and early in-vivo pharmacodynamics, and early dose-finding studies). These non-GLP studies were not considered to compromise the scientific integrity or affect the experimental results.

Scientific advice concerning non-clinical studies was not sought.

**Pharmacology**

- Primary pharmacodynamics

The primary glucose-lowering property and effects on glucagon-like peptide-1 (GLP-1) plasma levels of dipeptidyl peptidase-4 (DPP-4) inhibition by sitagliptin (as the main basis for its efficacy for the

indication T2DM) have been shown. In order to see the effects on the plasma levels of glucose-dependent insulinotropic peptide (GIP), insulin and glucagon the Applicant described the effects of des-fluoro-sitagliptin, a closely related analogue (comparable in vitro potency, selectivity and in vivo efficacy), showing improved glucose tolerance and increased plasma GLP-1 levels in animals. In addition, the analogue also increased plasma insulin levels, accompanied by decreased plasma glucagon levels (in streptozotocin-induced diabetic mice); however, no preclinical data was included on plasma GIP levels. Though not considered outstanding, a proper assessment of this issue was not possible due to the lack of relevant pharmacological data on this analogue.
DPP-4 tissue distribution (RNA expression) was mainly high in blood T lymphocyte, kidney, salivary glands, prostate, placenta and intestinal tissue; the latter is consistent with its regulation of incretin hormone action. In rhesus monkeys and mice, DPP-4 RNA expression was high in intestinal tissues. Tissue distributions of DPP-8/9 were very broad. Therefore tissue distribution of DPP-4 appears to be quite specific and high in the intestinal tissues in humans and animals.

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 (IC50 values of ~5, >20, and >20 μM, respectively, versus 18 nM for sitagliptin). The DPP-4 activity of M3, M4, and M6 was not determined. Sitagliptin is a very selective DPP-4 substrate over DPP-8/9 (main targets causing severe toxicity if inhibited). Synthetic M5 metabolite has a low binding affinity (IC50 >100 μM) for DPP8/9. The human plasma levels of metabolite M6 are low (< 5% in plasma and bile) and will, therefore, not meaningful impact on the pharmacodynamic (PD) actions of sitagliptin.

- Secondary pharmacodynamics

Although inhibition of DPP-4 activity enhances incretin action in diabetic patients, DPP-4 exhibits catalytic activity against a broad number of peptide substrates. In general, most cell surface peptidases such as DPP-4 cleave a number of substrates *in vitro*; their endogenous substrate specificity, however, is harder to establish. In order to evaluate the potential secondary pharmacological effects of DPP-4 inhibition by sitagliptin, the Applicant discussed the biological importance of in vivo DPP-4 substrates, based on the following two criteria:

1 Elevated substrate levels are observed *in vivo* after DPP-4 inhibition or in DPP-deficient mice (simply establishing that the peptide or protein is a substrate in rodents) and
2 Substrate stabilization must have biological effects (cleavage results in activation or inactivation).

Based on these criteria, the only DPP-4 substrates are GLP-1 and GIP.

Other peptides that are cleaved in vitro by DPP-4 are glucagon family peptides (GHRH, IGF-1 and GLP-2), neuropeptides (substance P/bradykinin: no effects) and chemokines (e.g., SDF-1α: cleavage after in vitro DPP-4 inhibition). It should be noted that in vitro cleavage of given peptide by DPP-4 does not always translate to in vivo regulation to its bioactivity by the enzyme. Conclusive studies to determine whether these *in vitro* substrates are regulated by DPP-4 *in vivo* have not occurred largely owing to the lack of suitable assays for measurement of endogenous levels of these proteins/peptides and their putative products. Therefore, even though in vitro experiments show a wide variety of DPP-4 substrates, the biological relevance in vivo remains uncertain**.**

As part of its secondary pharmacology, 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 biomolecules (generally >100 μM). Only a weak affinity tosome ion channels and 5-$HT_2$ receptors was demonstrated. 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. However, in order to elucidate whether other receptors have (high) affinity for sitagliptin the Applicant provided an overview of the potential binding of sitagliptin to an extensive battery of molecular targets. Based on its low potency ($IC_{50}$ value >10 μM) it has been shown that sitagliptin does not interact with receptors other than certain 5-$HT_2$

receptors, as specified earlier. Due to the high $C_{max}$ value that was achieved in safety pharmacology studies (~50 μM) it is not possible to ascertain that the observed minor cardiovascular effects are not due to activities at one or more of these receptors.

- Safety pharmacology programme

***DPP-4 activity:*** Except for some minor cardiovascular effects (blood pressure and heart rate), major effects were not observed with sitagliptin in other important systems. The observed sitagliptin-induced hypotension may be explained by its affinity/potency to other biomolecules (e.g., receptors).
It was described that a selective DPP-4 inhibitor had no effect on lymphocyte proliferation (immune system), and would not produce meaningful delayed gastric emptying in humans; while no data was available to suggest that altered DPP-4 activity *in vivo* would have any effect on tumour formation and metastasis.

***DPP-8/9 activity:*** No endogenous substrates have been identified, and thus the specific functions of these enzymes are unknown. Highly selective inhibitor of DPP8/9 attenuates T cell activation *in vitro*, and produce profound toxicity in preclinical species, including thrombocytopenia, anemia, splenomegaly, and mortality in rats, gastrointestinal toxicity in dogs, and edema of the skin in non-human primates. As sitagliptin has an IC50 of ~ 50 μM or greater for DPP-8 and DPP-9, no inhibition of these enzymes is anticipated at exposures required for glucose lowering in humans.

***Fibroblast activation protein (FAP) and Prolyl endopeptidase (PEP, prolyl oligopeptidase, POP) activity:*** As sitagliptin has an IC50 of > 100 μM or greater for FAP and PEP, no inhibition of these enzymes is anticipated at exposures required for glucose lowering in humans.

***DPP-6/10 activity:*** DPP6 and DPP10 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 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.

- Pharmacodynamic drug interactions

No experiments were performed.

**Pharmacokinetics**

Single dose studies were carried out with a solution of the phosphate salt of sitagliptin in saline for both intravenous (IV) and oral (gavage) administration. For the placental transfer and milk excretion studies, the phosphate salt was formulated in 0.5% aqueous methylcellulose containing 5 mM HCl. Most metabolism, excretion, and tissue distribution studies were carried out with [$^{14}$C]sitagliptin.

Plasma concentrations of sitagliptin (molecular weight of free base = 407.32) were determined by a validated LC-MS/MS assay that had a lower limit of quantification of 1.0 and 5.0 ng/mL (2.46 and 12.3 nM) in rat and dog plasma, respectively. The validated assay demonstrated good linearity and reproducibility for sitagliptin in the concentration range of 1.0 to 10,000 ng/mL in rat plasma, and 5.0 to 20,000 ng/mL in dog plasma. The within and between run assay precision were 11% or less for both rat and dog quality control (QC) samples, except at the limit of quantification where precision was better than 14%. Total radioactivity in tissues, blood, plasma, urine, bile, and feces was determined by liquid scintillation counting, with or without prior combustion. Metabolite identification was accomplished by LC-MS and by comparison with authentic synthetic standards (M1, *N*-sulfate conjugate only). Two of the metabolites (M2 and M5) were purified from dog urine and identified by NMR analysis and hydrogen-deuterium exchange.

The results of the non-clinical absorption, distribution, metabolism and excretion (ADME) studies indicated that sitagliptin was rapidly absorbed and was a moderate to high clearance drug, with a relatively short plasma half-life.

***Absorption:*** In rats, following single IV administration of sitagliptin at doses of 0.5, 2, and 5 mg/kg in males and 2 mg/kg in females, plasma concentrations of parent drug declined in a time dependent manner, with the pharmacokinetic parameters adequately described by non-compartmental analysis of the sitagliptin plasma concentration versus time data. The mean sitagliptin plasma clearance (CLp) was ~40 to 48 mL/min/kg at the three doses in males and 67 mL/min/kg in females; blood clearance was estimated to be approximately the same as plasma clearance (blood-to-plasma ratio was approximately unity). The mean values for the steady-state volume of distribution (Vdss) and terminal half-life (t1/2) were ~7 to 9 L/kg and ~2 hr, respectively, in both males and females. The renal clearance of unbound drug was calculated to be ~34 mL/min/kg, by dividing the mean total plasma clearance (~45 mL/min/kg) by the fraction unbound in plasma (0.67), and multiplying by the fraction of dose excreted unchanged into urine (~0.5). This value exceeded the glomerular filtration rate (~5 mL/min/kg in rats), implying that sitagliptin was subject to active renal elimination in rats.

The dose dependence of the oral pharmacokinetics of sitagliptin was evaluated after single administration of four dose levels in male rats (2, 20, 60, and 180 mg/kg) and 2 dose levels in female rats (2 and 180 mg/kg). The data indicated that over the dose range studied, absorption of sitagliptin was not saturable, while elimination may have decreased somewhat with dose, as indicated by the ~181- and 159-fold increase in the area under the plasma concentration-time curve (AUC) observed in male and female rats, respectively, between 2 and 180 mg/kg. Oral bioavailability at 2 mg/kg was 59% and 82% in male and female rats, respectively.

Sitagliptin plasma concentration-time data was collected in the dog following IV administration at 0.5 and 1.5 mg/kg. Mean CLp, Vdss, and t1/2 values were ~9 mL/min/kg, 3 L/kg, and 4 hr, respectively. Blood clearance was estimated to be approximately the same as plasma clearance (blood-to-plasma ratio was approximately unity).

Dose-dependent oral pharmacokinetics was evaluated after single administration at four dose levels (0.4, 1.6, 10, and 30 mg/kg). Plasma AUC increased proportionately with dose, indicating that absorption and elimination of sitagliptin were not saturable over the dose range studied. The oral bioavailability was 89% at 0.4 mg/kg and 97% at 1.6 mg/kg.

***Distribution:*** Sitagliptin was orally bioavailable, and exhibited fairly linear oral pharmacokinetics in rat and dog.

In rats, [$^{14}$C]sitagliptin-related radioactivity was distributed widely throughout the body following IV administration, but was cleared efficiently from all tissues. However, cecum, intestine, liver and kidneys contained relatively high concentrations of sitagliptin related material even after 24hr. Enterohepatic circulation can therefore not be ruled out.

Sitagliptin was seen to cross the rat and rabbit placenta readily.

Sitagliptin was shown to be a substrate of the mouse and human P-glycoprotein (Pgp), and the human renal organic anion transporter hOAT3. In the *in vitro* interaction studies via Pgp transport (studies PK012 and PK017), cyclosporine A (potent inhibitor of Pgp) was used as a positive control. A concentration of 10 μM cyclosporine A strongly inhibited basolateral to apical transport of sitagliptin in LLC-MDR1 cells. This suggested that drug interactions via Pgp were possible.

The potential of sitagliptin to cause drug interactions with hOAT1 and hOAT3 substrates was evaluated *in vitro*. At concentrations of 0.1 to 500 μM, sitagliptin had no inhibitory effect on hOAT1-mediated uptake of cidofovir, while probenecid, a known inhibitor of organic anion transporters, showed potent inhibition with an IC50 of 3.9 ± 0.9 μM. Sitagliptin was a weak inhibitor of hOAT3-mediated cimetidine uptake with an IC50 value of 160 ± 17 μM, whereas probenecid significantly inhibited hOAT3-mediated transport of cimetidine with an IC50 of 3.1 ± 1.2 μM. Since the IC50 values of sitagliptin for hOAT1 (>500 μM) and hOAT3 (160 μM) are so much higher than its plasma concentrations, $C_{max}$ ~1 μM at 100 mg, it is unlikely that it will cause clinically meaningful interactions with substrates of these transporters.

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 (2 μM) was evaluated *in vitro* using cell lines over-expressing this transporter. The concentration of sitagliptin in these experiments was much lower than its $K_m$ value of 162 μM in order to maximize the inhibitory effects. The Applicant stated that with the exception of probenecid, the IC50 values of all drugs tested were much higher than their maximum total or unbound concentration in plasma. However, besides probenecid also fenofibric acid, furosemide and ibuprofen had 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 OAT3 inhibitors. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

***Metabolism:*** *In vitro* assays indicated that at clinically relevant concentrations, sitagliptin did not inhibit cytochrome P450s or Pgp, nor did it induce human CYP3A4. The sitagliptin metabolites, which were present at low to trace levels in plasma, were 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 were observed in rat and dog, however, not all observed metabolites were present in the same matrix as observed in humans. Due to the minor metabolism of this compound, consequences of the differences in metabolism between human, rat and dog on the observed pharmacokinetics are not expected. The observed *in vitro* metabolism was in agreement with the *in vivo* metabolism. Only metabolite M1 was not observed *in vitro*.

***Excretion:*** *In vitro* plasma protein binding was low in mouse, rat, rabbit, dog, and human. Sitagliptin was excreted primarily unchanged in human, rat and dog. In dogs and humans, sitagliptin was cleared primarily by renal excretion of parent drug, while in rats it was cleared by both renal and biliary excretion. Approximately 5 to 16% of a radiolabeled dose was recovered as phase I and II metabolites in the excreta. Furthermore, sitagliptin observed in bile from dogs was significantly lower than in human faeces and rat bile. Sitagliptin was secreted into rat milk; this is mentioned in section 5.3 of the SPC. As it is unknown if sitagliptin is excreted into human breast milk, it should not be used during breast-feeding (see section 4.6. of SPC).

**Toxicology**

- Single dose toxicity

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

- Repeat dose toxicity (with toxicokinetics)

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 rats mortality was higher in males than females, while in mice it was higher in females.
In both mice and rats renal toxicity was observed at systemic exposure values above 58 times the human exposure levels, while the no-effect level was 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 was due to renal tubular necrosis.
The molecular mechanism of the renal toxicity is very likely related to the extremely high urinary concentrations resulting from rapid renal elimination of the drug in rodents. Since sitagliptin is virtually completely absorbed following an oral dose in rodents, the initial body burden of the drug is likely to be more directly related to the dosage on a mg/kg body weight basis than on a plasma AUC basis. This would result in more than 2 orders of magnitude greater exposure in these animal studies compared to humans based on dosage (500 versus 2 mg/kg/day). Given the very high renal elimination rate of the drug, in part due to its active transport into the kidney, the resulting renal exposures in rodents compared to humans is also correspondingly greater than predicted based on plasma AUC margins. The histological changes indicate a relatively non-specific cytotoxicity associated with these very high exposures. The specificity of the renal toxicity for rodents exposed to very high doses is also supported by the lack of any renal toxicity in dogs and rhesus monkeys (though no toxicology studies with rhesus monkeys were present in the Original Marketing Application, thus a safety margin for this species cannot be determined) treated within exposure margins of 26- to 28-fold compared to patients. In view of the much lower clinical exposures and body burden of the drug in humans at the clinical dose and the lack of any biochemical changes indicative of renal toxicity in patients, these high dose findings in rodents are not considered clinically relevant.
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. This was observed in male mice, and in male and female rats. Even though the mechanism for sitagliptin-induced renal and liver toxicity is not completely clear, the safety margins for these effects are sufficient.
In addition, no hepatotoxicity was found in dogs treated with maximum-tolerated doses of sitagliptin for up to 1 year and no signal for hepatotoxicity has been found in clinical trials conducted at twice the maximum-recommended clinical dose.
In rats sitagliptin caused upper incisor teeth abnormalities (broken and grossly thickened incisor teeth due to ameloblast and odontoblast degeneration), with a NOAEL of < 20 mg/kg/day. At 20mg/kg/day, exposure in rat is similar to the human exposure, based on AUC. Therefore no safety margin exists for teeth abnormalities. These effects were only observed on the continuously growing teeth. After revision of this data it was concluded that the broken teeth in the low-dose rat study were not treatment-related. This implies that the NOEL for broken or missing teeth is 500 mg/kg/day for long-term treatment, which corresponds to an acceptable safety margin. No NOEL can be established for discoloured incisor teeth after long-term treatment. However, discoloration was only observed in incisor teeth of rats, and no discoloration was observed in mice (2-year, max 500mg/kg, safety margin of 57), and dogs (1-year, 50mg/kg, safety margin 25) after long-term treatment. The intended indication of the current application is T2DM or adult onset diabetes, thereby excluding patients with ongoing tooth development. Therefore it is agreed that the discoloured incisor teeth in rats can be considered of little relevance for the intended patient population.
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 were 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 were observed in rats receiving high doses of sitagliptin (≥1500 mg/kg/day). The NOEL for neurological signs in dogs was 10 mg/kg. Examples of these neurological signs were open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture. The occurrence of these signs may be concentration dependent rather than exposure dependent. 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 were 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 Plan (RMP).

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, 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 in the phase 3 trials. However, in view of a safety margin of ≥6, this finding will be monitored in the Risk Management Plan.
In all species and at most doses tested, sitagliptin caused salivation. This effect was transient, started shortly after dosing, and lasted for several hours. This observation was not considered relevant for the human situation.

Of the preclinical program on necrotic skin lesions in monkeys, the 14-week repeated dose study with the selective DPP-8/9 inhibitor L-000233357 has not been finished yet. The Applicant committed that the report of this study will be provided as soon as it is completed.

- Genotoxicity

Sitagliptin showed no genotoxic effects in in vitro or in vivo assays on mutagenicity (Ames test), direct DNA damage (in vitro test in primary rat hepatocytes), or clastogenicity (in vitro chromosome aberration test in Chinese hamster ovary cells, in vivo mouse micronucleus test).

- Carcinogenicity

The carcinogenic potential of sitagliptin was determined in mice and rats. In the two-year mouse carcinogenicity study, there were no treatment-related increases in tumor incidence in any organ at all tested doses (50, 125, 250, 500 mg/kg/day). Treatment-related non-neoplastic changes were seen in both sexes and included centrilobular hepatocellular hypertrophy at 500 mg/kg/day and hydronephrosis at ≥250 mg/kg/day. At 500 mg/kg/day, there was a slight, but not significant decrease in survival due to an increased incidence of hydronephrosis. Based on these findings, the NOEL for induction of neoplasia was >500 mg/kg/day and the NOEL for non-neoplastic changes 125 mg/kg/day in male and female mice.
In the two-year rat carcinogenicity study, there was a treatment-related increase in hepatic tumors (adenomas and carcinomas) at systemic exposure levels 58-times the human exposure levels. There were no other treatment-related or statistically significant increases in tumor incidence in any other organ. Since hepatotoxicity (cystic degeneration, basophily and eosinophily in absence of necrosis) has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans. The historical controls in which 0.5% (w/v) methylcellulose in deionized water was used as vehicle indicated that in males the occurrence of hepatic carcinomas tended to be higher (3.2%) than in females (0.7%). The two control groups of the rat carcinogenicity study showed hepatic carcinomas in about 0-2% of females and in 2-6% of the males. Thereby these controls fell within the same range as the historical controls

- Reproduction Toxicity

Sitagliptin did not affect male or female fertility in rats at the limit dose of 1000 mg/kg/day. In the F0 females, a reduction in body weight and food consumption was seen at ≥ 250 mg/kg/day. No treatment-related effects on placental morphology were observed up to the highest dose of 1000 mg/kg/day. Sitagliptin was shown to cross the placental barrier with fetal exposure values 45 to 80% those in the dam and was also concentrated in milk about 4-fold compared to plasma. In the F1 pups, there were no external or visceral abnormalities and no fetal or postnatal developmental effects at ≤ 250 mg/kg/day; a reduction in body weight was seen at 500 mg/kg/day and a slight increase in the incidence of rib anomalies (absent, hypoplastic, and wavy ribs) relative to control was found at 1000 mg/kg/day. From these findings it is concluded that in rats the NOEL for maternal toxicity is 125 mg/kg/day and the NOEL for developmental toxicity 250 mg/kg/day. The safety margin at the NOEL for developmental toxicity is approximately 29, based on AUC values relative to the AUC in patients at the MRD. This margin is large enough to ensure the safety of sitagliptin for human reproduction.

In rabbits, maternal toxicity was seen at 500 mg/kg/day (decreased food consumption, no faeces). This resulted in early termination of this group, precluding fetal examination. There were no treatment-related effects on placental morphology and no developmental toxicity was found at the maximum evaluable dose of 125 mg/kg/day. At this dose, the AUC0-24 h was 189 μM•hr, resulting in a safety margin of about 22-fold relative to the AUC in patients at the MRD. It was concluded that this margin was large enough to ensure the safety of sitagliptin for human reproduction.

- Local tolerance

Local tolerability of sitagliptin was assessed as part of the oral toxicity studies described in the repeated-dose toxicity studies. Sitagliptin was not considered a dermal sensitizer based on an *in vivo* study in mice (local lymph node assay) or a dermal irritant based on two *in vivo* dermal irritation studies in rabbits, and on an *in vitro* study with human epidermal cells.

**Immunotoxicity**
Inhibition DPP-4 by sitagliptin does not seems 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 was no suggestion of an immunosuppressive effect of sitagliptin and there was no evidence of allergenicity in the local lymph node assay in mice (section on local tolerance).

**Phototoxicity**
Since sitagliptin has only a single absorption peak at 268 nM with no detectable absorption in the sunlight region of the electromagnetic energy spectrum (290 to 700 nM), no phototoxicity testing was performed with this drug.

**Impurities**
The specifications for the S-enantiomer of sitagliptin (regarded as an impurity since the synthesis is highly stereo-selective) are higher (≤0.5%) than the content in the batches used for the toxicity studies. Therefore the S-enantiomer may not be regarded as fully qualified (see also quality part of this Assessment report). However, it should be noted that the exposure towards both enantiomers of sitagliptin in the toxicology studies was much higher than under human therapeutic conditions even if the relative concentration of the S-enantiomer in the toxicologically tested batches was lower than in later batches.

**Ecotoxicity/environmental risk assessment**

Neither an assessment of the terrestrial compartment nor an assessment of bioaccumulation is needed.
Sitagliptin phosphate is not a vPvB substance, meaning it is not very persistent and very bioaccumulative, nor PBT (persistent and bioaccumulative and toxic), since the criterion for bioaccumulation is not fulfilled.
An acute ecotoxicity dataset on sitagliptin phosphate was reported. Given the therapeutic class of sitagliptin phosphate, acute tests on lethal endpoints (mortality, immobility) are considered irrelevant. The 21-day Daphnia reproduction study (OECD 211) and 33-day fish early life stage study (OECD 210) indicated a no-observable-effect concentration (NOEC) of 9.8 mg/L for Daphnia magna and a NOEC of 9.2 mg/L for Pimephales promelas in the fish early life stage study.
The risk of the use of sitagliptin to the aquatic environment is acceptable.

## 4. Clinical aspects

**Introduction**

Clinical efficacy was studied in 4 Phase II and 5 Phase III studies. Overall, 3884 patients were randomised into the sitagliptin Phase II (1477 patients) and Phase III studies (2407 patients) In the Phase II studies, 1116 patients were treated with sitagliptin (5mg to 100 mg per day); in the Phase III studies, 1538 patients were treated with sitagliptin (100 mg q.d. or 200 mg q.d) and an additional 65 patients with T2DM and chronic renal insufficiency were treated with doses adjusted for decreased renal function.

The applicant modified the initially proposed indication to: "Xelevia is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise plus metformin 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, Xelevia is indicated in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control." which was granted by the CHMP. The dose of Xelevia is 100 mg once daily. The dosage of metformin or PPARγ agonist should be maintained, and sitagliptin administered concomitantly.

Both in January 2004 and June 2004 the Applicant received Scientific Advice on the clinical development programme intended to provide data to support the originally proposed indication, on study design issues, on dosing in patients with chronic renal insufficiency and on toxico-pharmacological and clinical development. The company followed this scientific advice.

Sitagliptin was studied in patients with renal insufficiency. However in the case of moderate or severe renal insufficiency (creatinine clearance < 50 ml/min) the clinical experience was considered too limited and therefore, the use of the product in these patients is currently not recommended.

Sitagliptin was also studied in patients with mild to moderate hepatic insufficiency in which dose adjustment is not necessary; but not in patients with severe hepatic insufficiency.

Limited safety data was available in patients ≥ 75 years of age and care should be exercised when treating these patients.

No studies with sitagliptin were performed in the paediatric population, therefore the use of sitagliptin is not recommended in children below 18 years of age; this is addressed as a post authorisation follow up measure.

An overview of the relevant clinical studies contributing to efficacy profile of sitagliptin can be found in the Clinical Efficacy Section (see Table 1).

**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**

Twenty-seven studies including four studies in T2DM were conducted in the Clinical Pharmacology program to characterize the pharmacokinetic characteristics of sitagliptin.

**Absorption** Following oral administration of a 100 mg dose, maximal plasma concentrations of sitagliptin were reached within 1 to 4 hours. The absolute bioavailability 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.
**Distribution** Following 100 mg IV dose, the steady state volume of distribution 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.

**Metabolism** Generally, metabolism is a minor pathway of elimination. Following a [$^{14}$C]-labeled 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.

**Elimination** Plasma clearance following 100 mg IV dose 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 the human organic anion transporter-3 (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.

**Dose and time dependency** Following oral (5-600 mg) and IV (25-100 mg) doses, the AUC of sitagliptin increased dose-proportionally, indicating that the plasma clearance and the bioavailability are independent of the dose administered. $C_{max}$ increased in a modestly greater way than dose-proportional. This may be due to saturation of Pgp in the enterocytes at high sitagliptin concentrations resulting in faster absorption and higher $C_{max}$. Sitagliptin did not accumulate with once daily doses; the $AUC_{0\text{-}24hr}$ accumulation ratio for 100-mg daily oral doses was estimated to be approximately 1.10.

**Type 2 Diabetes** Patients with T2DM had similar pharmacokinetics of sitagliptin compared to healthy subjects.

**Special populations** Effect of gender, weight, age (elderly), race, renal and hepatic insufficiency on pharmacokinetics of sitagliptin were investigated adequately in phase I studies.

*Gender.* Phase I composite analysis showed a slightly higher exposure in females compared to males: the geometric mean ratios (female N=79, male N=193) and corresponding 90% were 1.11 (1.07, 1.15) for sitagliptin AUC0-∞ and 1.34 (1.26, 1.42) for Cmax. These slight differences were not clinically meaningful.

*Weight.* In a phase I study, sitagliptin $AUC_{0\text{-}\infty}$ was modestly lower, while $C_{max}$ was similar for young male obese subjects as compared to the young male non-obese subjects. The $AUC_{0\text{-}\infty}$ and $C_{max}$ geometric mean ratio (GMR) values (obese male/non-obese male) with corresponding 90% confidence intervals (CIs) were 0.77 (0.69, 0.86) and 0.91 (0.73, 1.14), respectively. No dose adjustment based on weight is necessary.

*Age.* Elderly subjects (65-75 years) had higher plasma sitagliptin concentrations as compared to the young (<45 years). Pooled across genders, the AUC0-∞ and $C_{max}$ GMR values (Elderly/ Young) with corresponding 90% CIs were 1.31 (1.19, 1.43) and 1.23 (1.04, 1.46), respectively. This was probably due to lower renal excretion associated with a lower creatinine clearance in the elderly patients. Pharmacokinetics of sitagliptin has not been evaluated in patients > 75 years of age. No dose adjustment other than based on creatinine clearance is necessary in elderly patients.

*Race.* In a composite analysis of pharmacokinetic parameters obtained in Phase I studies 136 Caucasians, 15 Blacks, 79 Hispanics and 42 Asians were included. The GMRs (Non-Caucasian/Caucasian) and corresponding 90% CIs from the composite analysis for AUC0-∞ were not different for Black 0.92 (0.86, 0.99), for Hispanic 0.95 (0.91, 0.99) and for Asian subjects 1.02 (0.97, 1.06).

*Hepatic insufficiency.* Ten patients with moderate hepatic insufficiency (score of 7 to 9 on the Child-Pugh's scale) and ten healthy matched control subjects were enrolled in a hepatic impairment study. AUC was increased by 21% (90% CI 1% , 46%) and $C_{max}$ by 13% (-9%, 42%). No dose adjustment is needed. Pharmacokinetics in subjects with severe hepatic insufficiency was not studied. This is adequately described in the SPC.

*Renal Insufficiency.* Sitagliptin plasma concentrations increased approximately 1.6-fold in patients with mild renal insufficiency as compared to subjects with normal renal function. Patients with moderate and severe renal insufficiency had approximately 2.3- and 3.8-fold, respectively, increased plasma drug exposure and patients with end stage renal disease (ESRD) requiring haemodialysis had an approximately 4.5-fold higher plasma drug exposure. Steady-state is expected to be reached later in patients with renal impairment. Based on this single dose study, no dose adjustment is required for mild renal impairment, however as experience still remains limited in patients with moderate to severe renal insufficiency, these should not be treated with sitagliptin. This is reflected in the SPC. Treatment in patients with moderate to severe renal insufficiency will be addressed as part of the post-authorisation follow up measures, and in the RMP.
The Applicant was requested to discuss the impact of non-renal clearance on the pharmacokinetics of sitagliptin in renally impaired subjects and to discuss potential interactions with drugs that affect CYP3A4 and CYP2C8 mediated metabolism. Study P008 that assessed metabolites suggested that the rate of metabolite formation is largely independent of renal function and that substantial accumulation of metabolites is not expected.
Results from this study also showed that effects of moderate CYP3A4 inhibition on sitagliptin pharmacokinetics are expected to be modest. However, the effects of potent metabolism inhibitors on sitagliptin exposure are anticipated to be strongly dependent on renal function (increase of <2-fold in moderate renal insufficiency and ≤5-fold increase with severe renal insufficiency) and have not been assessed in a clinical study. Therefore, there remains a concern that potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir and clarithromycin may increase sitagliptin exposure to a clinically relevant extent in patients with severe renal insufficiency or ESRD. This concern is reflected in section 4.5 of the SPC.

**Interactions** *In vitro* studies indicated that sitagliptin did not inhibit CYPs or induce CYP3A4 at physiological concentrations. As it is mainly excreted unchanged in the urine, it has low potential for cytochrome P450 mediated drug-drug interactions *in vivo*. The Applicant discussed that induction of sitagliptin metabolism and Pgp are unlikely to result in clinically relevant effects and showed that sitagliptin was not an inducer of CYP1A2 and CYP2C9.
Eight clinical drug-drug interaction studies were conducted: sitagliptin did not alter the pharmacokinetics of **metformin, glyburide, simvastatin, rosiglitazone, warfarin or oral contraceptives** to a clinically relevant extent.
Sitagliptin at 100 and 200 mg doses slightly increased the **digoxin** $C_{max}$ plasma concentrations with 18% and 24% respectively. No digoxin dose adjustment is needed, and only patients at risk of digoxin toxicity need to be monitored.
Co-administration of **metformin** 1000mg bid had no effect on pharmacokinetics of sitagliptin 50 mg bid.
**Cyclosporine A** (600 mg qd) increased the $C_{max}$ of sitagliptin (100 mg qd) 1.7-fold (68%) and the AUC 1.3-fold (29%) but had no significant effect on its renal clearance. The observed effects with cyclosporine A, a potent Pgp inhibitor, suggest that sitagliptin is a Pgp substrate *in vivo* but Pgp appears not to be involved in its renal excretion. The effects of high dose of cyclosporine A were modest probably due to the high absolute bioavailability of sitagliptin and are considered to be clinically insignificant. Therefore, no meaningful interactions are expected with other Pgp inhibitors. (see Non-Clinical section).

As stated previously in the Non-Clinical section, *in vitro* studies indicated that an hOAT3 transporter may be involved in the renal excretion of sitagliptin. Data indicate that sitagliptin is a substrate for OAT3, but is unlikely to perpetrate or be susceptible to clinically meaningful drug-drug interactions with other OAT3 substrates. As noted above, drug-drug interaction data with other OAT or OCT substrates suggest that the magnitude of change in plasma concentrations resulting from these interactions is modest. Sitagliptin is also eliminated by non-renal mechanisms. Taken together, sitagliptin is not expected to be a perpetrator or victim of drug-drug interactions in a clinically meaningful way.

**Pharmacodynamics**

Pharmacodynamics was studied in 9 trials, including 252 healthy volunteers and 58 T2DM patients. In these studies the effects of sitagliptin were investigated on DPP-4 activity, incretins, and on glucose, insulin, C-peptide and glucagon levels.
Since theoretically a DPP-4 inhibitor might stabilize potentially vasoactive peptides such as substance P, an ambulatory blood pressure study was conducted in 18 hypertensive patients, stably treated with one or more antihypertensive agents.

- Mechanism of action

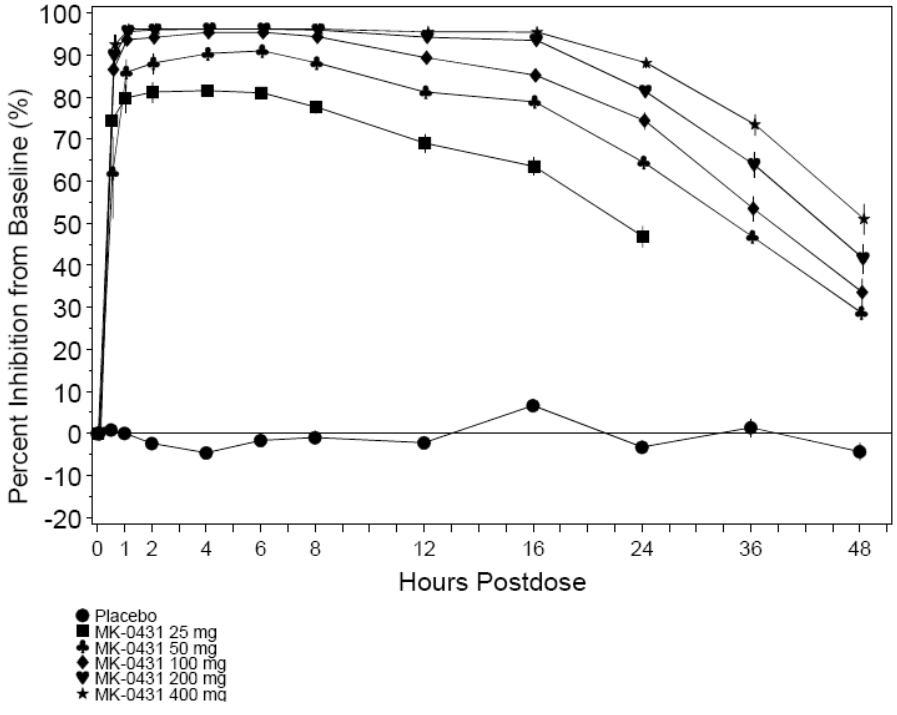
Sitagliptin is the first of a novel class of antihyperglycaemic agents, dipeptidyl peptidase-4 inhibitors. Although several actions potentially contribute to the glucose-lowering effect of DPP-4 inhibitors, the most likely mechanism is through elevated incretin concentrations that lead to enhancement 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.

- Primary and Secondary pharmacology

**Primary pharmacology**

Single dose pharmacodynamics were studied in **P001, P001C1, P003 and P013**, including a total of 90 healthy male volunteers, healthy elderly male and female subjects, young female subjects, obese males and 18 Japanese subjects. Multiple dose pharmacodynamics were investigated in **P004, P007, RC715A111 and RC431A112** including a total of 162 healthy male volunteers, middle-aged, obese male and female subjects, and 60 healthy young male Japanese subjects. Single dose pharmacodynamics in T2DM patients were investigated in **P005**, including 58 drug naïve patients with mild to moderate T2DM.
Proximal biomarkers were DPP-4 activity and incretins (GLP-1 and GIP-levels, active and total). Distal biomarkers included glucose, insulin, C-peptide and glucagon levels.
In both normoglycaemic healthy subjects and patients with T2DM, sitagliptin inhibited plasma DPP-4 activity in a dose and concentration-dependent manner. Results of study P001 are shown in **Figure 1**.

**Figure 1: Mean Percent Inhibition (%) of DPP-4 Activity From Baseline Versus Time (Hours) Post-dose After Single Oral Doses of MK-0431 in Healthy Young Male Subjects (N=6) (P001, P001C1) (Mean ± SE).**



Results from other studies were similar. Race, gender and age did not have meaningful effects on the relationship between sitagliptin plasma concentrations and DPP-4 activity.
Sitagliptin increased post-meal (in healthy subjects and T2DM patients) and post-oral glucose tolerance test (OGTT) (in T2DM patients) active GLP-1 levels by approximately 2-3-fold, as compared to placebo. Active GIP levels were similarly increased following an OGTT in patients with T2DM. Sitagliptin did not increase total GLP-1 or GIP plasma levels.
In **normoglycaemic healthy** subjects, sitagliptin had no consistent, treatment-related effect on fasting or post-meal levels of glucose, C-peptide, insulin or glucagon levels. In **middle-aged obese** individuals, sitagliptin reduced post-OGTT glucose excursion. In **T2DM patients** single oral doses of sitagliptin reduced post-OGTT glucose excursion, increased insulin/C-peptide levels and decreased glucagon levels.
Pharmacokinetic and pharmacodynamic analyses from the single dose study P005 in T2DM patients suggested that near-maximal reduction of post-challenge glucose excursion was associated with sitagliptin plasma concentrations of approximately 100 nM or higher, plasma DPP-4 inhibition of 80% or higher and augmentation of post-challenge active GLP-1 levels of 2-fold or higher. It was reasoned that for optimal chronic glucose lowering in T2DM patients, plasma DPP-4 inhibition should be 80% or greater at trough. These data served as the basis for selecting doses in the Phase II dose range finding studies P010 and P014.
As GLP-1 has been demonstrated to slow gastric emptying, it was thought that this effect might also be seen with sitagliptin. No Phase II study investigating gastric emptying was performed. This issue was examined in the larger Phase III studies; selected gastrointestinal adverse events (AEs) (including nausea, vomiting, abdominal pain, and diarrhoea) were subjected to additional statistical analysis to define increases in their occurrence, and all gastrointestinal AEs were carefully reviewed.
Further information on gastric emptying will be submitted as part of the post authorisation follow-up measures.

**Secondary pharmacology**
Study **P011** was performed in 18 patients with mild-to-moderate hypertension on stable treatment with one or more antihypertensive agents to evaluate the influence of sitagliptin on ambulatory blood pressure as well as safety and tolerability. Small but statistically significant or nearly significant decreases in mean 24-hour blood pressure between both 100 mg b.i.d. and 50mg compared to placebo were observed for systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

To fulfil recent draft regulatory guidance (ICH E14) study **P032** was performed in 86 (79 available for final QTc analysis) healthy subjects to assess the potential effect of therapeutic and supratherapeutic doses of sitagliptin on SBP and QTc interval prolongation. 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 ($IC_{50}$ 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.

**Clinical efficacy**

Clinical efficacy was studied in 4 phase II and 5 phase III studies. Table 1. gives an overview of the Phase II/III studies contributing to the efficacy profile of sitagliptin.

**Table 1: Overview of phase II and phase III studies contributing to efficacy profile of sitagliptin**

| Study ID | Design | Treatment arms (n patients/arm) | Duration | Primary Endpoint |
|---|---|---|---|---|
| **Phase II Monotherapy** | | | | |
| P010 | DB, R, PC, AC, Dose finding | • Placebo (125)<br>• Sitagliptin 5 mg b.i.d. (125)<br>• Sitagliptin 12.5 mg b.i.d. (123)<br>• Sitagliptin 25 mg b.i.d. (123)<br>• Sitagliptin 50 mg b.i.d. (124)<br>• Glipizide 5-20 mg (elective titration) (123) | 12 weeks | HbA1c |
| P014 | DB, R, PC, Dose finding | • Placebo (111)<br>• Sitagliptin 25 mg q.d. (111)<br>• Sitagliptin 50 mg q.d. (112)<br>• Sitagliptin 100 mg q.d. (110)<br>• Sitagliptin 50 mg b.i.d. (111) | 12 weeks | HbA1c |
| P015 | DB, R, PC, CO | • Sitagliptin 50 mg b.i.d./placebo (15)<br>• Placebo/MK-0431 50 mg b.i.d (13) | 2 x 4 weeks | 24-hour weighted mean glucose (WMG) |
| RC431A201 | DB, PC, Japan | • Placebo (76)<br>• Sitagliptin 100 mg q.d. (75) | 12 weeks | HbA1c |
| **Phase II extension studies** | | | | |
| P010X1 | Extension of P010 | • Sitagliptin 5 mg b.i.d. (85)<br>• Sitagliptin 12.5 mg b.i.d. (82)<br>• Sitagliptin 25 mg b.i.d. q.d. (92)<br>• Sitagliptin 50 mg b.i.d. (91)<br>• Placebo/ Sitagliptin q.d. (80)<br>• Glipizide 5-20 mg (continuing base study titrated dose) (79)<br>‡All pat's switched to 100 mg q.d. | 40 weeks | No prim. endpoint.<br>Sec: HbA1c, FPG, mean daily SBGM data (7-point fingerstick glucose average), and body weight |
| P014X1 | Extension of P014 | • Sitagliptin 25 mg q.d. (70)<br>• Sitagliptin 50 mg q.d. (69)<br>• Sitagliptin 100 mg q.d. (65)<br>• Sitagliptin 50 mg b.i.d. (71)<br>• Placebo/Metformin 850 mg b.i.d. (63)<br>‡ All pat's switched to 100 mg q.d. | 40 weeks | No prim. endpoint.<br>Sec: HbA1c, FPG, mean daily SBGM data (7-point fingerstick glucose average), and body weight |
| **Phase III studies, monotherapy** | | | | |
| P021V1† | DB, R, PC, AC | • Sitagliptin 100 mg q.d. (238)<br>• Sitagliptin 200 mg q.d. (250)<br>• Placebo (253) | 24 weeks PC, 80 weeks AC | HbA1c |
| P023V1† | DB, R, PC, AC | • Sitagliptin 100 mg q.d. (205)<br>• Sitagliptin 200 mg q.d. (206)<br>• Placebo (110) | 18 weeks PC, 36 weeks AC | HbA1c |
| **Phase III studies, combination with Metformin** | | | | |
| P020V1† | DB, R, PC, AC | • Sitagliptin 100 mg q.d. (464)<br>• Placebo (237) | 24 weeks PC, 80 weeks AC | HbA1c |
| P024V1 | DB, R, AC | • Sitagliptin 100 mg q.d. (588)<br>• Glipizide (584) | 104 weeks | HbA1c |
| **Phase III study, combination with Pioglitazone** | | | | |
| P019 | DB, R, PC | • Sitagliptin 100 mg q.d. (175)<br>• Placebo (178) | 24 weeks | HbA1c |
| **Phase III study - renal insufficiency** | | | | |
| P028V1† | DB, R, PC | • Placebo (26)<br>• Sitagliptin 25 – 50 mg (considered as one sitagliptin treatment group -- patients are stratified according to severity of renal insufficiency) (65) | 12 weeks PC, 42 weeks AC | No prim or sec efficacy endpoint.<br>Other: HbA1c, FPG. |

† P020V1, P021V1, P023V1, P028V1 studies include 2 phases of the double-blind treatment period. For each study, data from Phase A only are included herein.

‡ Once results from the Phase II dose-range finding studies were available, an amendment to the extension study protocol provided for patients not on sitagliptin 100 mg to be switched to this dose for the remainder of the extension study. For this reason, patients on sitagliptin were switched at different time-points during the extension studies to sitagliptin 100 mg q.d.

b.i.d. = Twice daily; q.d.= once daily; FPG= fasting plasma glucose; HbA1c = hemoglobin A1c; MTT= meal tolerance test; PMG= post-meal glucose; SBGM=self-blood glucose monitoring; WMG= weighted mean glucose.

DB = double-blind; R = randomised; PC = placebo controlled; AC = active controlled; CO = cross-over

- Dose response studies

Results of P010 and P014 (dose finding) showed that sitagliptin provided improvements in glucose control, as reflected by reductions across glycaemic endpoints examined (e.g. $HbA_{1c}$, FPG, and fructosamine). A total daily dose of 100 mg per day, given either as 100 mg once daily (q.d.) (P014) or 50 mg twice daily (b.i.d.) (P010) provided maximum glucose lowering; there was no meaningful difference in efficacy between these dosing regimens. Thus, these studies supported selection of the sitagliptin 100 mg q.d. for further development. The dose-response relationship was very flat for all efficacy endpoints studied. Therefore, it was difficult to conclude superiority of a 100 mg compared to a 50 mg daily dose. On the other hand, since the safety profile of sitagliptin did not appear to be dose-dependent, the choice of the 100 mg daily dose was acceptable. Since no clear plateau between 50 and 100 mg per day was established however, doses above 100 mg per day were considered to have the potential of providing additional glycaemic benefit. For this reason, a dose of 200 mg per day was included in selected Phase III studies.

- Main studies

The pivotal studies were two monotherapy trials (P021V1, P023V1), two combination trials (P020V1, P019) and active comparator trial P024V1. Study P028V1 and P015 were considered supplementary trials. Study P024V1 was submitted as part of the answers to the D120 LoQ.

METHODS

Monotherapy studies
**P021V:** A multicenter randomised, double-blind, study to evaluate the safety and efficacy of sitagliptin monotherapy in patients with type 2 diabetes mellitus who have inadequate glycaemic control.
**P023V1:** A multicenter, randomised, double blind study of sitagliptin in patients with type 2 diabetes mellitus who have inadequate glycaemic control.

Combination studies
**P019:** 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 pioglitazone therapy.
**P020V1:** 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.

Active comparative trial
**P024V1:** A multicenter, double-blind, randomised study to evaluate the safety and efficacy of the addition of sitagliptin compared with sulfonylurea therapy in patients with type 2 diabetes with inadequate glycaemic control on metformin monotherapy.

*Study Participants*

Male and female patients, ages 18 to 78 years, who were either not on an antihyperglycaemic agent (AHA), on an AHA monotherapy or low dose combination therapy at ≤50% of maximum dose of either agent, were eligible to participate in the monotherapy studies. Patients who met enrolment criteria entered an up to 13-week diet/exercise and, for patients on an AHA, a wash-off run-in period.

A wide range of T2DM patients were eligible to be screened for the combination studies and active comparator study, including patients not currently on an AHA, patients on monotherapy, and patients on dual oral combination therapies. Patients entered a run-in period in which their AHAs were discontinued, and treatment with the single agent was initiated, titrated as necessary, and then maintained at a stable dose.

*Treatments*

In the **monotherapy** studies, patients who had HbA1c within ≥7 to ≤10% after the run-in period were randomised, after completion of a 2-week single-blind placebo treatment period, to placebo or sitagliptin 100 or 200 mg q.d. (1:1:1 ratio for P021V1 and 1:2:2 ratio for P023V1). There was no stratification in either study.
P021V1 had a 24-week double-blind treatment period (Phase A). At week 24 patients on placebo were switched to glipizide (Phase B), a 36-week active treatment period. The second-year of Phase B is currently ongoing.
P023 had an 18-week double-blind treatment period (Phase A), and also a longer-term (Phase B) treatment period.
An additional feature of both studies was rescue therapy with metformin in patients with poor glycaemic control. This rescue treatment was used as add-on therapy and was provided so as to allow patients to benefit from continued participation in the study and to support collection of a larger database of safety and tolerability information while avoiding prolonged exposure to poorer control.
In the **combination** studies P019 (+PIO) and P020V1 (+MET), patients who had inadequate glycaemic control (HbA1c ≥7 and ≤10%) after the dose-stable run-in period were eligible to be randomised after completing a 2-week, single-blind, placebo run-in period. Patients were randomised to either placebo or to sitagliptin 100 mg q.d. (1:1 ratio for P019 and 1:2 ratio for P020V1). Rescue therapy was also included in both trials.

The percentage of patients with rescue therapy seen in studies P020V1 (monotherapy) and P021V1 (+MET) reached substantial figures (4-7% in treatment groups, 12-18% in placebo groups). To avoid the confounding influence of rescue therapy on efficacy comparisons in Phase A, 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. These patients had high HbA1c values just before rescue therapy. If the actual values for HbA1c had been used, the rescue patients would have had on average lower values for HbA1c after initiation of rescue therapy. Therefore, the decrease in HbA1c within groups would have been larger with the actual values for HbA1c compared to using the LOCF values for HbA1c after initiation in rescue patients. The difference in mean change in HbA1c between the groups was larger with the LOCF values substituted in rescue patients compared to using the actual HbA1c values. As a consequence, the difference in change from baseline between the treatment and placebo was larger in the All-Patients-Treated (APT) analysis than in the completers analysis. The Applicant was requested to submit the mean change HbA1c within groups and mean difference between groups with the actual values for HbA1c in rescue patients in order to assess the sensitivity on the outcome for various analysis methods. Once submitted, this data did not change the overall conclusions.

In P024V1 (active comparator) patients who were already on metformin at a stable dose (for at least 10 weeks) of ≥1500 mg/day with inadequate glycaemic control (i.e., $HbA_{1c}$ ≥6.5% but ≤10%) entered a 2-week, single-blind placebo run-in period, and after completion were eligible to be randomised. Patients currently on other AHA(s) had these discontinued and were started on metformin monotherapy, as were patients not currently on AHA(s). Patients already on metformin continued on metformin monotherapy. The dose of metformin was titrated to at least 1500 mg per day within 6 weeks, and after up-titration, patients entered a metformin dose-stable period of variable length, depending on patient characteristics, of at least 6 to 10 weeks in duration.
Patients on metformin ≥1500 mg/day were randomised in a 1:1 ratio to sitagliptin 100 mg q.d. or glipizide, which was initiated at a dose of 5 mg/day for a 104-week double-blind treatment period. Up-titration of glipizide was performed over 18 weeks to a maximum dose of 20 mg. After 18 weeks no increase in glipizide dose was permitted, as a result of which the full potential of this drug may have been prevented.

*Objectives*

The primary objectives of the **monotherapy studies** were:

**P021V**: (1) After 24 weeks, to assess the effect of treatment with sitagliptin compared with placebo on HbA1c. (2) To assess the safety and tolerability of sitagliptin.
**P023V1**: (1) After 18 weeks, treatment with sitagliptin compared with placebo will provide greater reduction in HbA1c; (2) sitagliptin will be well tolerated.

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

**P019**: (1) After 24 weeks, to assess the effect of the addition of treatment with sitagliptin compared with placebo on HbA1c. (2) To assess the safety and tolerability of sitagliptin.
**P020V1**: (1) After 24 weeks, to assess the effect of the addition of treatment with sitagliptin compared with placebo on HbA1c; (2) To assess the safety and the tolerability of sitagliptin
**P024V1**: (1) After 52 weeks, to assess the effect of the addition of sitagliptin compared with glipizide on HbA1c (2) To assess the safety and the tolerability of sitagliptin compared with glipizide.

*Outcomes/endpoints*

The primary efficacy endpoint for the 5 Phase III studies was the change from baseline in HbA1c; fasting plasma glucose was a key secondary endpoint in all studies.

*Sample size*

In P021V1, P023V1, P020V1 and P019, sample sizes were calculated to detect a true difference of 0.5% in mean change from baseline in HbA1c between sitagliptin 100 mg and placebo for a two-tailed test at $\alpha$=0.05 with a power of 99%.

In P024V1 it was calculated that a sample size of 375 patients per group had greater than 96% power to declare non-inferiority for a margin of $\delta$ = 0.3% assuming that the true mean difference in $HbA_{1c}$ between sitagliptin and glipizide was 0%. The power calculation was based upon a two-tailed test at = 0.05.

*Blinding*

Blinding was accomplished by random, masked assignment of allocation numbers to the treatment groups and by ensuring the drug supplies administered in the treatment groups appeared identical.

*Statistical methods*

In all pivotal studies an analysis of covariance (ANCOVA) model was used to compare the treatment groups in the continuous efficacy parameters, focusing on $HbA_{1c}$ change from baseline (Week 0) at study endpoint. Analyses are adjusted for baseline values and presence or absence of AHA medication.

The primary hypothesis in studies P021V1, P023V1, P020V1 and P019, regarding superiority of sitagliptin to placebo in decreasing $HbA_{1c}$ was assessed using a closed testing procedure.
The primary approach to handling missing data was the last observation carried forward (LOCF) method.
A maximum likelihood approach for repeated measurements was used as the secondary approach for handling missing data and a completers analysis.

The similarity hypothesis in P024V1 (active comparator trial) was assessed as a non-inferiority hypothesis, that is, that sitagliptin was not clinically inferior to (or no worse than) glipizide in lowering $HbA_{1c}$ by more than a defined amount, $\delta$=0.3%, the non-inferiority margin.
The primary population for efficacy analysis was the “per-protocol” (PP) population. The ANCOVA model included terms for treatment, prior diabetes pharmacotherapy, and baseline $HbA_{1c}$ as a covariate. If the upper boundary of the two-sided 95% CI for the mean difference between sitagliptin

and glipizide was less than the margin, =0.3%, then sitagliptin could be declared as non-inferior to glipizide in terms of $HbA_{1c}$.

Safety and tolerability were assessed by a review of safety parameters including adverse events (AEs), laboratory safety parameters, body weight, vital signs, and ECG. The analysis of safety parameters followed a multi-tiered approach. For tier 1 clinical AEs (hypoglycaemia and selected gastrointestinal adverse events) and body weight, inferential testing provided statistical significance levels for between-group comparisons. For other AEs (not in tier 1) and predefined limits of change in laboratory and ECG variables, 95% CIs for between-group differences were obtained when the incidence was at least 2% in one or more treatment groups.

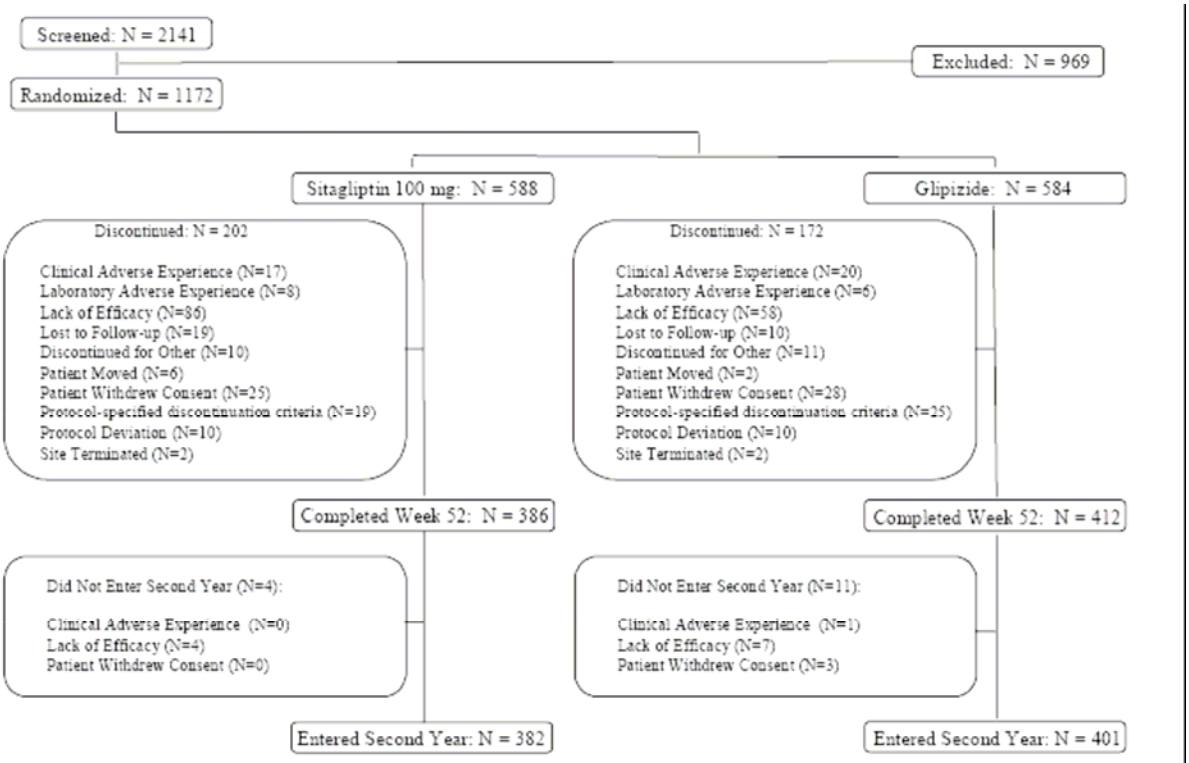
## RESULTS

### *Participant flow*

**Table 2: Patient disposition in pivotal trials P021V1, P023V1, P020V1 and P019**

| **Study** | **P021V1** | | | **P023V1** | | | **P020V1** | | **P019** | | **Total** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Screened (N) | 1807 | | | 1387 | | | 1464 | | 928 | | 5586 | | |
| Excluded (N) | 1066 | | | 866 | | | 763 | | 575 | | 3270 | | |
| Randomised (N) | 741 | | | 521 | | | 701 | | 353 | | 2316 | | |
| | Sitagliptin | | Pla | Sitagliptin | | Pla | Sitagliptin | Pla | Sitagliptin | Pla | Sitagliptin | | Pla |
| | 100mg | 200mg | | 100mg | 200mg | | 100mg | | 100mg | | 100mg | 200mg | |
| | 238 | 250 | 253 | 205 | 206 | 110 | 464 | 237 | 175 | 178 | 1082 | 456 | 778 |
| Discontinued | 29 | 36 | 37 | 17 | 22 | 19 | 48 | 45 | 26 | 20 | 120 | 58 | 121 |
| Clinical AE | 5 | 4 | 4 | 1 | | 4 | 11 | 5 | 11 | 2 | 28 | 4 | 15 |
| Laboratory AE | | | 1 | | 2 | | 6 | 4 | | | 6 | 2 | 5 |
| Lack of efficacy | 3 | 5 | 9 | | 4 | 6 | 7 | 13 | 0 | 2 | 10 | 9 | 30 |
| Lost to follow up | 5 | 4 | 2 | 3 | 3 | 2 | 4 | 5 | 3 | 1 | 15 | 7 | 10 |
| Other reason | 2 | 3 | 5 | 1 | 1 | | 6 | 4 | 4 | 5 | 13 | 4 | 14 |
| Pat moved | 3 | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 1 | 1 | 7 | 2 | 6 |
| Pat withdrew consent | 10 | 17 | 11 | 6 | 7 | 3 | 10 | 10 | 5 | 6 | 31 | 24 | 30 |
| Protocol deviation | 1 | 2 | 4 | 5 | 4 | 3 | 2 | 1 | 2 | 3 | 10 | 6 | 11 |
| Completed Phase A | 209 | 214 | 216 | 188 | 184 | 91 | 416 | 192 | 149 | 158 | 962 | 398 | 657 |
| Did not enter Phase B | 19 | 16 | 49 | 6 | 1 | 0 | 23 | 28 | | | 48 | 17 | 77 |
| Clinical AE | | | | 3 | 1 | | 1 | 1 | | | 4 | 1 | 1 |
| Laboratory AE | | | | | | | 1 | | | | 1 | | |
| Lack of efficacy | 3 | 1 | 8 | | | | 2 | 2 | | | 5 | 1 | 10 |
| Other reason | 16 | 10 | 38 | 1 | | | 18 | 24 | | | 35 | 10 | 62 |
| Pat moved | | 1 | | | | | | | | | | 1 | |
| Pat withdrew consent | | 2 | 1 | 2 | | | 1 | | | | 3 | 2 | 1 |
| Protocol deviation | | 2 | 2 | | | | | 1 | | | | 2 | 3 |
| Entered Phase B | 190 | 198 | 167 | 182 | 183 | 91 | 393 | 164 | | | 765 | 381 | 422 |

**Table 3: Patient disposition in pivotal trial P024V1**



*Baseline data*

Baseline demographic and disease specific data for the pivotal studies are presented in Table 4 and Table 5.

In the **monotherapy** trials, although mean baseline $HbA_{1c}$ was similar across treatment groups, there were differences in its distribution at baseline. In the placebo groups more patients had $HbA_{1c}$ <8% [P021V1: placebo 132 (52.2) vs 200mg 129 (51.6); P023V1: placebo 63 (57.8) vs 200mg 99 (48.3)], while in the 200mg groups more patients had $HbA_{1c}$ ≥9% [P021V1: placebo 36 (14.2) vs 200mg 52 (20.8); P023V1: placebo 20 (18.3) vs 200mg 44 (21.5)].

In the **combination** studies, baseline characteristics were similar across treatment groups. Study population of P020V1 was considered as representative for the claimed indication add-on with metformin, as patients were inadequately controlled by metformin ≥1500 mg daily. In study P019, a wider range of patients was included than permitted for pioglitazone monotherapy. However, patients who are intolerant for metformin have not been reported to be distinct in other characteristics from the general population of T2DM patients. Metformin is contraindicated in patients with renal insufficiency or congestive heart failure requiring pharmacologic therapy. Pioglitazone is also contraindicated in patients with congestive heart failure; therefore such patients were not included into the trial. A separate study was performed in patients with renal insufficiency (P028); however in that study monotherapy or combination therapy with insulin was used. Although the study population in study P019 included a wide range of diabetic patients (beyond the current label for pioglitazone), it is believed that these subjects adequately represented the subset of patients for which pioglitazone can be prescribed.

**Table 4: Baseline Demographic and Anthropometric Characteristics by Treatment Group Phase III Monotherapy Studies**

| | P021V1 | P023V1 |
|---|---|---|
| | All | All |
| **Age (Years)** | | |
| N (%) | 741 | 521 |
| Mean (SD) | 54.2 (9.9) | 55.1 (9.7) |
| Range | 18.0-75.0 | 27.0-76.0 |
| **Body Mass Index (kg/m2)** | | |
| -N (%) | 739 | 520 |
| Mean (SD) | 30.5 (5.3) | 32.0 (5.3) |
| Range | 19.1 to 44.7 | 18.9 to 43.6 |
| **Baseline HbA1c (%)** | | |
| N | 739 | 516 |
| Mean (SD) | 8.0 (0.9) | 8.1 (0.9) |
| Range | 6.3-10.9 | 6.2-10.5 |
| **Distribution of HbA1c at Baseline, N(%)** | | |
| N | 739 | 516 |
| <8% | 396 (53.6) | 265 (51.4) |
| ≥8% to <9% | 216 (29.2) | 158 (30.6) |
| ≥9% | 127 (17.2) | 93 (18.0) |
| **Baseline Fasting Plasma Glucose (mg/dL)** | | |
| N | 732 | 521 |
| Mean (SD) | 173.7 (43.7) | 182.2 (44.8) |
| Range | 73.0 to 427.0 | 92.0 to 335.0 |
| **Duration of Type 2 Diabetes Mellitus (Years)** | | |
| N | 740 | 519 |
| Mean (SD) | 4.4 (4.8) | 4.5 (4.3) |
| Range | 0.0 to 38.0 | 0.0 to 30.0 |
| **Use of Anti-Hyperglycaemic Medication at Screening, N (%)** | | |
| Present | 363 (49.0) | 308 (59.1) |
| Absent† | 378 (51.0) | 213 (40.9) |
| Total | 741 | 521 |

N=Randomised number per treatment group; SD=standard deviation.† Off Medication for ≥8 weeks. ‡ Using the definition of the National Cholesterol Education Program, Adult Treatment Panel III

**Table 5: Baseline Demographic and Anthropometric Characteristics by Treatment Group Phase III Combination therapy studies**

| | P020V1 | P019 |
|---|---|---|
| | All | All |
| **Age (Years)** | | |
| N (%) | 701 | 353 |
| Mean (SD) | 54.5 (10.2) | **56.2 (10.8)** |
| Range | 19.0-78.0 | **24.0 to 87.0** |
| **Body Mass Index (kg/m2)** | | |
| N (%) | 701 | 353 |
| Mean (SD) | 31.1 (5.2) | **31.5 (5.1)** |
| Range | 19.6 to 43.9 | **20.1 to 44.2** |
| **Baseline HbA1c (%)** | | |
| N | 698 | 352 |
| Mean (SD) | 8.0 (0.8) | **8.0 (0.8)** |
| Range | 6.4 to 11.0 | **6.4 to 10.4** |
| **Distribution of HbA1c at Baseline, N(%)** | | |
| N | 698 | 352 |
| <8% | 381 (54.6) | 185 (52.6) |
| ≥8% to <9% | 217 (31.1) | **109 (31.0)** |
| ≥9% | 100 (14.3) | **58 (16.5)** |
| **Baseline Fasting Plasma Glucose (mg/dL)** | | |
| N | 700 | 352 |
| Mean (SD) | 171.5 (41.3) | **166.8 (39.3)** |
| Range | 86.0 to 312.0 | **94.0 to 315.0** |
| **Duration of Type 2 Diabetes Mellitus (Years)** | | |
| N | 699 | 353 |
| Mean (SD) | 6.2 (5.2) | **6.1 (5.6)** |
| Range | 0.1 to 34.0 | **0 to 38.0** |
| **Use of Anti-Hyperglycaemic Medication at Screening** | | |
| Metformin /PPARγ-based Combination Therapy N (%) | 229 (32.7) | 106 (30.1) |
| Monotherapy N (%) | 431 (61.5) | 212 (60.2) |
| Absence N (%) | 41 (5.8) | 34 (9.7) |
| Total | 701 | 352 |
| **Prior PPARγ Status at Visit 1** | | |
| On PPARγ N (%) | - | 173 (49.0) |
| Not on PPARγ N (%) | - | 180 (51.0) |
| Total | - | 353 |

*N=Randomised number per treatment group; SD=standard deviation; † Off Medication for ≥8 weeks; ‡ Using the definition of the National Cholesterol Education Program, Adult Treatment Panel III*

In **active comparator trial**, P024V1, demographic, anthropometric and baseline disease characteristics were generally balanced across the treatment groups and were similar between the PP cohort and the all randomised cohort. The PP cohort exhibited a better baseline glycaemic control, a slightly shorter mean duration of diabetes, and a slightly smaller fraction of previously combination therapy treated patients relative to the APT cohort. The baseline $HbA_{1c}$ values in both the PP and the APT cohort reflected a relatively mild degree of baseline hyperglycaemia. In the PP cohort 73% of patients had baseline $HbA_{1c}$ values <8%, and 7% of patients had baseline $HbA_{1c}$ values >9%; in the APT cohort these values were 65% and 10% respectively.

*Numbers analysed*

Tables, 6, 7, 8 show the number of patients included in each analysis for each of the pivotal trials.

**Table 6: Patient accounting in the analysis of $HbA_{1c}$ at week 24 (study P021V1) or week 18 (study P023V1)**

| | P021V1 | | | | P023V1 | | | |
|---|---|---|---|---|---|---|---|---|
| | Number (%) | | | | | | | |
| | Sitagliptin 100 mg | Sitagliptin 200 mg | Placebo | Total | Sitagliptin 100 mg | Sitagliptin 200 mg | Placebo | Total |
| Total Randomised | 238 | 250 | 253 | 741 | 205 | 206 | 210 | 521 |
| Included in the APT† Analysis | 229 (96.2) | 238 (95.2) | 244 (96.4) | 711 (96.0) | **193 (94.1)** | **199 (96.6)** | **103 (93.6)** | **495 (95.0)** |
| Included in the Completers Analysis | 189 (79.4) | 198 (79.2) | 176 (69.6) | 563 (76.0) | **168 (82.0)** | **161 (78.2)** | **74 (67.3)** | **403 (77.4)** |
| Excluded from the APT† Analysis | 9 (3.8) | 12 (4.8) | 9 (3.6) | 30 (4.0) | 12 (5.9) | 7 (3.4) | 7 (6.4) | 26 (5.0) |
| No Baseline Data | 2 (0.8) | 0 (0.0) | 0 (0.0) | 2 (0.3) | 3 (1.5) | 1 (0.5) | 1 (0.9) | 5 (1.0) |
| No On-treatment Data | 7 (2.9) | 12 (4.8) | 9 (3.6) | 28 (3.8) | 9 (4.4) | 6 (2.9) | 6 (5.5) | 21 (4.0) |
| Excluded from the Completers Analysis‡ | 40 (16.8) | 40 (16.0) | 68 (26.9) | 148 (20.0) | 38 (18.4) | 38 (18.4) | 29 (26.4) | 92 (17.7) |
| Rescued Prior to Week 24/18§ | 17 (7.1) | 10 (4.0) | 45 (17.8) | 72 (9.7) | 13 (6.3) | 17 (8.3) | 15 (13.6) | 45 (8.6) |
| No Data at Week 24/18‖ | 23 (9.7) | 30 (12.0) | 23 (9.1) | 76 (10.3) | 12 (5.9) | 21 (10.2) | 14 (12.7) | 47 (9.0) |

† APT: All-Patients-Treated.
‡ The completers population is a subset of the APT population including all patients with Week 24 data.
§ Efficacy data obtained on a patient after initiation of rescue therapy are treated as missing.
‖ For patients not on rescue medication.

**Table 7: Patient accounting in the analysis of $HbA_{1c}$ at week 24, study P020V1 and P019**

| | P020V1 | | | P019 | | |
|---|---|---|---|---|---|---|
| | Number (%) | | | | | |
| | Sitagliptin 100 mg | Placebo | Total | Sitagliptin 100 mg | Placebo | Total |
| Total Randomised | 464 | 237 | 701 | 175 | 178 | 353 |
| Included in the APT† Analysis | 453 (97.6) | 224 (94.5) | 677 (96.6) | 163 (93.1) | 174 (97.8) | 337 (95.5) |
| Included in the Completers Analysis | 399 (86.0) | 171 (72.2) | 570 (81.3) | 131 (74.9) | 136 (76.4) | 267 (75.6) |
| Excluded from the APT† Analysis | **11 (2.4)** | **13 (5.5)** | **24 (3.4)** | **12 (6.9)** | **4 (2.2)** | **16 (4.5)** |
| No Baseline Data | **1 (0.2)** | **2 (0.8)** | **3 (0.4)** | **1 (0.6)** | **0 (0.0)** | **1 (0.3)** |
| No On-treatment Data | **10 (2.2)** | **11 (4.6)** | **21 (3.0)** | **11 (6.3)** | **4 (2.2)** | **15 (4.2)** |
| Excluded from the Completers Analysis‡ | **54 (11.6)** | **53 (22.4)** | **107 (15.3)** | **32 (18.3)** | **38 (21.3)** | **70 (19.8)** |
| Rescued Prior to Week 24§ | **18 (3.9)** | **28 (11.8)** | **46 (6.6)** | **11 (6.3)** | **23 (12.9)** | **34 (9.6)** |
| No Data at Week 24‖ | 36 (7.8) | 25 (10.5) | 61 (8.7) | **21 (12.0)** | **15 (8.4)** | **36 (10.2)** |

† APT: All-Patients-Treated.
‡ The completers population is a subset of the APT population including all patients with Week 24 data.
§ Efficacy data obtained on a patient after initiation of rescue therapy are treated as missing.
‖ For patients not on rescue medication.

**Table 8: Patients accounting in the analysis of $HbA_{1c}$ at Week 52, P024V1**

| | Number (%) Sitagliptin 100 mg | Glipizide | Total |
|---|---|---|---|
| TOTAL RANDOMISED | 588 | 584 | 1172 |
| INCLUDED IN PP[†] ANALYSIS | 382 (65.0) | 411 (70.4) | 793 (67.7) |
| INCLUDED IN APT[‡] ANALYSIS | 576 (98.0) | 559 (95.7) | 1135 (96.8) |
| EXCLUDED FROM PP ANALYSIS | 206 (35.0) | 173 (29.6) | 379 (32.3) |
| No Baseline Data | 2 (0.3) | 2 (0.3) | 4 (0.3) |
| No Treatment Data at Week 52 | 197 (33.5) | 167 (28.6) | 364 (31.1) |
| Major Protocol Violators | 18 (3.1) | 7 (1.2) | 25 (2.1) |
| Drug Compliance <75% | 3 | 1 | 4 |
| Used of Prohibited AHA[§] | 3 | 1 | 4 |
| Used of Corticosteroid[#] | 1 | 0 | 1 |
| Change in Metformin Dose[¶] | 10 | 4 | 14 |
| Incorrect Doubled-Blind Study Medication[¶] | 1 | 1 | 2 |
| EXCLUDED FROM APT ANALYSIS | 12 (2.0) | 25 (4.3) | 37 (3.2) |
| No Baseline Data | 2 (0.3) | 2 (0.3) | 4 (0.3) |
| No On-Treatment Data | 10 (1.7) | 23 (3.9) | 33 (2.8) |

[†] PP: Per Protocol.
[‡] APT: All-Patients-Treated.
[§] Patients taking any prohibited antihyperglycaemic medications after randomisation (Visit 4) for a total of ≥14 days or ≥7 consecutive days.
[#] Patients taking corticosteroid for ≥14 days during the last 90 days of Week 52.
[¶] Change in metformin dose or incorrect double-blind study medication for ≥12 consecutive weeks during the study period of interest, or for a total of ≥14 days during the last 90 days of Week 52.

*Outcomes and estimation*

All four **superiority trials** suggested that sitagliptin at the recommended dose of 100 mg per day effectively reduced $HbA_{1c}$ in patients with T2DM. The primary analysis performed was appropriate. The results clearly showed that sitagliptin reduced baseline $HbA_{1c}$ in the treatment group in a period of 18-24 weeks. The p-values for testing the difference in mean change in the treatment and placebo group were <0.001. Although there were a number of treatment subgroup interactions, treatment effects in subgroups were generally consistent.

Results on $HbA_{1c}$ in the **monotherapy** Phase III trials are shown in Table 9**.**

For the APT population, sitagliptin appeared to be superior to placebo in lowering $HbA_{1c}$ at both the 100 and 200 mg dose [least square (LS) mean difference form placebo (95% CI) –0.74, -0.49 and –0.88, -0.64 respectively]. The analyses conducted on the completers populations supported these results. The sitagliptin treatment groups showed larger within-group decreases from baseline in the completers analysis than in the APT analysis; however, the placebo-adjusted treatment effects were smaller in the completers analysis (-0.65 and –0.75% for MK-0431 100 mg vs. placebo and MK-0431 200 mg vs. placebo, respectively), than in the APT analysis (-0.79 and –0.94% for sitagliptin 100 mg vs. placebo and sitagliptin 200 mg vs. placebo, respectively). This attenuation of the placebo-subtracted decrease in $HbA_{1c}$ was due to the removal of a larger number of rescued/discontinued patients from the placebo group than from the sitagliptin groups in the completers population, relative to the APT population. Rescued/discontinued patients generally had poorer $HbA_{1c}$ responses compared with patients who completed without rescue therapy, and thus the completers placebo group showed a greater reduction from baseline when the imputed week 24/18 values for the rescued/discontinued subset were removed.

**Table 9: Change from Baseline in $HbA_{1c}$ (%) at Study Endpoint All-Patients-Treated Population P021V1, P023V1 Phase III Monotherapy Studies**

| Treatment | N | Mean (SD) | | Change From Baseline | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Study Endpoint | Mean (SE) | LS Mean (SE) | 95% CI for LS Mean | LS Mean Difference From Placebo (95% CI) |
| **P021V1 (Study Endpoint=Week 24)** | | | | | | | |
| Sitagliptin 100 mg q.d. | 229 | 8.01 (0.88) | 7.39 (1.15) | -0.62 (0.07) | -0.61† (0.06) | (-0.74, -0.49) | -0.79† (-0.96, -0.62) |
| Sitagliptin 200 mg q.d. | 238 | 8.08 (0.94) | 7.31 (1.14) | -0.78 (0.06) | -0.76† (0.06) | (-0.88, -0.64) | -0.94† (-1.11, -0.77) |
| Placebo | 244 | 8.03 (0.82) | 8.20 (1.37) | 0.17 (0.07) | 0.18‡ (0.06) | (0.06, 0.30) | - |
| **P023V1 (Study Endpoint=Week 18)** | | | | | | | |
| Sitagliptin 100 mg q.d. | 193 | 8.04 (0.82) | 7.58 (1.15) | -0.46 (0.06) | -0.48† (0.07) | (-0.61, -0.35) | -0.60† (-0.82, -0.39) |
| Sitagliptin 200 mg q.d. | 199 | 8.14 (0.91) | 7.81 (1.31) | -0.34 (0.07) | -0.36† (0.06) | (-0.48, -0.23) | -0.48† (-0.70, -0.26) |
| Placebo | 103 | 8.05 (0.90) | 8.21 (1.35) | 0.16 (0.09) | 0.12 (0.09) | (-0.05, 0.30) | - |

† $p<0.001$, ‡ $p<0.05$.

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error.

Results on fasting plasma glucose (FPG) and Post-meal glucose confirm the effect of sitagliptin.
Both in the monotherapy studies and in the combination studies, treatment with sitagliptin resulted in a reduction in FPG at study endpoint. Furthermore, in study P021V1 and P020 (+MET), sitagliptin was superior to placebo in lowering glucose 2 hours after administration of a standard meal challenge.
Results on $HbA_{1c}$ for the **Combination studies** are shown in **Table 10**.
In both studies a decrease in $HbA_{1c}$ was measured in the APT-Population at week 24. The difference with placebo was –0.65 (95% CI -0.77, -0.53) and –0.70 (95% CI -0.85, -0.54) respectively and was statistically significant.
In study P020V1 (+MET), approximately 61% (428/701) of the randomised patients were on metformin doses ≥2000 mg per day. Results from the analyses of change from baseline in $HbA_{1c}$ at week 24 in this subset of patients were similar to the overall population.
In study P019 (+PIO), approximately 85% (286/334) of the patients were pioglitazone "responders". These included patients not on AHA therapy who were started on pioglitazone during the screening period and had at least a 20 mg/dL (1.1mmol/L) decrease in FPG by the start of the 2-week placebo-blind run-in period; or patients who were switched directly to pioglitazone from another AHA monotherapy, and showed no meaningful deterioration in $HbA_{1c}$ (≤0.2% increase in $HbA_{1c}$); or patients who were washed-off of their prior AHA therapy, and then had at least a 20 mg/dL (1.1 mmol/L) reduction during the run-in pioglitazone treatment period. Patients entering the study on PPARγ medication (either alone or in combination) were also considered to be responders. Results of an analysis of change from baseline in $HbA_{1c}$ at week 24 in pioglitazone responders showed results that were similar to results based on the overall study population.

Both combination studies suggested that sitagliptin was more effective than placebo in reducing $HbA_{1c}$ at 24 weeks. In the pioglitazone combination study a small reduction in $HbA_{1c}$ was also seen in the placebo group, which suggested that the optimal effect of pioglitazone had not yet been reached at study randomisation.

**Table 10: Analysis of change in HbA1c (%) at week 24; All-Patients-Treated Population; Study P020V1 (+MET) and P019 (+Pio)**

| Study P020V1 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Mean (SD) | | Change from Baseline | | | |
| Treatment | N | Baseline | Week 24 | Mean (SE) | LS Mean (SE) | 95% CI for LS Mean | p-Value |
| MK-0431 100 mg | 453 | 7.96 (0.81) | 7.26 (0.97) | -0.70 (0.03) | -0.67 (0.05) | (-0.77, -0.57) | <0.001 |
| Placebo | 224 | 8.03 (0.82) | 7.95 (1.10) | -0.08 (0.06) | -0.02 (0.06) | (-0.15, 0.10) | 0.700 |

| Between Treatment Difference | Difference in LS Means (95% CI) | p-Value |
|---|---|---|
| MK-0431 100 mg vs. Placebo | -0.65 (-0.77, -0.53) | <0.001 |

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

Root Mean Square Error of Change =0.76

| Study P019 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Mean (SD) | | Change From Baseline | | | |
| Treatment | N | Baseline | Week 24 | Mean (SE) | LS Mean (SE) | 95% CI for LS Mean | p-Value |
| MK-0431 100 mg | 163 | 8.05 (0.81) | 7.17 (0.91) | -0.88 (0.05) | -0.85 (0.07) | (-0.98, -0.72) | <0.001 |
| Placebo | 174 | 8.00 (0.83) | 7.82 (1.10) | -0.18 (0.06) | -0.15 (0.06) | (-0.28, -0.03) | 0.017 |

| Between Treatment Difference | Difference in LS Means (95% CI) | p-Value |
|---|---|---|
| MK-0431 100 mg vs. Placebo | -0.70 (-0.85, -0.54) | <0.001 |

| p-Value for ANCOVA Effects | |
|---|---|
| Baseline Value | <0.001 |
| Treatment | <0.001 |
| Prior Anti-hyperglycaemic Medication | 0.026 |

Root Mean Square Error of Change =0.73

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error

Results from the **active comparator trial** on $HbA_{1c}$ are shown in Figure 2 for the PP population. In both analyses (i.e. PP and APT) glipizide provided greater initial lowering of $HbA_{1c}$, with the maximum between-group difference observed at week 24. In the secondary (APT) analysis, using the LOCF method for imputing missing data, the difference was greater than in the PP analysis. In both analyses, there was a rise in mean $HbA_{1c}$ in both treatment groups after Week 24. The rate of rise from nadir in the glipizide group was greater than the rate of rise in the sitagliptin group, such that by week 52 very similar reductions from baseline in the two treatment groups were seen in both the PP and APT populations.

The additional analysis performed on week 30 and week 24 data gave similar results as those from week 52.

More patients in the sitagliptin group discontinued due to lack of efficacy as compared to glipizide treated patients (86 [15%] vs 58 [10%]). Sitagliptin users 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.

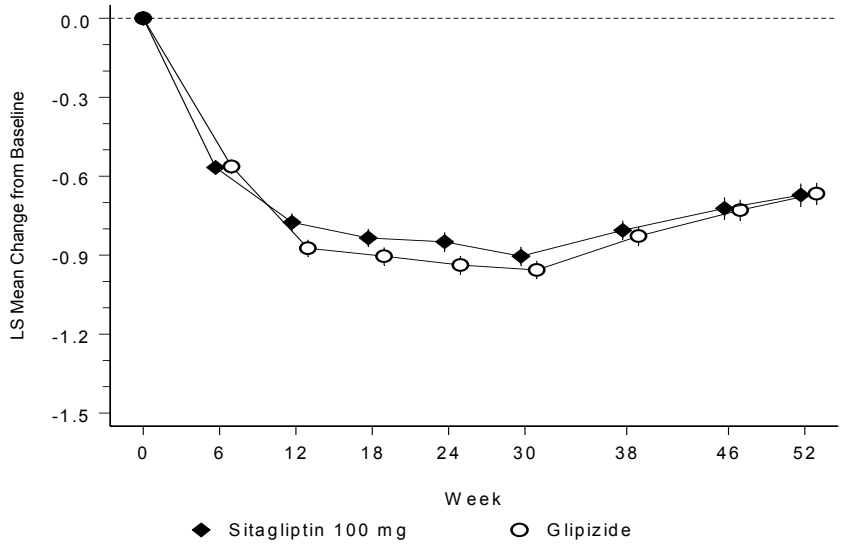
Results concerning FPG showed that similar changes were observed after 52 weeks of treatment in both groups. In the PP analysis the LS Means were –10.0 mg/dL (-0.56 mmol/L) and –7.5 mg/dL (-0.42 mmol/L) for the sitagliptin and glipizide treatment groups, respectively.

Profiles over time showed that both treatment groups achieved the maximal FPG effect at week 24 with subsequent attenuation of FPG-lowering efficacy. The course of the FPG change from baseline in the two treatment groups was similar. Both PP and APT analyses showed similar trends.

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).
It is concluded that sitagliptin at the recommended dose of 100 mg per day was shown to have a significant and clinically relevant effect on glycaemic control, and that efficacy is considered similar to glipizide in this patient population with predominantly mild to moderate hyperglycaemia on monotherapy with metformin as described in the SPC, section 5.1, but non-inferior efficacy compared to sulfonylureas was not unequivocally proven. The latter conclusion was based on the restrictions regarding dose titration of glipizide possibly preventing assessment of the full potential of this drug. Furthermore, although not designed and powered to compare efficacy, in study P010 (dose finding), glipizide performed statistically better and in study P020V1 (+MET) numerically better than sitagliptin. To address the point of non-inferiority, a description of study P024V1, including the dose titration of glipizide has been described in the SPC, section 5.1.

**Figure 2: LS Mean Change From Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group Per-Protocol Population**




*Ancillary analyses*

In Phase III studies, several endpoints were included to assess changes in β-cell function with sitagliptin therapy including HOMA-β, measurement of fasting insulin secretion, and proinsulin to insulin ratio, intended to assess improvement in beta-cell function.
In P021V1 (monotherapy), there was a significant reduction in the proinsulin to insulin ratio relative to placebo in all treatment groups. In P023V1 (monotherapy), there was a significant reduction in this ratio relative to placebo for the 100 mg dose (p<0.05); this was also seen for the 200 mg dose but it did not reach statistical significance. In these studies showed a significant increase in HOMA-β at both doses.
In study P020V1 (+MET), significant treatment group differences for sitagliptin compared to placebo (p<0.05) were observed for change from baseline in the proinsulin to insulin ratio; similarly, the results presented for HOMA-β also show a statistically significant increase with sitagliptin 100 mg q.d. relative to placebo (p<0.001). In study P019 (+PIO), a significant decrease in the fasting proinsulin to insulin ratio with sitagliptin was seen. Sitagliptin provided a statistically significant increase (p<0.001) from baseline in HOMA-β. A more modest increase in HOMA-β was observed in the placebo treatment group that was statistically significant (p=0.027). However, with the small increase observed in the placebo group, the between-treatment group difference was not statistically significant (p=0.080).

- Clinical studies in special populations

Study P028V1 was designed to examine the safety of dose-adjusted sitagliptin monotherapy or combination therapy with insulin in T2DM patients with moderate to severe chronic renal insufficiency, including those with ESRD on dialysis, who had inadequate glycaemic control on diet and exercise, or inadequate glycaemic control on insulin monotherapy.
After 12 weeks, an improvement was seen in glycaemic control in sitagliptin treated patients. However, efficacy was not a primary endpoint in this study and only descriptive statistics were provided for glycaemic variables ($HbA_{1c}$, FPG, and fructosamine).
Results on efficacy are therefore not further described here. See Safety section for further information on the results of this study.

**Clinical safety**

Potential safety issues considered in the development program of sitagliptin, which impacted the design of the clinical studies, were based upon (1) issues arising from the results of preclinical toxicology studies and (2) potential issues that are based upon the mechanism of action of sitagliptin.

*Issues from preclinical toxicology studies* were skeletal muscle degeneration and neurological toxicity. Furthermore, skin necrosis was seen in monkeys treated with other DPP-4 inhibitors. No skin findings have been seen in clinical studies with sitagliptin.

*Issues based on the mechanism of action* were:
1. Gastrointestinal AEs related to increased active GLP-1 levels with DPP-4 inhibition.
2. Effects related to the fact that DPP-4 is present on immune cells.
3. Effects of inhibition of DPP-4 on other DPP-4 peptide substrates.

Therefore the list of potential safety issues which was followed closely during the clinical development was: based on the preclinical findings, slight muscle degeneration and neurological toxicity; and based upon theoretical concerns, allergic phenomena/angioedema, hypoglycaemia, hypotension, gastrointestinal AEs, and infections/immune phenomena.

Initially, safety assessment of sitagliptin was hampered by the fact that no overall data was presented and data from ongoing studies at that moment was not submitted. Concerns on missing data were addressed in the responses to the D120 LoQ, when comparisons of safety data were submitted. These were:

**Comparison 1**: Sitagliptin vs Placebo as Add on to Metformin (based upon P020V1 [Placebo-controlled Study of Sitagliptin as Add on to Metformin]). *This clinical study report for this study was submitted as part of the marketing application.*
**Comparison 2**: Sitagliptin vs Glipizide as Add-on to Metformin (based upon the recently completed 52 week period of P024V1, the Active- Comparator [Glipizide] Controlled Study of Sitagliptin as Add on to Metformin).
**Comparison 3**: Sitagliptin vs Placebo as Add on to PPARγ Agonist (based upon P019 [Placebo-controlled Study of Sitagliptin as Add on to PPARγ Agonist]. *This clinical study report for this study was submitted as part of the marketing application.*
**Comparison 4**: Sitagliptin vs Placebo in Monotherapy (from Pooled Monotherapy Studies).
**Comparison 5**: Sitagliptin Exposed vs Non-Exposed based upon a new Pooled Phase II/III Population.

Comparison 5 included results from Phase II studies (P010 and P014 base and extension periods), results from Phase III studies that were in the original marketing application (P019, P020V1, P021V1, P023V1), additional results through 1-year from two of these studies (P020V1 and P023V1), and results from three studies that were completed after the filing of the marketing application: P024V1, P035 and P036. Therefore this was the comparison that included nearly all submitted data.

- Patient exposure

Phase I studies

The total number of patients exposed to sitagliptin in the Phase I studies was 561, with doses ranging from ≤25 mg to 800 mg.

Phase II/III studies

A total of 3832 patients were randomised to receive sitagliptin in the pooled phase II/III studies: 590 to doses of sitagliptin <100mg/day, 2786 to sitagliptin 100mg/day, and 456 to sitagliptin 200mg/day. The non-exposed group comprised 2355 patients. Since sitagliptin 100mg was the most common dose across the Phase II/III studies, this dose group is the largest and hence most robust.

- Adverse events

Phase I studies

The most common clinical AEs (occurring in >1% of any sitagliptin subjects) that were of numerically slightly higher incidence than placebo included dizziness (4.9% vs. 2.2%), headache (21.0% vs. 15.4%), and somnolence (4.1% vs. 2.2%) though these adverse experiences were infrequent and the differences were small. In the rising single-dose and multiple-dose studies, during which single doses of 800 mg and multiple doses up to 600 mg were administered, there were no clear differences in the incidence of any AE from placebo (including those noted above) and no increase in the incidence of AEs (overall or specific) with increasing dose. AEs related to theoretical concerns or preclinical toxicities showed a similar incidence rate to placebo (i.e. allergic, musculoskeletal, and gastrointestinal phenomenon, hypotension, hypoglycemia, and infections). A slightly higher incidence of AEs related to neurological events following treatment with sitagliptin was seen versus placebo.
Two serious AEs occurred in Phase I studies; these were acute myocardial infarction (healthy subject) and primary atypical pneumonia (T2DM subject). Both subjects recovered and both events were determined to be 'probably not' related to study drug by the investigators.
There were no apparent treatment or dose-dependent clinically meaningful effects on laboratory safety parameters. In addition, there was no evidence for dose-dependent, meaningful effects on the growth hormone axis. No dose-dependent, treatment-related, clinically relevant effects were seen on vital signs. Sitagliptin did appear to modestly reduce blood pressure in patients with hypertension.

Phase II/III studies

"SITAGLIPTIN EXPOSED VS NON-EXPOSED"

Clinical AEs were reported for 1788 (64.2%) patients in the sitagliptin exposed 100 mg group and 1484 (63.0%) patients in the non-exposed group (patients receiving placebo or other oral antidiabetic drug(s)), who received at least one dose of double-blind study medication. The incidences of deaths, patients discontinued due to serious or non-serious AEs, serious drug-related AEs, and patients discontinued due to serious drug-related AEs were similar in both groups. The incidences of drug-related AEs and patients discontinuing due to drug-related AEs were higher in the non-exposed treatment group.

The comparison of sitagliptin "Exposed vs Non-Exposed" based upon the new Pooled Phase II/III Population, seen in Table 11, showed that in general treatment with sitagliptin 100 mg was associated with an increased incidence (≥1% in one or more treatment groups) or event rate in AEs in the SOCs of:

- **Gastrointestinal Disorders** (18.6% in sitagliptin exposed vs 16.4% in non-exposed),
- **Infections and Infestations** (33.8% in sitagliptin exposed vs 29.9% in non-exposed),

- **Musculoskeletal and Connective Tissue Disorders** (16.4% in sitagliptin exposed vs 14.3% in non-exposed), and
- **Skin and Subcutaneous Tissue Disorders** (6.6% in sitagliptin exposed vs 5.6% in non-exposed)

The incidences of AEs grouped by SOC for **Blood and Lymphatic System Disorders**, **Infection and Infestations**, **Gastrointestinal Disorders** and **Musculoskeletal and Connective Tissue Disorders** SOCs were higher in the exposed group, with 95%-CI's not including "0".
When event rates were grouped by SOC (i.e., for each treatment group, total number of events occurring within a SOC divided by mean duration of exposure for the group) the between-group differences for the **Infection and Infestation**, **Gastrointestinal Disorders**, and **Musculoskeletal and Connective Tissue Disorders** SOCs were smaller (Infection and Infestations: 76 and 74.8 events per 100 patient-years in sitagliptin exposed vs non-exposed; Gastrointestinal Disorders: 41.8 and 39.1 events per 100 patient-years in sitagliptin exposed vs non-exposed; Musculoskeletal and Connective Tissue Disorders: 32.6 and 31.5 events per 100 patient-years in sitagliptin exposed vs non-exposed.
The difference in SOC for Blood and Lymphatic System Disorders (incidence 0.9 vs 0.3%; number of events per patient-year were 1.5 vs 0.6 for sitagliptin 100mg and non-exposed group) was mainly due to anaemia and iron deficiency in the sitagliptin 100mg group.
Similarly, in study P024V1 (comparison with glipizide as add-on to metformin) difference was observed in change from baseline in haemoglobin in the sitagliptin 100mg relative to glipizide treatment group (difference –0.07 g/dL). It is unlikely that these differences have clinical importance.

**Table 11: Specific Clinical Adverse Events by System Organ Class; Pooled Phase II/III Population; (Incidence ≥1.0% in One or More Treatment Groups); Number (%) of Patients by Treatment Group; Excluding Data After Initiation of Glycaemic Therapy**

| | MK-0431 100 mg (N = 2786) | | MK-0431 Non-Exposed (N = 2355) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Patients With One Or More Adverse Events | 1788 | (64.2) | 1484 | (63.0) |
| Patients With No Adverse Event | 998 | (35.8) | 871 | (37.0) |
| **Cardiac Disorders** | 93 | (3.3) | 73 | (3.1) |
| **Ear And Labyrinth Disorders** | 41 | (1.5) | 45 | (1.9) |
| Vertigo | 22 | (0.8) | 23 | (1.0) |
| **Eye Disorders** | 90 | (3.2) | 85 | (3.6) |
| **Gastrointestinal Disorders** | 517 | (18.6) | 386 | (16.4) |
| Abdominal Pain | 28 | (1.0) | 29 | (1.2) |
| Abdominal Pain Upper | 44 | (1.6) | 22 | (0.9) |
| Constipation | 70 | (2.5) | 44 | (1.9) |
| Diarrhoea | 125 | (4.5) | 114 | (4.8) |
| Dyspepsia | 51 | (1.8) | 27 | (1.1) |
| Gastrooesophageal Reflux Disease | 27 | (1.0) | 12 | (0.5) |
| Nausea | 70 | (2.5) | 52 | (2.2) |
| Toothache | 25 | (0.9) | 24 | (1.0) |
| Vomiting | 38 | (1.4) | 22 | (0.9) |
| **General Disorders And Administration Site Conditions** | 198 | (7.1) | 163 | (6.9) |
| Fatigue | 48 | (1.7) | 44 | (1.9) |
| Oedema Peripheral | 49 | (1.8) | 38 | (1.6) |
| **Hepatobiliary Disorders** | 30 | (1.1) | 22 | (0.9) |
| **Infections And Infestations** | 942 | (33.8) | 705 | (29.9) |
| Bronchitis | 79 | (2.8) | 44 | (1.9) |
| Cellulitis | 22 | (0.8) | 23 | (1.0) |
| Gastroenteritis | 48 | (1.7) | 32 | (1.4) |
| Influenza | 116 | (4.2) | 101 | (4.3) |
| Nasopharyngitis | 183 | (6.6) | 118 | (5.0) |
| Pharyngitis | 36 | (1.3) | 21 | (0.9) |
| Sinusitis | 63 | (2.3) | 39 | (1.7) |
| Upper Respiratory Tract Infection | 214 | (7.7) | 179 | (7.6) |
| Urinary Tract Infection | 81 | (2.9) | 64 | (2.7) |
| **Injury, Poisoning And Procedural Complications** | 210 | (7.5) | 152 | (6.5) |
| **Investigations** | 106 | (3.8) | 102 | (4.3) |
| Blood Glucose Decreased | 10 | (0.4) | 23 | (1.0) |
| Blood Glucose Increased | 31 | (1.1) | 31 | (1.3) |
| **Metabolism And Nutrition Disorders** | 169 | (6.1) | 323 | (13.7) |
| Hyperglycaemia | 28 | (1.0) | 31 | (1.3) |
| Hypoglycaemia | 94 | (3.4) | 261 | (11.1) |
| **Musculoskeletal And Connective Tissue Disorders** | 458 | (16.4) | 336 | (14.3) |
| Arthralgia | 95 | (3.4) | 69 | (2.9) |
| Back Pain | 106 | (3.8) | 83 | (3.5) |
| Muscle Spasms | 30 | (1.1) | 28 | (1.2) |

| | | | | |
|---|---|---|---|---|
| Myalgia | 27 | (1.0) | 20 | (0.8) |
| Osteoarthritis | 40 | (1.4) | 16 | (0.7) |
| Pain In Extremity | 68 | (2.4) | 41 | (1.7) |
| Shoulder Pain | 33 | (1.2) | 28 | (1.2) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | 51 | (1.8) | 31 | (1.3) |
| **Nervous System Disorders** | 344 | (12.3) | 272 | (11.5) |
| Dizziness | 68 | (2.4) | 51 | (2.2) |
| Headache | 143 | (5.1) | 105 | (4.5) |
| **Psychiatric Disorders** | 109 | (3.9) | 90 | (3.8) |
| Anxiety | 27 | (1.0) | 18 | (0.8) |
| Depression | 30 | (1.1) | 21 | (0.9) |
| Insomnia | 30 | (1.1) | 28 | (1.2) |
| **Renal And Urinary Disorders** | 67 | (2.4) | 53 | (2.3) |
| **Reproductive System And Breast Disorders** | 62 | (2.2) | 63 | (2.7) |
| **Respiratory, Thoracic And Mediastinal Disorders** | 204 | (7.3) | 155 | (6.6) |
| Cough | 63 | (2.3) | 56 | (2.4) |
| Pharyngolaryngeal Pain | 34 | (1.2) | 23 | (1.0) |
| **Skin And Subcutaneous Tissue Disorders** | 183 | (6.6) | 132 | (5.6) |
| Rash | 28 | (1.0) | 17 | (0.7) |
| **Vascular Disorders** | 120 | (4.3) | 103 | (4.4) |
| Hypertension | 74 | (2.7) | 63 | (2.7) |

The most frequent AEs reported, regardless of causal relationship to medication, and occurring in at least 5% and more commonly in patients treated with sitagliptin, included upper respiratory tract infection (7.7%) and nasopharyngitis (6.6%).

In study P024V1 (comparison with glipizide as add-on to metformin) the main AEs were in the same SOCs, with an additional SOC of **Nervous System Disorders**. Furthermore, compared to placebo, most frequently reported AEs were in these SOCs too.

The following specific clinical adverse events occurred at a higher *incidence* (i.e., confidence interval around the between-group difference did not include "0") in the primary safety analysis in the sitagliptin 100 mg group compared to the non-exposed group: abdominal pain upper, dyspepsia, chills, bronchitis, nasopharyngitis, tooth abscess, meniscus lesion, osteoarthritis, nasal congestion, and contact dermatitis. Although psychiatric disorders occurred at similar frequencies, the higher incidence of suicide ideation/completed suicide in sitagliptin exposed vs. non-exposed individuals (4 vs. 1, respectively) was considered disturbing; as CNS effects of sitagliptin cannot be excluded, these events will be monitored post-marketing.
The incidence of drug-related clinical AEs overall was lower for the sitagliptin 100 mg group compared to the non-exposed treatment group (13.1% vs. 18.0%).
Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microl difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microl) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Overall, it was concluded that sitagliptin treatment was 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 in the RMP.

COMBINATION WITH METFORMIN

In **study P020V1**, a 24-week study of sitagliptin 100 mg in combination with metformin, the incidence of AEs considered as drug-related in patients treated with sitagliptin/metformin compared to treatment with placebo/metformin was 9.3 % and 10.1 %, respectively.
The most frequent ADRs reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with placebo can be seen in table 12.
Nausea was the only drug-related AE that occurred at an incidence of ≥1%, occurring in 5 patients (1.1%) in the sitagliptin treatment group compared to 1 patient (0.4%) in the placebo group.

**Table 12: Drug-Related Clinical Adverse Events (%) of Patients by Treatment Group Excluding Data After Initiation of Glycaemic Rescue Therapy**

| SOC and Specific AE | Sitagliptin 100 mg (N=464) n (%) | Placebo (N=237) n (%) |
|---|---|---|
| **Gastrointestinal Disorders** | **14 (3.0)** | **4 (1.7)** |
| Nausea | 5 (1.1) | 1 (0.4) |
| Abdominal Pain Upper | 4 (0.9) | 1 (0.4) |
| Diarrhoea | 3 (0.6) | 0 (0.0) |
| **Nervous System Disorders** | **7 (1.5)** | **2 (0.8)** |
| Somnolence | 2 (0.4) | 0 (0.0) |
| **Investigations** | **4 (0.9)** | **5 (2.1)** |
| Blood Glucose Decreased | 2 (0.4) | 0 (0.0) |

SAEs were reported with a generally similar frequency between treatment groups for 13 (2.8%) and 7 (3.0%) patients in the sitagliptin and the placebo treatment groups, respectively. None of the SAEs was considered to be drug-related.

In **study P024V1**, 1-year study of sitagliptin 100 mg in combination with metformin compared to sulfonylurea/metformin, clinical AEs were reported by 419 (71.3%) patients in the sitagliptin treatment group and 444 (76.0%) patients in the glipizide treatment group, who received at least one dose of double-blind study medication. There was a slightly higher incidence of overall AEs in the glipizide treatment group, and a moderately higher incidence of drug-related AEs reported in the glipizide treatment group (30.3%) compared to the sitagliptin treatment group (14.5%). The differences in overall and drug-related AEs were primarily due to the higher incidence of **hypoglycemia** reported in the glipizide treatment group (32%) compared to the sitagliptin group (5%). No meaningful differences were observed for the sitagliptin treatment group compared to the glipizide treatment group in incidence of SAEs, serious or non-serious AEs leading to discontinuation, or other summary measures of clinical AEs analyzed. For all of these summary measures, the 95% CI for the between-group differences included "0".

In pooled studies of up to 1 year in duration comparing sitagliptin/metformin to a sulfonylurea agent/metformin (**P020V1 and P024V1**), the incidence of drug-related AEs was notably lower in the sitagliptin treatment group than in the glipizide treatment group due to the higher incidence of drug related **hypoglycemia** in the glipizide treatment group. The drug-related AEs of hypoglycemia and of weight gain occurred at a notably higher rate in the glipizide treatment group. The adverse reactions considered as drug-related reported in patients treated with sitagliptin 100 mg occurring in excess (> 0.2 % and difference > 1 patient) of that in patients receiving the sulfonylurea agent were from the following SOCs:
**Investigations**: weight decreased (4 patients [0.4%] and 0, respectively)
**Metabolism and nutrition disorders**: anorexia (4 patients [0.4%] and 1 patient [0.1%], respectively).

COMBINATION WITH A PPARγ AGENT (PIOGLITAZONE)

**Study P019** (+PIO), had a duration of 24 weeks and was considered a priori too short for an appropriate safety assessment, especially in terms of cardiovascular safety. The incidence of peripheral oedema in this study was somewhat increased (4.0% vs 2.8%, 7 vs. 5 patients) when sitagliptin was added to pioglitazone compared to the addition of placebo. Though not considered a strong signal the data were also not considered reassuring. The Applicant agreed to follow up on the cardiovascular safety of this patient population in the approved indications as a post-authorisation commitment.
The incidence of AEs considered as drug-related in patients treated with sitagliptin/pioglitazone compared to patients treated with placebo/pioglitazone was 9.1 % and 9.0 %, respectively. Adverse reactions considered as drug-related reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 patient) of that in patients receiving placebo were as follows:

**Table 12: Drug-Related Clinical Adverse Events (%) of Patients by Treatment Group Excluding Data After Initiation of Glycaemic Rescue Therapy**

| SOC and Specific AE | MK-0431 100 mg (N=175) n (%) | Placebo (N=178) n (%) |
|---|---|---|
| **Gastrointestinal Disorders** | **3 (1.7)** | **3 (1.7)** |
| Flatulence | 2 (1.1) | 0 (0.0) |
| **Metabolism and Nutrition Disorders** | **3 (1.7)** | **1 (0.6)** |
| Hypoglycaemia | 2 (1.1) | 0 (0.0) |

MONOTHERAPY

Results from comparison 4, showed that in the monotherapy studies of up to 24 weeks duration, AEs considered as drug-related reported in patients treated with sitagliptin in excess (> 0.2 % and difference > 1 patient) of that in patients receiving placebo were headache (1.3 %), hypoglycaemia (1.1 %), constipation (0.7 %), and dizziness (0.6 %). These results were obtained excluding data after initiation of glycaemic rescue therapy.

- Serious adverse event/deaths/other significant events

Information on all deaths with a cut-off date of 7-July-2006, including results from completed and ongoing studies, regardless of occurrence prior to or after initiation of rescue glycaemic therapy was submitted. 30 deaths were reported in the development program for sitagliptin: 23 deaths were reported in the Phase II/III studies in patients with T2DM (excluding P028), and 7 deaths were reported in P028. No deaths were considered related to study drug.
Of the 23 deaths reported in the Phase II/III studies, 4 were reported prior to randomisation (all during the run-in period in Phase III studies) and 19 after randomisation. Among the 19 patients who died after randomisation, 5 occurred in Phase II studies (P010 and P014 base period or study extensions) and 14 occurred in Phase III studies. Of the 5 post-randomisation deaths in Phase II studies, 3 occurred in patients in a sitagliptin group and 2 occurred in patients on glipizide.
Of the 14 post-randomisation deaths in Phase III studies, 7 occurred in a sitagliptin treatment group, and 7 occurred in a non- exposed group. Since this information includes deaths that occurred in ongoing studies as well as completed studies, the exact exposure in the sitagliptin and the non-exposed treatment groups was not available. However, in the Phase II and III studies, 3832 patients were randomised to a sitagliptin treatment group, and 2355 patients were randomised to a non-exposed group. Since patients in the placebo group in studies P010 (dose finding) and P021V1 (monotherapy) were switched to a sitagliptin treatment group, the actual number of patients exposed to sitagliptin was larger than that indicated by the original randomised patient numbers. However, based upon the number of patients randomised to a sitagliptin or to a non-exposed group in the Phase II and III studies, 0.26% of patients randomised to sitagliptin died and 0.38% patients randomised to a non-exposed group died.

In study P028, 65 patients were randomised to sitagliptin and 26 patients were randomised to treatment with placebo (switched at week 12 to glipizide). Of the 7 deaths reported, one was reported prior to randomisation, 5 deaths were reported in patients randomised to sitagliptin and one was reported in a patient randomised to glipizide treatment. One additional patient, who had severe renal insufficiency and who had been allocated to the placebo/glipizide group, died of bowel ischemia in the post-study period. Looking at the randomisation ratio the difference is higher than expected. In the sitagliptin group, 4 of the 5 patients died due to cardiac AEs, while there was no cardiac death in the glipizide group. . It was observed, however, that in addition to the larger size of the sitagliptin treatment group (65 vs 26 patients), the proportion of patients in the sitagliptin group with prior cardiac disease at baseline was also higher than in the placebo Although, study P028 was very small, precluding an appropriate safety assessment, this finding was of some concern. The data was considered in general too limited to confirm the safe use of sitagliptin in patients with moderate to severe renal insufficiency, therefore sitagliptin is not recommended in this patient population and this has been reflected as such in the SPC.

The incidence of serious non-fatal clinical AEs was similar in the sitagliptin 100 mg (5.9%), 200 mg (5.0%) and the non-exposed (5.5%) treatment groups, and slightly higher in the sitagliptin <100 mg (7.8%). There was no apparent pattern of specific serious non-fatal clinical AEs observed in the sitagliptin 100 mg treatment group.

In the whole Pooled Phase II/III Population there were 2 patients with a serious laboratory AE. One patient in the sitagliptin 100 mg group had increased lipase; one patient in the sitagliptin 200 mg group experienced decreased blood potassium and blood sodium.

- Laboratory findings

Laboratory AEs were reported for 271 (9.8%) patients in the sitagliptin 100 mg group and 221 (9.5%) patient in the non-exposed group who received at least one dose of double-blind study medication and had at least one laboratory test performed post-baseline. The incidences of laboratory AEs, drug-related laboratory AEs and patients discontinued due to a laboratory AE were generally similar in the sitagliptin 100 mg group compared to the non-exposed group although all incidences were low. For all of these summary measures, the 95% CI for between group differences included “0”.
There were no meaningful differences between the treatment groups in the incidence of specific laboratory AEs, or all specific laboratory AEs, the CIs around the between group differences included "0". The incidence of specific drug-related laboratory AEs was generally similar in the sitagliptin 100mg and the non-exposed groups.

- Safety in special populations

Safety data of elderly patients was presented for the Pooled Phase II/III Population. No meaningful differences were observed in younger compared to older patients in the overall incidence of either clinical or laboratory AEs by SOC, or any specific AEs. Older patients had a higher overall incidence of serious clinical AEs, as might be expected; however, there was no meaningful difference observed in the sitagliptin treatment groups relative to the non-exposed group. A slightly greater proportion of older patients discontinued due to SAEs in the sitagliptin 100 mg group compared to the non-exposed group, but this was not observed in the sitagliptin 200 mg group. Review of the specific SAEs leading to discontinuation did not show any discernable pattern in the types of SAEs observed in the sitagliptin groups relative to non-exposed group.
Review of safety results from older and younger patients showed that the incidence of AEs by SOC or of specific AEs in the sitagliptin treated relative to the non-sitagliptin treated patients was not meaningfully different. No particular AEs appeared to occur with sitagliptin treatment at a meaningfully higher incidence in older patients relative to younger patients.

Overall, safety and tolerability of sitagliptin are considered acceptable. However, patients with moderate to severe renal insufficiency should not use sitagliptin, as safety in these patients has not been demonstrated sufficiently, as is mentioned in several sections of the SPC. Additionally, further data on cardiovascular safety in the patient population to be treated with sitagliptin will be addressed as part of the post-authorisation follow-up measures.

## 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 issue** | **Proposed Pharmacovigilance Activities** | ***Proposed Risk Minimization Activities*** |
|---|---|---|
| **Important Identified Safety Issues** | | |
| Gastrointestinal disorders, including nausea, constipation, diarrhoea, upper abdominal pain, flatulence and related terms (dyspepsia, gastritis, and abdominal pain) | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | Labelling - SPC Section 4.8 Undesirable effects |
| Infections, including nasopharyngitis, upper respiratory tract and related terms (bronchitis/acute bronchitis, pharyngitis, sinusitis, and rhinitis) | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | Labelling - SPC Section 4.8 Undesirable effects |
| **Important Potential Safety Issues** | | |
| Neurotoxicity, including tremor, ataxia, and balance disorders | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | |
| Suicidal ideation/suicide, including depression | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | |
| Muscle disorders, including myalgia, myopathy, and muscle weakness | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | |
| Skin reactions, including urticaria, and other clinically important and serious skin reactions | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | |
| Drug-drug interactions in renal insufficiency patients | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | |
| **Missing or Limited Information** | | |
| Exposure in patients <18 years of age | Monitoring of exposure in children (<18 years of age) by monitoring misuse/overdose | Labelling - SPC 4.2: Not recommended for use in children below 18 years of age |
| Exposure during pregnancy | Routine Pharmacovigilance<br><br>Analysis of ongoing and planned clinical safety data† | Labelling - SPC 4.6: Not to be used during pregnancy due to lack of human data |
| Adverse events in renal insufficiency patients | Enhanced safety surveillance<br><br>Analysis of ongoing and planned clinical safety data† | Labelling - SPC 4.2 Posology and method of administration "Patients with renal insufficiency" |

† Ongoing clinical trials include: P020 Phase B, P021 Phase B, P024, P035, P036, P036-10, P040, P047, P052, P801, P053, P055, P056, P057, and P058. Planned clinical trials include: P051, P054, P060, P063, and P064. See General Investigational Plan of Completed, Ongoing, and Planned Clinical Trials Yielding Safety Information for MK-0431.

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

## 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 primary glucose-lowering property and effects on GLP-1 plasma levels of DPP-4 inhibition by sitagliptin have been shown. Except for some minor cardiovascular safety effects through DPP-4 inhibition, inhibition of other enzymes such as DPP-8/9 are not anticipated at exposures required for glucose lowering in humans.

Sitagliptin was rapidly absorbed, was bioavailable, and exhibited fairly linear oral pharmacokinetics. It is a moderate to high clearance drug, with a relatively short plasma half-life. Metabolism of the drug is minor, being excreted primarily unchanged in human, rat and dog

*In vitro* assays indicated that the risk for clinically meaningful interactions is low. At clinically relevant concentrations, sitagliptin did not inhibit cytochrome P450s or Pgp, nor did it induce human CYP3A4. However interactions could be of greater importance in patients with severe renal insufficiency or ESRD. This has not been assessed in clinical studies.

Skin necrosis was seen in monkeys treated with other DPP-4 inhibitors; this was considered in the development program of sitagliptin, and studies are still ongoing to this respect. No skin findings were seen in clinical studies with sitagliptin

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight-to-slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas; however, these neoplastic changes are not considered relevant for the situation in humans.

No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating. Reproductive toxicity studies showed a slight treatment-related increased incidence of fetal rib malformations in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. These findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1), and was seen to cross the rat and rabbit placenta readily. Based on this pre-clinical data, and the lack of human studies, sitagliptin should not be used during pregnancy or breast-feeding.

**Efficacy**

Sitagliptin 100mg or 200mg qd was compared to placebo in two monotherapy trials (P021V1/P023V1). The duration of these studies was of 18 and 24 weeks, both presenting extension phases. These studies showed that sitagliptin at the recommended 100mg dose clearly and clinically relevantly reduced baseline HbA1c for the duration of the studies.
In the combination studies sitagliptin was added to metformin (P020V1) or pioglitazone (P019), and compared to the effect of addition of placebo. These studies had 24-week durations, with an extension to 104 weeks in the metformin combination study. The results of these combination studies also showed that sitagliptin 100mg effectively reduced $HbA_{1c}$ in patients with diabetes mellitus for the duration of the studies.

In the active comparator study P024V1 (Sitagliptin+Metformin compared to Metformin+Glipizide), sitagliptin 100 mg per day was shown to have a significant and clinically relevant effect on glycaemic control. Sitagliptin was similar to glipizide in reducing HbA1c in this patient population with predominantly mild to moderate hyperglycaemia on monotherapy with metformin, but non-inferior efficacy compared to sulfonylureas has not unequivocally been proven. The latter conclusion was based on the restrictions regarding dose titration of glipizide possibly preventing assessment of the full potential of this drug. Furthermore, although not designed and powered to compare efficacy, in study P010, phase II dose finding study in monotherapy, glipizide performed statistically better than sitagliptin; and in study P020V1 numerically better than sitagliptin.

Studies P021V1, P020V1 and P024V1 provided long-term efficacy data. The results from the monotherapy and combination studies showed that sitagliptin treatment resulted in an improvement in $HbA_{1c}$ with a nadir observed at week 30, followed by a rise but still maintenance of $HbA_{1c}$ lowering at week 54. Glipizide treatment in Phase B of study P020V1 as add-on to metformin resulted in a greater reduction in $HbA_{1c}$ values, but the difference was small. In P024V1, there was a rise in mean $HbA_{1c}$ in both treatment groups after Week 24. The rate of rise from nadir in the glipizide group was greater than the rate of rise in the sitagliptin group, such that by week 52 very similar reductions from baseline in the two treatment groups were seen. More patients in the sitagliptin group discontinued due to lack of efficacy as compared to glipizide treated patients.

**Safety**

Overall, it can be concluded that sitagliptin treatment was associated with an increased incidence in infections, gastrointestinal disorders, musculoskeletal disorders, and nervous system. These adverse events have been included in the SPC. Event rate was increased for skin and subcutaneous tissue disorders. These adverse events are seen as potential risk and have been included in the risk management plan.
In favour of sitagliptin, studies indicate that the risk of hypoglycaemia is decreased as compared to glipizide treatment. In addition, sitagliptin was shown to have a favourable impact on body weight compared to glipizide.

Specific adverse drug reactions that were increased in the Xelevia group vs. placebo when sitagliptin was combined with metformin were: somnolence, nausea, upper abdominal pain, diarrhoea, blood glucose decreased, anorexia and weight decreased.

In the combination with pioglitazone, specific adverse drug reactions that were increased in the Xelevia group vs. placebo when sitagliptin was combined with pioglitazone were: hypoglycaemia and flatulence. There was also a slight increase in the frequency of peripheral oedema as an adverse event.

Safety data of elderly patients were presented for the Pooled Phase II/III Population. No meaningful differences were observed in younger compared to older patients in the overall incidence of either clinical or laboratory adverse events by SOC or of specific adverse events.
In the study on renal insufficiency (P028), there were more cardiac adverse events and more patients died in the sitagliptin group compared to the placebo/glipizide group. Although, study P028 was very

small, precluding an appropriate safety assessment, this finding was of some concern. The data was considered in general too limited to confirm the safe use of sitagliptin in patients with moderate to severe renal insufficiency, therefore sitagliptin is not recommended in this patient population and this has been reflected as such in the SPC.

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 target patient groups "user consultation" was assessed as part the applicant's responses to the D120 List of Questions.

**Risk-benefit assessment**

In conclusion, the benefit-risk ratio for sitagliptin is considered positive in the treatment of patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ agonist (e.g. thiazolidinedione) when diet and exercise plus the single agent do not provide glycaemic control. However, more safety data are needed in patients with moderate or severe renal insufficiency before the use of sitagliptin can be recommended in this patient population.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Xelevia in the treatment of patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin do not provide adequate glycaemic control, and also for patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control was favourable and therefore recommended the granting of the marketing authorisation .