SCIENTIFIC DISCUSSION

1 Introduction

The pathophysiology of Type 2 diabetes mellitus (T2DM) is characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, and/or compromised insulin action in peripheral target tissues (insulin resistance). This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycaemia, contribute to microvascular and macrovascular complications.
T2DM accounts for approximately 85% to 95% of diabetes cases in developed regions like the European Union. Age and weight are established risk factors for T2DM. The majority of patients with T2DM are overweight or obese. Diet modification and exercise is the first line of treatment for T2DM. Pharmacologic intervention with one oral antidiabetic drug (OAD) is usually the next step in treatment. After 3 to 9 years of OAD monotherapy, patients typically require an additional intervention. The recommended first line treatment is metformin, which restrains hepatic glucose production and decreases peripheral insulin resistance. Sulphonylureas, which are insulin secretagogues, may be used as an alternative to patients intolerant to metformin, or as an addition to metformin. Other second line oral treatment alternatives include alpha-glucosidase inhibitors, meglitinides and thiazolidinediones. Although being efficient in attenuating hyperglycaemia, all of these treatment alternatives have more or less serious side effects and there is a need for development of efficient drugs without metabolic or other side effects.

Vildagliptin belongs to a new class of oral anti-diabetic drugs and is a selective and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), the enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), hormones which significantly contribute to the maintenance of glucose homeostasis.

The therapeutic indication granted is: Treatment of type 2 diabetes mellitus as dual oral therapy in combination with

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

The recommended dose is 100 mg daily administered either once daily or divided into two doses of 50 mg given in the morning and evening, except for the combined use with a sulphonylurea, where the recommended dose is 50 mg given in the morning.

2 Quality aspects

Introduction

Galvus an immediate release dosage form is presented as tablets containing 50 mg and 100 mg of vildagliptin as active substance. The other ingredients are microcrystalline cellulose, lactose anhydrous, sodium starch glycolate and magnesium stearate.

The film-coated tablets are marketed in aluminium/aluminium (PA/Al/PVC//Al) blisters.

Active Substance

The active substance is vildagliptin. Its chemical name is (S)-1-[2-(3-Hydroxyadamantan-1-ylamino) acetyl]pyrrolidine-2-carbonitrile according to the IUPAC nomenclature.
Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder and no polymorphs or solvates have been identified so far. Vildagliptin is non-hygroscopic and freely soluble in water and

polar organic solvents. The above-mentioned active substance has one chiral centre and is used as a single enantiomer (S).

- **Manufacture**

Vildagliptin is synthesised in two reactions steps followed by purification (recrystallisation). The manufacturing process for vildagliptin 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 elemental analysis, ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, and mass spectroscopy. The molecular weight was determined by elemental analysis which is in agreement with the expected molecular weight. The proposed molecular structure was confirmed by X-ray powder diffraction and X-ray single crystal structural analysis.

- **Specification**

The vildagliptin specifications include tests for appearance (slightly yellowish or slightly greyish powder), particle size (by laser light diffraction), identification (by IR-KBr, IR-ATR and X-ray diffraction), Related substances (HPLC and IC), R-enantiomer of vildagliptin (HPLC), residual solvents (Head-space GC), loss on drying (thermogravimetry), sulphated ash, heavy metals, clarity of solution, colour of solution, assay (by HPLC) and microbiological limit tests.
It was verified that all specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.
Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances 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 and temperature exposure. The results of the long-term and accelerated studies fulfil the proposed specification and for that reason support the proposed retest period.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
Galvus tablets were developed five tablet strengths which were used in clinical trials. However, only two tablet strengths (50 mg and 100 mg) will be marketed.
The main aim of the applicant was to develop robust final formulation that would be suitable for routine manufacturing at the production scale for that reason different formulation containing different excipients were investigated and optimised.
Having investigated different formulations the applicant selected for commercialisation a direct compression tablet formulation.
Lactose monohydrate is manufactured from bovine milk. The supplier confirms that the milk used in the manufacture of the lactose is sourced from healthy animals under the same conditions as for human consumption.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, blending and compressing.
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 finished product specifications were established according the ICH guidelines and include the following tests: appearance, identification (TLC and HPLC), mean mass, dissolution, water (Karl Fischer), degradation products (HPLC), uniformity of dosage units by mass variation (Ph Eur), or, alternatively, uniformity of dosage units by content uniformity (Ph Eur), assay (HPLC) and microbial limits (Ph Eur).
All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
Batch analysis data on three stability batches and three production scale batches (validation batches) confirm satisfactory uniformity of the product at release.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Three full production scale batches of each strength, as well as a supportive production batch of 100 mg have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch per strength was stored under elevated temperature conditions for 3 months and at ICH conditions, and under low temperature conditions for 6 months and for photostability at ICH conditions.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the 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 CHMP and ICH 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.

3. Non-clinical aspects

Introduction

All pivotal toxicology and safety studies were performed in accordance with GLP regulations.

Pharmacology

- Primary pharmacodynamics

In vitro studies
The non-clinical pharmacology program has demonstrated that vildagliptin is a selective and potent inhibitor of DPP-4. The IC_{50} value for inhibition of human DPP-4 is about 3 nM and similar activity was observed with the rat enzyme, demonstrating the lack of species selectivity. Vildagliptin showed some activity at the related enzymes DPP-8 and DPP-9 (Ki values of 506 nM and 65 nM, respectively). Although these values are 253 and 32 times higher than the Ki for DPP-4, activity at C_{max} in humans (2.3 μM) is likely. No assays exist allowing evaluation of DPP-8/DPP-9 inhibition in vivo. The possibility of activity at one or both of these targets is considered a safety concern in relation to the occurrence of skin lesions in monkeys (see below). No, or minimal, inhibition was seen with other related enzymes.

In vivo studies
In vivo pharmacodynamic studies were performed in rats and monkeys. These studies demonstrated the in vivo inhibition of DPP-4 and increased plasma levels of GLP-1. Studies in diabetic rats and in insulin-resistant monkeys demonstrated a glucose-lowering effect of vildagliptin. Chronic effects of vildagliptin were studied in pre-diabetic and insulin-treated diabetic monkeys. Beneficial effects were observed on HbA1c, fasting insulin, fibrinogen and PAI-1.

Vildagliptin increased β-cell mass in neonatal rats, and improved β-cell function in streptozotocin-induced diabetic mice. These data could suggest that vildagliptin has the potential to mitigate the progressive loss of islet function in type 2 diabetes patients.

- Secondary pharmacodynamics

Vildagliptin showed no significant effect on gastric emptying in monkeys. This is in contrast to what has been observed with exogenously-administered GLP-1 and GLP-1 analogues.

As discussed above, activity at the related enzymes DPP-8 and/or DPP-9 can not be excluded at clinical exposures. Concerns related to secondary pharmacology can also arise from the importance of DPP-4 in enzymatic and non-enzymatic functions other than inhibiting the inactivation of GLP-1 and GIP.

DPP-4 (CD26) is present as a cell surface molecule on immune cells and has been characterised as an important costimulatory molecule in immune activation. Although some studies applying DPP-4 inhibitors have suggested a role for the enzyme activity for the immune function, other studies have suggested costimulation to be unrelated to the enzyme activity. The studies performed with vildagliptin and discussed in the dossier support the view that the immune function of CD26 is independent of its enzyme activity.

There are no indications for safety issues related to other DPP-4 substrates than GLP-1 and GIP.

Potential effects on the immune system, resulting in an increased risk for infections and on substance P and neurokinin resulting in an increased risk of angioedema are discussed in the Risk Management Plan. No increased risk has been observed during clinical development for any of these adverse events.

- Safety pharmacology programme

Safety pharmacology studies have been conducted to evaluate neuropharmacological, respiratory and cardiovascular effects of vildagliptin in animals.
Cardiovascular changes were observed in dogs at high doses, occasionally resulting in mortality. Possible mechanisms were examined in an extensive battery of *in vitro* and in *vivo* studies of cardiovascular parameters. These effects are possibly related to inhibition of SCN5A sodium channels

which was observed in in vitro studies. Based on dog exposure data (Cmax > 7-fold higher at NOAEL than seen at maximum dose in humans) and the in vitro IC_{50} for sodium channels (365 μM versus clinical Cmax of 2 μM), a clinical effect is unlikely. However, conduction disturbances were further investigated in humans.

- Pharmacodynamic drug interactions

The effects of combinations of vildagliptin with the rapid-onset insulinotropic agent, nateglinide (Starlix) and with the insulin sensitizer, pioglitazone (Actos) were assessed in Zucker fatty rats and resulted in an additive or more than additive effect on several plasma glucose-related parameters.

Pharmacokinetics

Vildagliptin was rapidly absorbed with a high bioavailability in all species. There were no important differences in pharmacokinetic parameters between the tested animal species and humans.

Vildagliptin showed low binding to plasma proteins in all species (<10%). In a whole body autoradiography study in rats, vildagliptin-related radioactivity was widely distributed to most tissues. Drug-related radioactivity was bound to melanin. There was a low passage for drug-related radioactivity across the blood-brain barrier. No radioactivity was detected in any tissue at 48 h post-dose. Studies in pregnant rats and rabbits demonstrated placental transfer of vildagliptin.

The parent compound was one of the major circulating components in all species and all metabolites observed in humans were also found in the animal species. Hydrolysis was the main mechanism of vildagliptin metabolism in all species and exposure to the major metabolites was broadly similar in the rat, dog and human. In humans, the predominant metabolic pathway was hydrolysis at the cyano moiety to form a carboxylic acid metabolite (M20.7/LAY151), accounting for approximately 55% of circulating drug-related material following an oral dose. M20.7 was the main metabolite both in the rat (54%) and the dog (33%). In the rabbit, another hydrolysis product M15.3 was the main metabolite (53%).

Vildagliptin is produced as a pure S-enantiomer. A clinical study showed that chiral conversion *in vivo* is unlikely.

Urinary excretion was the main route in all species except the rat, where equal amounts were excreted with urine and feces. Milk transfer of vildaglitin and metabolites were demonstrated in the rat, which is therefore mentioned in the SPC section 4.6, with a milk/plasma ratio for total radioactivity of 4.

In vitro studies demonstrated that vildagliptin is unlikely to exhibit a potential for pharmacokinetic drug interactions. Vildagliptin did not inhibit Pgp or any of a series of CYP enzymes. There was no evidence for enzyme induction.

Toxicology

- Single dose toxicity

Vildagliptin exhibits low acute toxicity. In mice and rats no toxicological signs were observed after a single oral dose of 2000 mg/kg.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicity studies were performed in rats (up to 26 weeks) and dogs (up to 52 weeks). These models are considered relevant, based on the lack of species specificity for the pharmacological activity of vildagliptin, and the similarities in metabolism to humans.

The main toxicological effect noted in rats was the accumulation of clusters of foamy alveolar macrophages in the lung. Similar observations were made in mice. This finding was proposed to be

due to an exaggerated pharmacological effect of DPP-4 inhibition in the rat. The clinical relevance of the lung findings in rats cannot be fully excluded. There is a considerable safety margin (5 x human AUC at NOAEL) and the findings are considered of limited importance.

The most consistent toxicological finding in the dog was the appearance of gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhea and at higher doses, faecal blood. These signs were observed at relatively low systemic exposures (observed already at lowest dose representing 2 x human AUC). GI findings were not observed in any other species and according to the applicant no GI disorders have been observed in clinical trials. The CHMP was of the opinion, that these findings are unlikely to be of clinical importance.

- Genotoxicity

The data from genotoxicity studies conducted with vildagliptin in several standard genotoxicity tests do not indicate a genotoxic potential.

- Carcinogenicity

Life-time carcinogenicity studies were performed in mice and rats. No evidence for a carcinogenic potential was observed in the rat. An increased incidence of hemangiosarcomas was observed at the highest dose in female rats while in male rats, the incidence was slightly decreased. Given the mouse findings discussed below, a relation to treatment cannot be fully excluded. In the mouse there was an increased incidence of hemangiosarcomas and mammary carcinoma. The increased incidence of hemangiosarcoma in mice occurred only in organs where this tumour occurs as a relatively common spontaneous finding in the mouse (liver, spleen, uterus etc.). It is suggested that a predisposition to spontaneous hemangiosarcoma at the affected site is needed for vildagliptin to promote an increased incidence. A study in the mouse demonstrated that vildagliptin inhibits VEGF-induced angiogenesis. Based on these mechanistic data the applicant proposes a mechanism whereby inhibition of VEGF-induced angiogenesis over a long period exerts selection pressure in favour of endothelium that proliferates independently of VEGF and hence increases the likelihood of endothelial neoplasia. There was a disproportionate increase in hemangiosarcoma involving the liver in treated male mice at $\geq$ 250 mg/kg/day. At the same time there was a decreased incidence of hepatocellular carcinoma in male mice. The applicant hypothesizes that hemangiosarcomas may originate within early hepatocellular tumours or preneoplastic lesions followed by obliteration of the hepatocellular tumour and its replacement with the more aggressive hemangiosarcoma. There is a substantial safety margin (exposure margin at NOAEL = 16). It was considered that vildagliptin is likely to act by promoting development of a tumour form that appears commonly mice, and that the data do not suggest an increased risk for hemangiosarcoma development in humans where this tumour form is uncommon. The fact that the incidences of other common spontaneous tumours were not increased by vildagliptin treatment supports the view that a more general tumour promoting effect of vildaglitin is unlikely. The applicant will further study the mechanism for tumour development in the liver of mice, and the findings were considered by the CHMP not to represent a significant risk to humans.

In the case of mammary adenocarcioma, the applicant suggested that tumours noted in the mouse carcinogenicity study are likely the result of an effect on the pituitary-gonadal axis that is unlikely to be of relevance to humans. In mammary tissue from mice treated with vildagliptin for 53 weeks there was a dramatic upregulation of genes related to milk production, such as casein-beta, casein-gamma and lactalbumin, suggesting that hormonally-driven changes are occurring in the mammary gland of mice treated with vildagliptin. The CHMP was of the opinion that these effects are unlikely to be of relevance to humans.

- Reproduction Toxicity

Vildagliptin showed no effects on fertility, reproductive performance or early embryonic development in the rat. Embryo-foetal toxicity was evaluated in rats and rabbits. In the rat, an increased incidence of wavy ribs was observed at $\geq$ 225 mg/kg/day, in association with reduced maternal body weight parameters. Although classified as a malformation, literature data suggest that wavy ribs in the rat may

be reversible. In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted in rabbits at 150 mg/kg/day, in the presence of severe maternal toxicity (including mortality). It is concluded that vildagliptin is not selectively embryotoxic and does not exhibit a teratogenic potential. In the peri- and postnatal toxicity study in rats, maternal toxicity was observed at all doses. Transient decrease in F1 generation body weight and a decreased number of central beam breaks in open-field motor activity tests were observed at ≥ 150 mg/kg/day.

- Local tolerance

Local tolerance of vildagliptin was investigated as part of the intravenous toxicity. No local effects due to vildagliptin were observed in either species. A skin irritation study conducted in rabbits did not indicate any dermal irritant properties.

- Other toxicity studies

Vildagliptin showed no effect on the immune response in KLH-immunised rats. As discussed in the section on Pharmacology, the lack of immunotoxicity supports the view that the immune function of DPP-4/CD26 is independent of its enzymatic activity.

No toxicity studies with metabolites were performed. The main human metabolites were present at similar amounts in the toxicology species. In patients with renal impairment, the exposure to the pharmacologically inactive metabolite LAY151 may be increased up to 6 times. There are no indications for any toxicity related to the metabolite and no further studies are warranted.

Drug impurities requiring toxicological qualification were tested in repeat-dose toxicity and genotoxicity studies with a vildagliptin preparation spiked with the impurities at levels of 2-3%. There were no findings suggesting a change in toxicity profile.

Available data indicate that the administration of DPP-4 inhibitors to monkeys results in dose and duration-dependent increases in necrotic lesions of the tail, digits, ears, nose and scrotum. The mechanism is unknown and such lesions have not been described in humans, rats or dogs. Data from the safety pharmacology study in monkeys suggest that vildagliptin may cause skin lesions in the monkey. A 13-week toxicology in cynomolgus monkeys shows occurrence of necrotic lesions with a lack of safety margin and lack of reversibility at higher doses. The skin lesions are proposed to result from peripheral vasoconstriction.The skin lesions were observed at doses that produced a tachycardic and a prohypertensive action indicating a sympathomimetic effect of vildagliptin at these doses in monkeys.The applicant argues that these findings were related to DPP4 inhibition, and that monkeys are much more sensitive to DPP4 inhibition than humans. The lack of skin lesions with sitagliptin in rhesus monkeys speaks against this proposal suggesting that other factors may be involved in causing the skin lesions result, such as inhibition of DPP8 and or DPP9, the occurance of which in vivo is not known.

Based on mechanistic considerations, no firm conclusion on the relevance of the skin lesions in monkeys for clinical safety can be drawn at this time. The CHMP considered these findings acceptable for a market authorisation, considering the clinical safety documented so far, and appropriate means taken by the applicant to identify any signals in the post-marketing phase. Further studies on the mechanism of skin lesions in the monkeys will be performed as follow-up measures. In addition to describing the findings in SPC section 5.3, a warning is included in section 4.4 with a reference to section 5.3.

Ecotoxicity/environmental risk assessment

The environmental risk assessment does not indicate any important risk to the environment.

4. Clinical aspects

Introduction

Vildagliptin is a selective and reversible inhibitor of DPP-4, and thus belongs to a new class of oral anti-diabetic drugs.

The applicant received repeated Scientific Advice from the CHMP on 21 November 2003, 24 June 2004 and on 22 October 2004. The Scientific Advice focused on clinical aspects, including study design, documentation of cardiac safety, and discussion of study endpoints.

During the clinical development program, there were 2 events of note:
1. The 100 mg dose was initially discontinued by amendment in 2 phase II dose selection studies (because of cardiac findings in dogs at very high exposures, which were subsequently mitigated) and resumed in phase III studies.
2. Unreliable HbA1c assessments in 6 key phase III studies and the 1 phase III dose regimen study required reanalysis in retention samples. As some patients had no retention samples for re-analysis, and others did not reach the entry requirements for HbA1c upon re-analysis, replacement patients were recruited in each study prior to database lock and patients without reliable baseline values or required entry values were excluded from the full analysis in accordance with ICH guidance.

The therapeutic indication for vildaglitpin claimed by the applicant was treatment of T2DM:

- As monotherapy, in patients inadequately controlled by diet and exercise for whom metformin is inappropriate because of intolerance or contraindications,
- As dual oral therapy with metformin, a sulfonylurea, or a thiazolidinedione, in patients with insufficient glycaemic control despite maximal tolerated doses of monotherapy with these agents,
- In combination with insulin.

During the evaluation of the MAA, the CHMP had concerns about the proposed monotherapy indication, as well as about the proposed use in combination with insulin. The applicant initially proposed a further restriction of the combination usage with insulin but finally withdrew this part of the indication. In addition, on 5 July 2007, the applicant also withdrew the part of the indication proposing vildagliptin as monotherapy in patients inadequately controlled by diet and exercise for whom metformin is inappropriate because of intolerance or contraindications, thus addressing the remaining concerns by the CHMP.

The therapeutic indication finally granted is therefore: treatment of T2DM, as dual oral therapy in combination with

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

The recommended dose is 100 mg daily administered either once daily or divided into two doses of 50 mg given in the morning and evening, except for the combined use with a sulphonylurea, where the recommended dose is 50 mg given in the morning.

No study in the paediatric population was performed and therefore the use in this population is not recommended. Experience in patients aged 75 years and older is limited and caution should be exercised with the use in this population.

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

A total of 38 clinical pharmacology studies enrolling approximately 1014 subjects have been conducted with vildagliptin to evaluate PK, dose-response, PK/PD relationship, mode of action and potential for drug-drug interactions.

Vildagliptin is analyzed in plasma and urine using a specific LC-MS method. The analytical methods are adequate for accurate determination of vildagliptin (LAF237) and its major inactive metabolite LAY151 in human biological fluids.

- Absorption

Bioavailability: Vildagliptin is rapidly absorbed with a median t_{max} of about 1.5 hr after oral dosing and has a mean absolute oral bioavailability of 85%. An *in vitro* study with Caco-2 cell monolayer suggests that vildagliptin is a substrate of P-gp, with low affinity, however.

The rate of absorption is reduced when vildagliptin final marketing tablets are taken with a high fat meal and there is also a slight reduction of extent of absorption as reflected by an increase in t_{max} from 1.75 h under fasting conditions to 2.5 h after a high fat meal, a 19% decrease in C_{max} and 10% decrease in AUC. These effects are not considered clinically relevant. Galvus can be taken with or without food (mentioned in the SPC, section 4.2).

Bioequivalence: Formulations used in early studies included a solution and a pilot capsule formulation, respectively. Subsequent phase I and II clinical studies used a tablet formulation (market formulation, MF). The capsule was shown to be of similar bioavailability to the Phase 2 MF tablet. Subsequent pivotal Phase 3 studies employed the FMI (final marketing image) formulation, which was also used in subsequent PK, PK/PD and mechanistic studies. Bioequivalence has been shown between the Phase 2 MF tablet and the FMI tablet.

The mean AUC in patients with Type 2 diabetes mellitus at the therapeutic dose (2160 ± 520 ng·hr/mL, N=71) was comparable to healthy subjects (2275 ± 459 ng·hr/mL, N=150).

- Distribution

The protein binding of vildagliptin to human plasma is low (9.3%). Vildagliptin distributes equally between plasma and red blood cells. The volume of distribution (Vss) is 70.7±16.1 L, indicating distribution to the extravascular tissue compartment. Drug-drug interactions linked to protein displacement are not expected.

- Elimination

Vildagliptin is eliminated mainly by metabolism and subsequent urinary excretion of metabolites. After administration of ^{14}C-vildagliptin 100 mg oral solution 85.4±4.4% of the dose was excreted in urine and 14.8±3.5% in faeces. About 33% of dose was excreted in urine as unchanged vildagliptin after intravenous administration. Mean total plasma clearance (CL) determined after intravenous administration of 25 mg was 40.6±8.97 L/hr and renal clearance (CL_R) 13.0±2.35 L/hr (> 216 ml/min). Hence, tubular secretion by active transport proteins is involved in vildagliptin elimination to some extent. The mean plasma elimination half-life ($t_{1/2}$) of vildagliptin oral administration was about 2-3 h at doses of 50-100 mg.

The metabolism of vildagliptin has been well characterised. It is extensive since only 1/3 of the dose is recovered as unchanged drug. Compound M20.7 or LAY151 is the major and inactive metabolite with plasma exposure 3-fold that of vildagliptin. Glucuronidation is only a minor pathway accounting for less than 5% of the initial dose and oxidation accounts only for 1.6% of the dose. Multiple tissues can hydrolyse vildagliptin to the major metabolite LAY151. CYP450 isoenzymes are involved in vildagliptin metabolism only to a minor extent. Hence, the potential for interactions with vildagliptin metabolism is very small. Vildagliptin is an S-enantiomer. Available data suggest that *in vivo* inter-conversion to the D-enantiomer is unlikely.

- Dose proportionality and time dependencies

Dose and time dependency
The pharmacokinetic of vildagliptin is roughly dose proportional. Data on single dose administration of 25-600 mg and multiple dose administration of 25 – 400 mg show that AUC and C_{max} increase slightly more than in proportion to dose, however, the deviation from linearity is minor with a 2.2-fold increase in AUC as the dose is increased 2-fold.

No accumulation of vildagliptin is observed following single administration per day of a dose ranging from 25 mg to 200 mg for 10 days. This suggests that the clearance is not time-dependent.

Variability
The inter-subject coefficient of variation for plasma AUC is in the range of 15-20% and in C_{max} about 25% in healthy volunteers after an oral dose. The inter-individual variability in CL/F was 42% in the population PK analysis.

Target population
The applicant has submitted sufficient documentation to demonstrate that vildagliptin pharmacokinetics are similar in diabetic patients when compared to healthy subjects.

- Special populations

The influence of renal and hepatic function, gender, age, weight and race on the pharmacokinetics of vildagliptin has been evaluated both in specific studies and in a population PK analysis. The population PK analysis identified renal function and gender as significant covariates affecting CL/F and lean body weight affecting V/F. The effects of these covariates on the pharmacokinetics were quite small and not considered clinically relevant. There were some deficiencies in the population analysis limiting the robustness of the analysis and the reliability in the results. The evaluation of PK in special populations has mainly been based on data from other studies.

Vildagliptin total and renal clearance are decreased in patients with renal impairment. Vildagliptin AUC was increased by 101%, 32%, 134% and 42%, respectively, in patients with mild, moderate and severe renal impairment, and ESRD. The relationship between renal function (as determined by creatinine clearance) and vildagliptin total clearance is variable, while vildagliptin renal clearance is better correlated to renal function. The applicant's explanation that vildagliptin is eliminated by filtration, tubular secretion and metabolism (hydrolysis) in the kidney and that GFR is a poor predictor of renal metabolism of vildagliptin is plausible.
The exposure of LAY151 increased several-fold and was closely related to renal function. $AUC_{0\text{-}24h}$ of the main metabolite (LAY151) was 1.6, 2.4, 5.4 and 6.7 - fold, respectively, in patients with mild, moderate and severe renal impairment, and ESRD. Estimates of $AUC_{0\text{-}\infty}$ suggest 1.7, 3.1, 13 and 17-fold increase in exposure respectively, in patients with mild, moderate and severe renal impairment, and ESRD. Use in moderate and severe renal impairment and ESRD is not recommended (mentioned in the SPC, section 4.2, 4.4, and 5.2).
The applicant intends to conduct additional studies to evaluate the pharmacokinetics, efficacy and safety in patients with moderate and severe renal impairment.

Hepatic impairment has a limited influence of vildagliptin PK, with no effect in mild and moderate hepatic impairment and only a 22% increase in vildagliptin AUC in patients with severe hepatic

impairment. AUC of LAY151 increased with decreased hepatic function. There was a 2-fold increase in exposure of LAY151 in severe hepatic impairment. It is agreed that no dose adjustment is needed in patient with mild or moderate liver disease but use in severe hepatic impairment is not recommended due to inexperience of use
Gender, age, weight and race had no clinically significant effects on vildagliptin exposure.
Vildagliptin pharmacokinetics has not been evaluated in children or adolescents.

- Pharmacokinetic interaction studies

The main metabolic pathway is hydrolysis accounting for about 60% of the dose. Glucuronidation is a minor elimination pathway accounting for 4.4% of the dose and oxidation accounts only for 1.6% of the dose. Multiple tissues can hydrolyse vildagliptin to the major metabolite LAY151. CYP450 isoenzymes are involved in vildagliptin metabolism only to a minor extent. Hence, the potential for interactions with vildagliptin metabolism is very small. Vildagliptin is a substrate of P-gp. However, the risk for clinically relevant interactions with inhibitors of P-gp or other transport proteins seems to be low.
In vitro studies suggested a low potential for interaction with CYP450 isoenzymes. The potential for inhibition of CYP1A2, 2D6, 2C8, 2C9, 2C19, 2E1, 3A4 and P-gp and potential for induction of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A, UGT1A1, Pgp and MRP2 has been evaluated *in vitro*. Data on potential for inhibition of CYP2B6, UGT1A1 and MRP2 are lacking and this is addressed as a post-authorisation follow-up measure.

In vivo interaction studies were conducted with other antidiabetic agents (glyburide, pioglitazone, metformin), some cardiovascular drugs (amlodipine, valsartan, ramipril, simvastatin) and the narrow therapeutic drugs digoxin and warfarin. There were no clinically relevant pharmacokinetic interactions between vildagliptin and the studied drugs. A small effect on digoxin renal clearance (19% reduction) might suggest a mild inhibition of P-glycoprotein. However, this is unlikely to be clinically relevant for digoxin or for other P-gp substrates. Simvastatin is a substrate for CYP3A4, S-warfarin is a substrate of CYP2C9 and pioglitazone is a substrate of CYP2C8. Lack of *in vivo* interaction with these substrates support the *in vitro* prediction that vildagliptin is not expected to affect the PK of substrates of CYP3A4, CYP2C9 and CYP2C8.

In conclusion, the pharmacokinetic interaction potential of vildagliptin is considered to be low.
Overall, the pharmacokinetics of vildagliptin has been well documented.

Pharmacodynamics

Pharmacodynamics was studied in 133 healthy volunteers and 185 diabetic patients.

- Mechanism of Action

Vildagliptin belongs to a new class of oral anti-diabetic drugs and acts as a selective and reversible inhibitor of DPP-4. This enzyme inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). The inhibition of DPP-4 therefore increases the levels of these hormones which is likely to be the most significant contribution to the improvement of glucose homeostasis by vildagliptin.

- Primary and Secondary Pharmacology

Mechanistic studies focused on examining each of the components of the proposed mechanism of action:

- DPP-4 inhibition (main action)
- Increase in GLP-1 and GIP levels (intended response)
- Effects on pancreatic islet cell function and on insulin resistance
- Glucose-lowering effects (on post-prandial (PPG) or fasting glucose (FPG), on glucose profiles, and endogenous glucose production)
- Post-prandial lipid-lowering effect and effect on gastric emptying

A single dose of vildagliptin in patients with T2DM lead to inhibition of DPP-4 activity in plasma by more than 90% at all doses from 10 to 400 mg. The duration of DPP-4 inhibition was dose dependent and to achieve a lasting result the DPP-4 inhibition should be >70 % which corresponds to a vildagliptin dose of >10 mg bid. PK/PD modelling and simulations showed that with 50 mg bid dosing DPP-4 inhibition is maintained at >80% over the entire dosage interval, while with 100 mg qd DPP-4 inhibition is decreased to about 60% at the end of the dosage interval. Increases of GLP-1 and GIP concentrations are the expected results of DPP-4 inhibition and studies confirmed that meal-stimulated as well as between-meal concentrations were raised after 4 week treatment with vildagliptin. The expected result of increased concentrations of incretin hormones is increased sensitivity to glucose of both the alpha- and beta-cells stimulation resulting in increased secretion of insulin and reduced glucagon secretion when glucose levels are greater than normal fasting levels. These effects were shown using several different analyses in a number of studies.

Measures of insulin resistance assessed during mechanistic studies of vildagliptin showed tendencies towards increased insulin sensitivity. An improved metabolic state associated with lower glucose levels is predicted to reduce the demand for insulin and thus by definition attenuate insulin resistance. There are few, if any evidences that vildagliptin has an effect per-se on insulin resistance. It is suggested that relief from lipotoxicity may contribute to the amelioration of insulin resistance, but this explanation must be considered as hypothetical.

Chronic treatment as well as treatment with a single dose of vildagliptin resulted in reductions of postprandial glucose. The areas under the glucose concentration time profiles during treatment with vildagliptin 25 mg and 100 mg bid were significantly lower compared to that during placebo treatment, but no effects on the glucose profiles were observed with the vildagliptin 10 mg bid.

One-hundred mg and 200 mg vildagliptin was equally effective. There were also evidences for reduced fasting and mean 24 hour glucose. It was found that vildagliptin could decrease endogenous glucose production which most likely is a result of decreased glucagon to insulin ratio concentrations. Vildagliptin reduced postprandial chylomicron TG in one study. The underlying mechanisms and clinical significance of these findings remain to be more fully explored. Vildagliptin had no effects on gastric emptying in the referred studies.

Animal studies showed that vildagliptin has an inhibitory effect on rapid inward sodium channels at high concentration. Based on human therapeutic plasma levels, the exposure ratio demonstrates a safety margin of 159-fold for the sodium channel blockage. The inhibition of cardiac sodium currents may theoretically lead to a negative inotropic effect. Myocardial contractility was not directly measured in preclinical studies, but macroscopic and microscopic investigations in the general toxicity studies did not reveal any indications of effects on myocardial contractility.
There are unanswered questions concerning secondary pharmacology as the risk of inhibition or activation of other DPP-4 substrates is unclear. These could potentially include vasoactive intestinal peptide (VIP) and neuropeptide Y (potential to alter blood pressure control), bradykinin and substance P (associated angioedema in patients with low DPP-4 activity and taking ACEIs), gastrin and growth hormone release mediators, or immune cytokines. Potential risks associated with these effects are identified in the risk management plan.

In conclusion, the pharmacodynamic actions of vildagliptin fully explain the lowering of blood glucose.

Clinical efficacy

Overview
Data establishing the clinical efficacy of vildagliptin are based on 9 core studies:
3 monotherapy placebo- and active comparator (metformin and rosiglitazone) controlled studies, 4 add-on placebo-controlled studies (add-on to metformin, pioglitazone, glimepiride and insulin) and 1 initial combination therapy with pioglitazone (Tab. 1). An additional monotherapy study (study 2384) has been finalised during the on-going MAA procedure and data from this study has been provided. Study 2384 included 354 patients and had a design identical to study 2301.

Tab.1: Summary of key controlled trials (monotherapy and add-on or initial combination therapy)

Study No.	Study objective, population	Randomized patients	Duration	Dosage	Primary efficacy
Monotherapy study (placebo-controlled)					
2301 (mono)	Multiple dose efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5% - 10%)	632	24 wks	vilda 50 mg qd, 50 mg bid vilda 100 mg qd placebo	change in HbA_{1c}
2384 (mono)	Multiple dose efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5% - 10%)	354	24 wks	vilda 50 mg qd, 50 mg bid vilda 100 mg qd placebo	change in HbA_{1c}
Monotherapy studies (active-controlled)					
2309 (mono)	Efficacy/safety in drug-naïve T2DM patients (HbA_{1c} 7.5% - 11%)	780	52 wks	vilda 50 mg bid metformin 1000 mg bid	change in HbA_{1c}
2327 (mono)	Efficacy/safety in drug-naïve T2DM patients (HbA_{1c} 7.5% - 11%)	786	24 wks	vilda 50 mg bid rosiglitazone 8 mg qd	change in HbA_{1c}
Add-on combination therapy studies (placebo-controlled)					
2303 (add-on met.)	Efficacy/safety in T2DM patients inadequately controlled by metformin (HbA_{1c} 7.5% – 11%)	544	24 wks	vilda 50 mg qd + metformin vilda 50 mg bid + metformin placebo + metformin	change in HbA_{1c}
2304 (add-on pio.)	Efficacy/safety in T2DM patients poorly controlled by a thiazolidinedione (HbA_{1c} 7.5% – 11%)	463	24 wks	vilda 50 mg qd + pioglitazone vilda 50 mg bid + pioglitazone placebo + pioglitazone	change in HbA_{1c}
2305 (add-on glim.)	Efficacy/safety in T2DM patients inadequately controlled by sulfonylurea (HbA_{1c} 7.5% - 11%)	515	24 wks	vilda 50 mg qd + glimepiride vilda 50 mg bid + glimepiride placebo + glimepiride	change in HbA_{1c}
2311 (add-on ins.)	Efficacy/safety in T2DM patients treated with insulin (HbA_{1c} 7.5% - 11%)	296	24 wks	vilda 50 mg bid + insulin placebo + insulin	change in HbA_{1c}
Initial combination therapy studies (active-controlled)					
2355 (pio. comb.)	Efficacy/safety in treatment-naïve T2DM patients not controlled by diet & exercise (HbA_{1c} 7.5% - 11%)	607	24 wks	vilda 50 mg qd + pio. 15 mg qd vilda 100 mg qd + pio. 30 mg qd vilda 100 mg qd + placebo placebo + pio. 30 mg qd	change in HbA_{1c}

Dose-finding studies

The doses of vildagliptin chosen for the phase III studies were based on 3 pharmacodynamic studies and 3 short-term monotherapy and add-on combination studies. In these studies there were indications that the doses 50 mg qd and 50 mg bid were equally effective. According to results from a meta-analysis, there is an increase in the placebo-subtracted effect of vildagliptin when the dose is increased from 50 mg to 100 mg. This increase is greater in patients with baseline HbA1c of 9.5% (-0.45%) than in those with baseline HbA1C of 8.5% (-0.28%). Although this difference is small, it was thus considered justified using 100mg instead of 50mg. The reductions in HbA_{1c} observed with the sulfonylurea combination are not meaningfully greater for 100 mg daily versus 50 mg daily and therefore a dose of 50 mg once daily is proposed for this indication.

Monotherapy studies

All trials followed the same general randomized, double-blind, parallel-group, multicenter study design, varying only in duration of the run-in and treatment period.

METHODS

Study Participants
Inclusion criteria were patients with T2DM, with no or only minimal prior treatment, aged 18-80 years (18-78 in study 2309), a BMI between 22 and 45 kg/m2, and an HbA1c of 7.5-11% (7.5-10% in study 2301).

Endpoints
The primary efficacy parameter was HbA_{1c}. Some of the secondary efficacy parameters included were: FPG, fasting lipids, body weight, some parameters indicative of beta-cell function and insulin resistance, responder rates: (Endpoint $HbA_{1c} < 7\% / \leq 6.5\%$. HbA_{1c} absolute reduction from baseline at endpoint $\geq 1\%$, / $\geq 0.7\%$, / $\geq 0.5\%$).

Statistical methods
The statistical methods used, including the approach to deal with the baseline HbA1c assay issue, were considered to be adequate. For non-inferiority trials, a pre-specified non-inferiority limit of 0.4% was used.

RESULTS

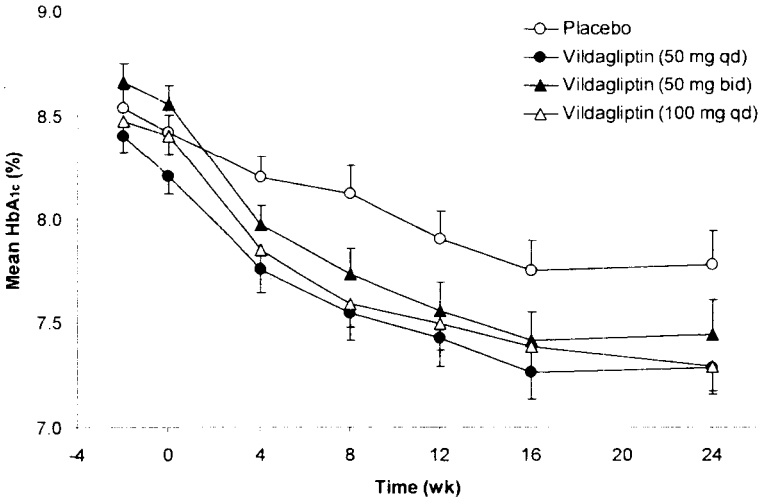
The percentages of completers were generally high (68.5-86.9%) in all study groups.

Baseline data
Mean baseline HbA1c was between 8.2 and 8.7% (having the lowest values in study 2301 compared to the other studies). Mean BMI was between 31.9 and 32.9 kg/m^2.

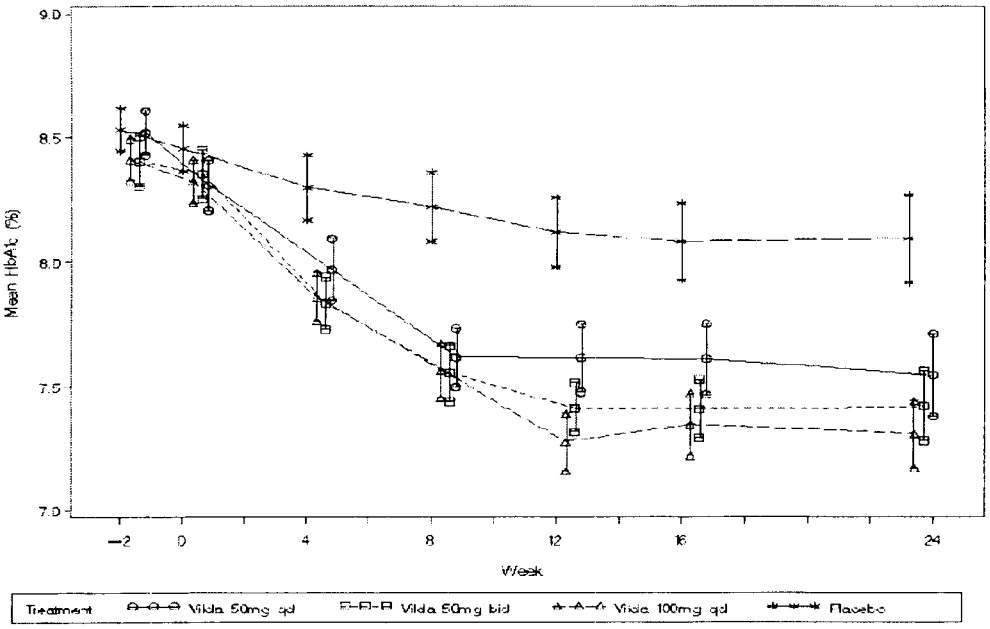
Outcomes
The 24-week data show reductions from baseline in HbA1c with vildagliptin in all studies, ranging from - 0.8% to - 1.1% (Fig.1, Tab. 2). In study 2301 (that included 39.2 % of patients diagnosed for < 3months), a considerable HbA1c reduction (-0.3%) was seen in the placebo group. In the group of patients that was diagnosed for ≥ 3 months, the placebo group showed little change in HbA1c (+0.2%).
Vildagliptin 50 mg bid was demonstrated to be non-inferior to rosiglitazone 8 mg qd in the reduction of HbA_{1c} at endpoint. At 24 weeks, the reduction in HbA_{1c} with vildagliptin 50 mg bid did not reach non-inferiority compared to metformin 1000 mg bid. The results in the full ITT population (if different from primary ITT population) did not differ from the results in the primary efficacy ITT population in any clinically significant manner.

Fig. 1: Change of mean HbA1c over 24 weeks in monotherapy studies

Study 2301



Study 2384



Study 2309