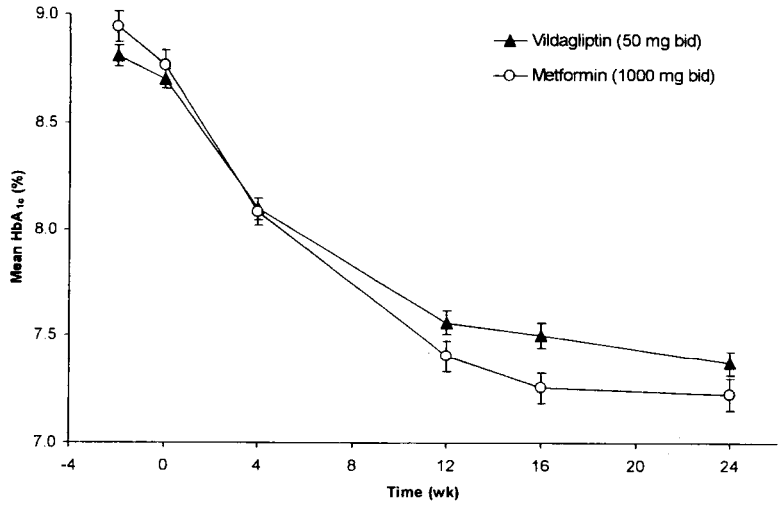
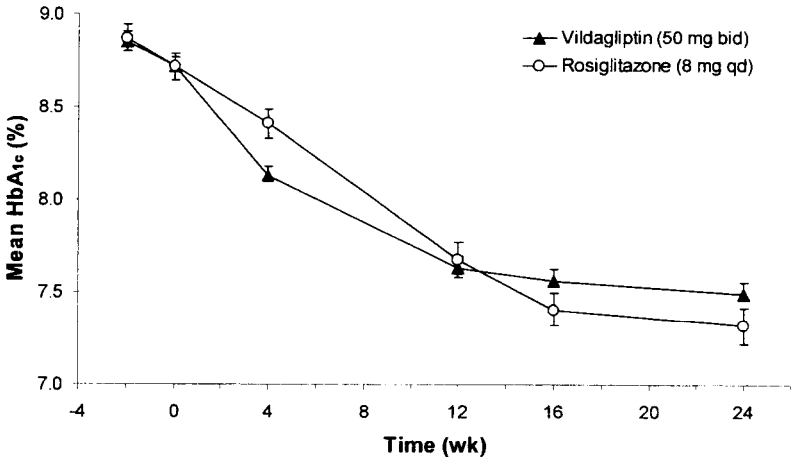


Study 2327



Tab. 2: Responder analyses in the monotherapy studies

	≥ 0.7% HbA_{1c} reduction			≥ 1.0% HbA_{1c} reduction			HbA_{1c} < 7%		
	Resp. rate %	**Diff. to control**	**p-value**	**Resp. rate %**	**Diff. to control**	**p-value**	**Resp. rate %**	**Diff. to control**	**p-value**
Primary efficacy ITT population (*ITT population for 1 study*)									
Study 2301 (24 weeks placebo-controlled monotherapy)									
vilda 50 mg qd	59.6%	18.1%	0.011	47.1%	9.9%	0.160	42.7%	17.2%	0.011
vilda 50 mg bid	65.6%	24.1%	0.001	54.4%	17.2%	0.019	39.3%	13.8%	0.046
vilda 100 mg qd	66.3%	24.8%	<0.001	56.5%	19.3%	0.008	40.2%	14.7%	0.033
placebo	41.5%	-	-	37.2%	-	-	25.5%	-	-
Study 2384 (24 weeks placebo-controlled monotherapy)									

	≥ 0.7% HbA_{1c} reduction			≥ 1.0% HbA_{1c} reduction			HbA_{1c} < 7%		
	Resp. rate %	**Diff. to control**	**p-value**	**Resp. rate %**	**Diff. to control**	**p-value**	**Resp. rate %**	**Diff. to control**	**p-value**
vilda 50 mg qd	44.0%	9.9%	0.181	28.6%	4.7%	0.483	25.3%	11.7%	0.053
vilda 50 mg bid	54.4%	20.3%	0.008	45.6%	21.7%	0.003	30.4%	16.8%	0.009
vilda 100 mg qd	57.3%	23.2%	0.002	50.6%	26.7%	<0.001	39.1%	25.5%	<0.001
Placebo	34.1%	-	-	23.9%	-	-	13.6%	-	-
Study 2309[§] (24 week data (not endpoint), active-controlled monotherapy)									
vilda 50 mg bid	65.3%	-8.2%	0.023	52.4%	-10.7%	0.005	37.6%	-8.6%	0.025
met 1g bid	73.5%	-	-	63.1%	-	-	46.2%	-	-
Study 2327 (24 weeks active-controlled monotherapy)									
vilda 50 mg bid	65.6%	-7.9%	0.032	54.5%	-6.8%	0.082	35.7%	-9.4%	0.016
rosi 8 mg qd	73.5%	-	-	61.3%	-	-	45.1%	-	-

Ancillary Analyses
Fasting plasma glucose: There were reductions from baseline in FPG with vildagliptin in all studies, ranging from - 0.8 to - 1.3 mmol/L.
Fasting lipids: Compared to placebo and metformin, there were modest improvements that were not generally statistically significant.
Body weight: Changes in body weight from baseline with vildagliptin treatment ranged from - 1.80 kg to - 0.02 kg across studies and doses. No relevant changes were found compared to placebo.

Summary of the monotherapy studies
The monotherapy studies included patients with characteristic baseline data for T2DM with a rather short duration of the disease. Vildagliptin therapy for 24 week resulted in a reduction of HbA1c (~1%) (Fig. 1) and FPG (~1 mmol/l). Vildagliptin was statistically inferior to metformin 1000 mg bid and may be clinically, although not statistically, inferior to rosiglitazone 8 mg qd (CI for difference between treatments -0.01 to 0.39, non-inferiority margin 0.40, ITT population). For HbA1c results in the PP population, the upper limit of the confidence interval of the difference between vildagliptin and rosiglitazone exceeded the pre-defined non-inferiority margin of 0.4%. At present there are no data comparing vildagliptin and SU,this is addressed as a post authorisation follow-up measure.
Vildagliptin treatment was largely lipid and weight neutral. There were indications of improvements in markers of beta cell function including HOMA-b (Homeostasis Model Assessment –b), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. However, in the phase III studies the effects on beta-cell function were not consistent across studies and depended on the parameters tested.

Add-on combination therapy 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
Patients with T2DM whose glycaemic control was not achieved despite treatment were treated for ≥ 3 months with anti-diabetic drugs and had not achieved adequate glycaemic control. The initial

combination therapy study (2355) was performed in drug-naive patients with T2DM (with no or only minimal prior treatment).
Patients were 18-80 years old (18-78 in study 2303), had a BMI between 22 and 45 kg/m2 and an HbA1c of 7.5-11%.
Further inclusion criteria:
Study 2303: Patients on a stable dose of at least 1500 mg metformin daily for a minimum of 4 weeks prior to first visit 1. For a maximum tolerated dose of metformin < 2000 mg daily, either an attempt to reach higher doses in the past was demonstrated or a start with a higher dose at the beginning of the trial was performed. The dose of metformin used at randomization had to be maintained unchanged throughout the trial.
Study 2304: Patients on a TZD for at least 3 months demonstrating a therapeutic response by a decrease in HbA_{1c} of ≥0.5% or a decrease in FPG of ≥30 mg/dL. Eligible patients were placed on pioglitazone 45 mg qd and randomized 4 weeks later. A 12-week pre-study period was offered to eligible patients in which they received open-label pioglitazone at a minimum dose of 30 mg.
Study 2305: Patients on a sulfonylurea for at least 3 months and at a stable dose (at least 7.5 mg glyburide qd, 7.5 mg glipizide qd, or 2 mg glimepiride qd) for a minimum of four weeks prior to first visit. Prior sulfonylurea monotherapy was switched to glimepiride 4 mg qd and could be reduced to 2 mg qd according to specific guidelines. Patients were offered a pre-study period in which they could receive open-label glimepiride 2 mg to 4 mg qd. Patients previously treated with low dose sulfonylurea monotherapy were offered a 4-week pre-study period. Patients previously receiving combination therapy with a sulfonylurea and metformin were offered an 8-week pre-study period.
Study 2311: Patients treated with insulin for at least 3 months, and at least 30 Units of insulin per day for a minimum of 4 weeks prior to first visit. The insulin dose could be reduced for safety reasons. Additionally, the daily dose of insulin could be reduced as clinically indicated but upward adjustments should not exceed 25% of the baseline insulin dose.

No studies comparing vildagliptin add-on to metformin with other add-on therapies were included in the application.

Overall, patients in study 2303 and 2305 were representative of the target population. The requirements for metformin dose was considered to be adequate. The required glimepiride dose was considered as rather low and therefore some concerns remained about whether these patients represent true SU failures.
The design of study 2355 involved initial combination therapy, which is not in accordance with current therapeutic guidelines, and thus was considered as only supportive.

Endpoints
The primary efficacy parameter was HbA_{1c}. The secondary efficacy parameters were in general the same as in the monotherapy studies.

RESULTS

The proportion of patients completing the studies were considered as rather high. As expected the proportions of patients withdrawing because of unsatisfactory therapeutic effect were higher in the placebo compared to the vildagliptin groups.

Baseline data
The mean baseline HbA1c of patients across studies and groups was 8.3% - 8.7%, with mean baseline FPG values ranging from 9.0 to10.9 mmol/L. The mean duration of diabetes was 5 to 8 years in the 3 studies conducted as on add-on to oral agents, and longer in the add-on to insulin study (14 to 15 years).Overall, baseline characteristics were well matched between treatment groups within the studies and were typical for T2DM populations.

Outcomes

Tab. 3: Change in HbA_{1c} from baseline at Week 24

	N	Baseline HbA_{1c} (%) mean (SE)	Change in HbA_{1c} (%) adj. mean (SE)	Difference to comparator mean (SE)	95% CI	p-value
Primary efficacy ITT population *(ITT population for 1 study)*						
Study 2303 (24 weeks, placebo-controlled add-on combination)						
vilda 50 mg qd + met	143	8.38 (0.08)	-0.51 (0.10)	-0.73 (0.14)	(-1.00, -0.47)	<0.001 *
vilda 50 mg bid + met	143	8.38 (0.09)	-0.88 (0.10)	-1.10 (0.14)	(-1.37, -0.84)	<0.001 *
placebo + met	130	8.30 (0.08)	+0.23 (0.10)			
Study 2304 (24 weeks, placebo-controlled add-on combination)						
vilda 50 mg qd + pio	124	8.62 (0.09)	-0.76 (0.10)	-0.46 (0.14)	(-0.73, -0.19)	0.001*
vilda 50 mg bid + pio	136	8.69 (0.11)	-0.97 (0.10)	-0.67 (0.14)	(-0.94, -0.40)	<0.001 *
placebo + pio	138	8.72 (0.10)	-0.30 (0.10)			
Study 2305 (24 weeks, placebo-controlled add-on combination)						
vilda 50 mg qd + glim	132	8.53 (0.08)	-0.58 (0.10)	-0.64 (0.13)	(-0.90, -0.39)	<0.001 *
vilda 50 mg bid + glim	132	8.55 (0.09)	-0.63 (0.09)	-0.70 (0.13)	(-0.95, -0.44)	<0.001 *
placebo + glim	144	8.53 (0.08)	+0.07 (0.09)			
Study 2311 (24 weeks, placebo-controlled add-on combination)						
vilda 50 mg bid + insulin	125	8.52 (0.09)	-0.51 (0.09)	-0.27 (0.12)	(-0.51, -0.04)	0.022
placebo + insulin	131	8.54 (0.09)	-0.24 (0.09)			
Study 2355[§] (24 weeks, active-controlled initial combination)						
vilda 50 mg qd + pio 15	139	8.76 (0.08)	-1.67 (0.09)	-0.26 [b] (0.13)	(-0.51,-0.01)	0.039
vilda 100 mg qd + pio 30	146	8.77 (0.09)	-1.93 (0.09)	-0.55 [a] (0.13)	(-0.80,-0.29)	<0.001
vilda 100 mg qd + placebo	150	8.61 (0.08)	-1.08 (0.09)			
placebo + pio 30	157	8.69 (0.08)	-1.39 (0.09)			

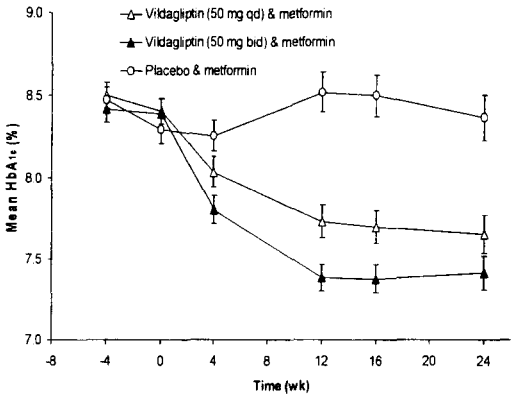
[a] = vs. placebo + pio 30 mg qd (1° object.), vs. vilda 100 mg qd + placebo (2° object.), diff was -0.82, $p < 0.001$

[b] = vs. placebo + pio 30 mg qd (2° object.) (using separate ANCOVA model with slightly diff. value of adj. means)

* statistically significant at 5% level according to the Hochberg step-up procedure

Fig. 2: Change of mean HbA1c over 24 weeks in add-on combination studies

Study 2303:



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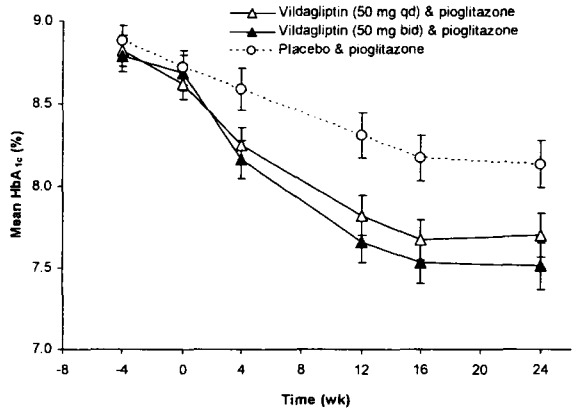
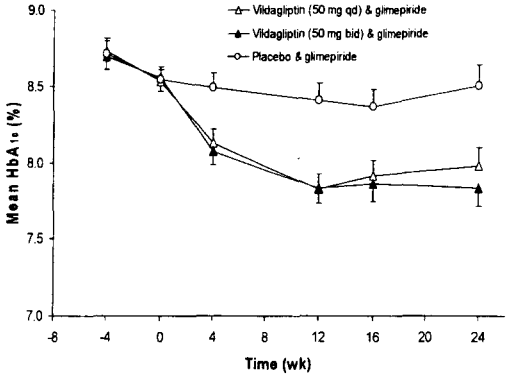
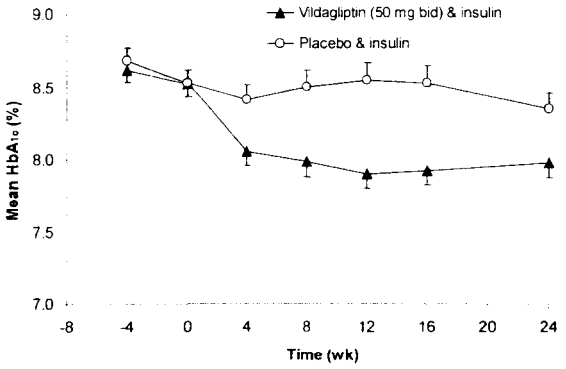


Study 2305:



Study 2311:



The addition of vildagliptin resulted in statistically significant decreases in HbA_{1c} (Tab. 3, Fig. 2). Efficacy was greater with vildagliptin 50 mg bid compared to 50 mg qd for the combinations with metformin and pioglitazone. However, in the population consisting of patients inadequately controlled on sulfonylurea therapy, the dose-dependency was less evident. The 50 mg qd dose of vildagliptin was not tested in combination with insulin.
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.

Tab. 4: Responder analyses for the add-on combination studies

	≥ 0.7% HbA_{1c} reduction			≥ 1.0% HbA_{1c} reduction			HbA_{1c} < 7%		
	Resp. rate %	**Diff. to control**	**p-value**	**Resp. rate %**	**Diff. to control**	**p-value**	**Resp. rate %**	**Diff. to control**	**p-value**
Primary efficacy ITT population (*ITT population for 1 study*)									
Study 2303 (24 weeks, placebo-controlled add-on combination)									
vilda 50 qd + met	46.2%	26.2%	<0.001	30.8 %	17.7%	<0.001	27.0%	17.6 %	<0.001
vilda 50 bid + met	60.1%	40.1%	<0.001	44.1 %	31.0%	<0.001	35.5%	26.1 %	<0.001
placebo + met	20.0%			13.1 %			9.4%		
Study 2304 (24 weeks, placebo-controlled add-on combination)									
vilda 50 qd + pio	54.0%	15.6%	0.011	47.6 %	19.3%	0.001	28.7%	13.9 %	0.007
vilda 50 bid + pio	68.4%	30.0%	<0.001	56.6 %	28.3%	<0.001	36.4%	21.6 %	<0.001
placebo + pio	38.4%			28.3 %			14.8 %		
Study 2305 (24 weeks, placebo-controlled add-on combination)									
vilda 50 qd + glim	47.0%	27.6%	<0.001	33.3 %	21.5%	<0.001	21.2%	9.2%	0.039
vilda 50 bid + glim	50.8%	31.4%	<0.001	40.2 %	28.4%	<0.001	24.8%	12.8 %	0.006
placebo + glim	19.4%			11.8 %			12.0%		
Study 2311 (24 weeks, placebo-controlled add-on combination)									
vilda 50 bid + ins	41.6%	11.8%	0.048	26.4 %	8.1%	0.120	16.5%	6.5%	0.126
placebo + ins	29.8%			18.3 %			10.0%		
Study 2355[§] (24 weeks, active-controlled initial combination)									
vilda 50 qd + pio 15	78.4%	2.6%	0.593[a]	73.4 %	6.5%	0.223[a]	53.6%	10.7 %	0.067[a]
vilda 100 qd + pio 30	88.4%	12.6%	0.005[a]	79.5 %	12.6%	0.014[a]	65.0%	22.1 %	<0.001[a]
vilda 100 qd+placebo	68.7%			59.3 %			42.5%		
placebo + pio 30	75.8%			66.9 %			42.9%		

[§] the primary efficacy ITT and ITT populations are identical (no HbA_{1c} assay issue)
[a] = compared to placebo + pio 30 mg qd

Ancillary Analyses
Clinically significant reductions of FPG were achieved with the 50 mg bid dosing.

As in the monotherapy studies vildagliptin was largely lipid neutral.
When added to metformin, vildagliptin dose-dependently increased weight up to 1.24 kg on average compared to metformin alone, but the combined effect of metformin and vildagliptin on weight compared to baseline values was largely weight-neutral. Similarly, when vildagliptin at 50 mg per day was added to glimepiride, weight increased only slightly (+.31 kg) compared to monotherapy, and the combined effect of a SU and vildagliptin on weight compared to baseline values is considered to be weight-neutral. Vildagliptin in the combination with pioglitazone resulted in a dose-dependent increase in weight up to 2.69 kg compared to the effect of pioglitazone alone (1.41 kg)

Summary of the add-on combination studies
The add-on therapy studies included patients with inadequate glucose control on monotherapy with metformin, SU, TZD or insulin. Add-on therapy with vildagliptin resulted in clinically and statistically significant reductions of HbA1c (mean reductions from baseline of 0.51 – 0.97 % on the 50 mg bid dose) and FPG (mean reductions of 0.44-1.13 mmol/l) compared to placebo in all studies. The HbA1c reduction in study 2305 (combination with glimepiride) was less pronounced compared to other add-on studies. However, the reduction in HbA1c was significantly larger compared to placebo and can be considered as clinically relevant.
Vildagliptin was largely weight neutral in combination with metformin and SU, but the combination with pioglitazone resulted in a dose-dependent increase in weight. No comparisons have been made with other often used add-on alternatives such as metformin plus SU, for which efficacy and safety is well documented. This is addressed as a post authorisation follow-up measure.

The addition of vildagliptin to insulin therapy resulted in a larger reduction in HbA1c compared to placebo. However, the CHMP had concerns, whether a difference of 0.27% would be clinically meaningful. Even though the results in the elderly population were more pronounced (-0.70%), the number of elderly patients was too small to draw reliable conclusions, and further mechanistic and clinical studies are needed to support these findings. The applicant therefore withdrew the indication for the combination with insulin, as claimed initially, during the evaluation of the MAA.

Special Populations

Two-hundred thirty eight patients older than 65 and 41 patients older than 75 years have been treated with the recommended dose of vildagliptin as monotherapy in the primary ITT population. The reduction in HbA1c was somewhat smaller in patients older than 75 years, but the number of patients was limited.
Non-obese patients responded better to vildagliptin than obese patients. This difference in efficacy may, at least partly, be explained by increased insulin resistance in obese subjects and may not be of clinical relevance.
The efficacy in male patients was larger compared to that in females and the efficacy in black people was smaller compared to that in Caucasians and Hispanics. There is no evident explanation to these differences in efficacy. However, a mean difference of 0.2% between men and women may not be of clinical relevance. Furthermore, no clinically relevant differences in the pharmacokinetics of vildagliptin have been observed between male and female healthy subjects or due to ethnicity.

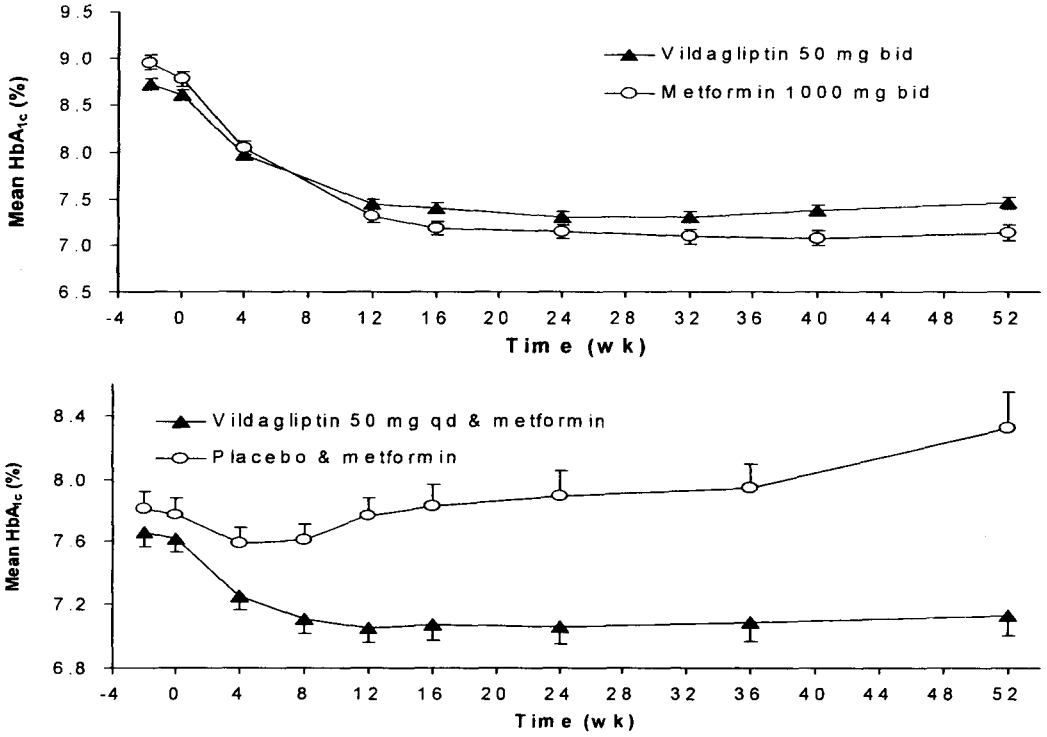
The efficacy of vildagliptin in patients with mild renal insufficiency is largely similar to that in patients with normal renal function. The limited number of subjects with moderate renal impairment that were treated with vildagliptin 50 mg bid had similar reduction in HbA1c (-0.90%) compared to subjects with normal or mild renal insufficiency. More data is needed before vildagliptin can be recommended in patients with moderate renal insufficiency.

Vildagliptin subgroups of patients with pre-existing CHF also had a decrease in HbA1c at the study endpoint. However, caution has to be exercised in interpreting efficacy in this subgroup due to the low patient numbers.

Long-term Efficacy data

Concerning long-term efficacy data for vildagliptin, results have been provided from one 52 week study (metformin-controlled, monotherapy, study 2309) and one 40 week extension study following a 12 week core study (add-on therapy to metformin, study 2204), both designed to show efficacy over 1 year (Fig. 3). The proportion of completers after 52 weeks in the monotherapy study was 72% of 780 randomised patients and thus this study provide 1 year efficacy data for vildagliptin as monotherapy in a substantial group of patients. The results achieved after 24 weeks in this study were less pronounced at the week 52 follow-up, but still clinically relevant (mean reduction of HbA1c = 0.96%).

Fig. 3 Mean HbA1c over time in long-term controlled studies (1 year) (monotherapy and add-on to metformin)



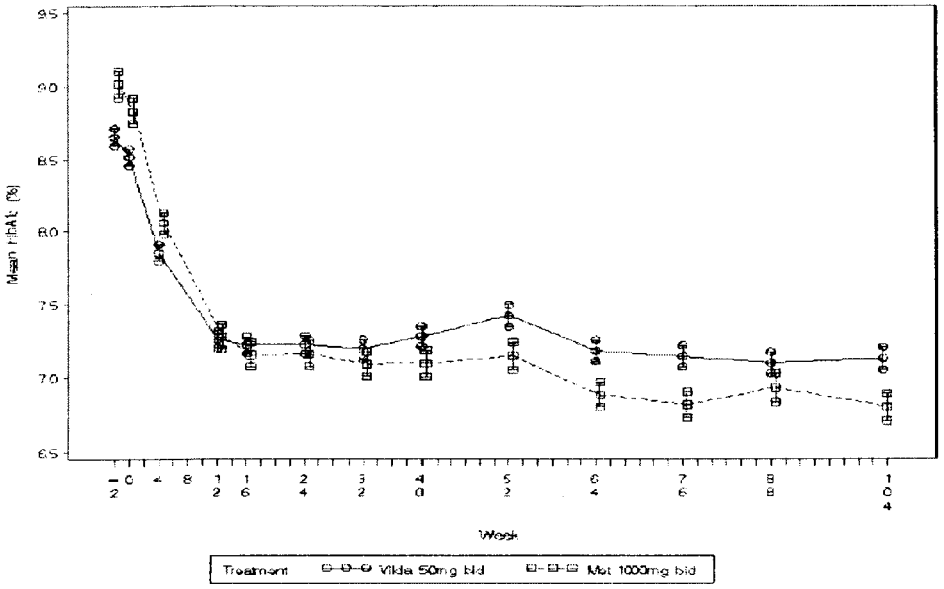
During the MAA procedure, data has been provided from a 1 year extension of the 52 week monotherapy study (2309 E1). At 2 years, a 1.0% reduction in HbA_{1c} was observed in the vildagliptin 50 mg bid treatment group compared to a 1.5% reduction in the metformin 1000 mg bid treatment group (Tab. 2, Fig. 4). However, the durability of the efficacy of vildagliptin will be formally assessed in an ongoing appropriately powered time to failure analysis intended to assess sustainability of glycaemic control.

Tab. 5: Change in HbA1c (%) from baseline to endpoint (ITT and extension ITT populations; LOCF) after 1 year (2309) and after an additional 1 year extension (2309E1)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Met 1000 mg bid (SE)	95% CI
2309					
vilda 50 mg bid	511	8.71 (0.05)	-0.96 (0.07)	0.48 (0.10)	(0.28, 0.67)
met 1000 mg bid	249	8.75 (0.07)	-1.44 (0.09)		
2309E1					
Vilda 50 mg bid	243	8.43 (0.06)	-0.98(0.09)	0.51 (0.13)	(0.25, 0.78)
Met 1000 mg bid	136	8.78 (0.09)	-1.49(0.12)		

Endpoint is the final available post-randomization assessment up to the last regular scheduled visit (2309) or the last available post-Week 52 assessment before or at the start of rescue medication or up to the last regular scheduled visit for patients not on rescue medication (2309E1).
n is the number of patients with observations at both core baseline and core study endpoint (2309) or at both core baseline and extension study endpoint (2309E1).

Fig. 4: Mean HbA1c over time in long-term controlled study over 2 years (monotherapy, compared to metformin, Study 2309E1)



Long-term efficacy data for vildagliptin as add-on therapy is more limited. Only 32 patients treated with vildagliptin plus metformin completed the extension study and these patients were not treated with the recommended dose 50 mg bid. Long-term extension studies are on-going and the Applicant has committed to provide results as FUM.

Clinical safety

- Patient exposure

Safety data was obtained from 3784 patients with T2DM in phase II or III trials of ≥ 12 weeks treatment duration, with 2264 patients receiving vildagliptin as monotherapy and 1520 patients receiving vildagliptin in combination with another medicinal product.The target dose of 100 mg vildagliptin was given to 2682 patients. 274 patients have been exposed to vildagliptin for ≥52 weeks as monotherapy which is considered as sufficient according to guidelines.

Overall, the ratios of completers were sufficiently high throughout studies. The number of patients discontinuing due to adverse events did not differ between vildagliptin and placebo groups except for an increased proportion in the vildagliptin+insulin group compared to placebo+insulin group due to gastrointestinal side effects.

- Adverse events

Adverse events in monotherapy studies
The overall incidences of AEs in the three vildagliptin dosing groups in the monotherapy studies were largely comparable to those in the placebo groups. Adverse drug reactions reported at an increased frequency compared to placebo included dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia.
Severe events in the vildagliptin 50 mg bid group were driven by infections and infestations (influenza, bronchitis, nasopharyngitis), occurring in 1.4% of patients versus 0.3% on placebo, and nervous system disorders (0.9% of patients) versus 0.6% on placebo.

Adverse events in combination studies
Adverse drug reactions reported in patients who received Galvus 100 mg in combination with metformin (n=208) included tremor, headache, dizziness, fatigue and nausea.
Tremor, headache, dizziness, asthenia, nasopharyngitis and constipation were more common when glimepiride was combined with vildagliptin (n=170) compared to placebo.
When vildagliptin 100mg was combined with pioglitazone 45 mg daily (n=158), the frequency of peripheral oedema was higher compared to pioglitazone plus placebo (7.0% versus 2.5%), and the absolute weight increases with placebo, Galvus 50 mg daily and Galvus100 mg daily were 1.4, 1.5 and 2.7 kg, respectively. Headache and asthenia were also more common than with placebo. The incidence of oedema when vildagliptin 100 mg was combined with pioglitazone 30 mg daily as dual initial therapy in drug naïve patients was however less than for pioglitazone alone (6.1% vs 9.3%).
The applicant has commited to further characterize the cardiac safety of the combination of vildagliptin and TZD as a post authorisation follow-up measure.

In the clinical pharmacology studies the adverse events did not differ from those seen in the clinical trials. With high doses of vildagliptin (400 mg and 600 mg), peripheral oedema, pain in extremities, myalgia and paresthesia emerged as dose-dependent AEs.

Angioedema
Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. These cases appear more frequent when vildagliptin is administered in combination with an ACE I. Angioedema will be followed as part of targeted post-marketing activities. Information concerning angioedema is included in section 4.8 of the SPC.

Cardiac adverse events
Since early studies had shown sudden deaths in dogs at high doses of vildagliptin, and a later telemetry study in dogs had shown an effect on cardiac conduction at peak concentrations of high doses of vildagliptin, special focus was placed on the potential for conduction disturbances in human subjects. ECG measurements during exposure to high doses in healthy volunteers showed no effect of vildagliptin on QT/QTc or QRS intervals with doses from 100mg daily up to 400mg. In the clinical studies, there was a higher incidence of first degree AV block in patients treated with vildagliptin as defined by the proportion of patients with PR >200 msec. A majority of the patients with first degree AV block had only moderately increased PR lengths. At this stage the association between vildagliptin and first degree AV block can be neither confirmed nor excluded. Conduction disorder and cardiac events of hypoxic and/or ischemic origin will be evaluated as part of targeted post-marketing activities.

Hypoglycaemia
In the monotherapy studies the number of patients with hypoglycaemic events was low in all treatment groups. However, the proportion of patients who reported hypoglycaemic events in the vildagliptin

groups was higher with vildagliptin monotherapy (0.4% on vildagliptin 100mg daily) as compared to placebo (0%), but similar compared to some active controls (0.4% in both the metformin and rosiglitazone groups and 0% in the pioglitazone group)

With the exception of vildagliptin plus insulin combination, this was also the case with vildagliptin add-on therapy In particular, the proportion of hypoglycaemic events in the vildagliptin plus glimepiride group was higher in a dose-dependent manner compared to placebo plus glimepiride. Because there was also no additional efficacy demonstrated for vildagliptin 100mg daily in combination with glimepiride, a limitation of the dose of vildagliptin to 50 mg once daily is therefore recommended for this indication, as described in the SPC.

No severe hypoglycaemic events were reported on vildagliptin.

Skin disorders
Due to the findings of skin lesions in monkeys, the Applicant has performed a review of reported skin disorders in the clinical study program for vildagliptin. Overall, the cases were rather few and of mild severity. The most frequently reported disorders were those of rash and rash-related events. However, rash-related disorders were not similar to the skin lesions observed in the monkey toxicity study. Adverse events such as skin lesions, blister and skin ulcer could potentially provide the closest clinical correlation to the types of lesions observed in the monkey study. The incidence rates of selected skin-related events (blister, skin lesion, exfoliation, ulcer and diabetic foot complications) observed for vildagliptin 50mg QD and 100mg daily were similar to the placebo incidence. There did not seem to be a relationship between the vildagliptin dose and skin events.
To alert prescribers to notice potential skin disorders and to provide information concerning the limited experience in patients with skin complications, a warning has been included in SPC section 4.4. Skin events will be part of targeted post-marketing activities

Other potential risks
Potential risks associated with vildagliptin due to hypothetical mechanistic considerations or non clinical findings include infections, muscle events, gastrointestinal haemorrhage and severe hypoglycaemia. These potential risks will be monitored in the PSURs and/ or in the planned post authorisation safety study (angioedema, foot ulcer, hepatic toxicity, serious infections, hypoxic/ischemic cardiac events, peripheral oedema).

- Serious adverse events and deaths

SAE were uncommon in all studies and there was no clustering of specific advents associated with vildagliptin treatment. In total, including ongoing studies, there were 50 SAEs with an outcome of death. Of these cases, 26 (6 female and 20 male) patients were exposed to vildagliptin mono- or add-on combination therapy. All 26 of these cases were considered not suspected to be related to study drug. The causes of death included a variety of different conditions and were largely similar in patients treated with vildagliptin and in patients in other treatment groups.

- Safety in special populations

Gender:
In both monotherapy and add-on studies the overall AE rates in females were higher than in males which was not the case in the placebo groups. There is no evident explanation to this difference. The applicant has committed to monitor this as part as routine pharmacovigilance acivities.

Elderly:
Elderly patients, in particular those with moderate renal dysfunction, have a notably higher incidence of AEs relative to cardiac disorders and eye disorders although caution is needed in interpretation of these difference due to the low patient numbers in this renal category. Safety data regarding this population will be monitored specifically.

Renal Insufficiency:
The number of subjects with MDRD estimated renal impairment for the monotherapy and add-on therapy datasets was 1870 patients. Of these 198 vildagliptin-treated patients had moderate renal impairment in both datasets combined. In the monotherapy studies there were indications of an increased incidence of overall AE and of gastrointestinal and nervous system disorders in patients with moderate renal insufficiency. Concerning the add-on studies, there were too few patients with moderate renal impairment in each treatment group for an adequate evaluation of safety. However, the overall incidence of AE in patients with moderate renal impairment tended to be higher when vildagliptin was combined with metformin and pioglitazone compared to placebo. Until more data in this patient group is available, vildagliptin should not be recommended to patients with moderate and severe renal impairment (mentioned in the SPC in section 4.2 as well as 4.4). The Applicant will, as a FUM, provide additional information in patients with moderate and severe renal failure.

Congestive Heart Failure:
A limitation of the vildagliptin database is that cardiac function was not proactively assessed at baseline; therefore the patients were only categorized as having CHF if they volunteered this information as part of the baseline past medical history. Furthermore, patients with heart failure NYHA III-IV were largely excluded from the clinical studies. Upon the concerns expressed by the CHMP, the applicant has identified 43 patients with a CHF history treated with vildagliptin in the current monotherapy and add-on datasets. In addition, cardiovascular safety data from additional 19 patients with CHF treated with vildagliptin 100 mg daily from an ongoing study has become available. In addition, a population with possible systolic dysfunction (CHF history at baseline, myocardial infarction history, cardiac bypass surgery history, ECG finding indicative of myocardial infarction, treatment with either digoxin/digitoxin, treatment with a combination of a renin-angiotension-system blocking agent and a loop diuretic) and high cardiac risk (criteria as above and coronary artery disease history or QRS > 120 msec at baseline) has been identified (n=629 on vildagliptin 100 mg daily). Even though the incidence of cardiac adverse events were rather low, there was no apparently different pattern of cardiac AE in this group of patients compared to patients treated with other comparators. Although the data in patients with CHF class NYHA I-II patients is therefore limited (currently N=62), such patients were included in the clinical trials and their safety profile was no different from that in patients without CHF. In the SPC, section 4.2, caution is therefore advised for the use in patients with CHF stage NYHA class I-II, and the use is not recommended at all for NYHA class III-IV. Further information in this population will be generated as part of the post-authorisation follow-up measures. The applicant proposed initially the use of vildagliptin in patients, in whom metformin could not be used (e.g. because of intolerance or contraindications). Of concern to the CHMP with regard to this indication was the fact, that contraindications for metformin largely overlap with restrictions of usage for vildagliptin, i.e. impaired cardiac function (class III-IV) and moderate to severe renal function. This would have limited the usage of vildagliptin with regard to this second-line monotherapy indication largely to patients intolerant to metformin, representing presumably a small subgroup. The applicant withdrew this part of the proposed indication on 5.July 2007, upon the concerns by the CHMP.

- Laboratory findings

A small numerical imbalance of reports of generally asymptomatic elevated transaminases was reported in patients treated with vildagliptin 100 mg daily in controlled clinical trials. Therefore, it is recommended in section 4.4 of the SPC that liver function tests be performed prior to the initiation of treatment with Galvus and periodically thereafter. Galvus should not be used in patients with severe hepatic impairment.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance System as described by the applicant fulfils the legislative requirements and provides evidence that the applicant has the services of a qualified person

responsible for pharmacovigilance and has the necessary means for notification of any adverse reaction suspected of occurring either in the community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Transaminase elevation	Routine PhV including targeted questionnaire	Warning in section 4.4: A small numerical imbalance of reports of generally asymptomatic elevated transaminases was reported in patients treated with vildagliptin 100 mg daily in controlled clinical trials (see section 4.8). Therefore, as per routine clinical practice, it is recommended that liver function tests be performed prior to the initiation of treatment with Galvus and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be monitored until the abnormality(ies) return to normal. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of 3 x ULN or greater persist, withdrawal of therapy with Galvus is recommended. GALVUS should not be used in patients with severe hepatic impairment.
Skin lesions with and without concurrent edema and vascular disorder	Routine PhV including targeted questionnaire. Skin lesions to be a component of post marketing epidemiologic study.	Precaution SPC section 4.4, with a cross reference to non clinical findings in the SPC section 5.3. The patient leaflet will include lay language on observing skin for potentially related manifestations.
Drug-induced liver injury	Routine PhV including targeted questionnaire. Drug-induced liver toxicity to be a component of postmarketing epidemiologic study.	Warning in section 4.4 of the SPC regarding transaminase rise.
Angioedema	Routine PhV including targeted questionnaire.Routine PVG and epidemiology study. Angioedema to be a component of post-marketing epidemiologic study.	SPC section 4.8.
Cardiac conduction disturbances	Routine PhV including targeted questionnaire. Routine PVG.	none
Muscle events with	Routine PhV including targeted	none

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
and without concurrent statin use	questionnaire. Routine PVG.	
Hypoglycemia	Routine PhVG.	Labelling SPC section 4.8.
Neurotoxicity	Routine PhV.	none
Serious infections	Routine PhV including targeted questionnaire. Routine PVG and epidemiology study. Serious infection, as well as those with an outcome of death, will be included in the matched cohort observational study.	none
Gender incidence/differences	Routine PhV.	none
Patients ≥75 years of age	Routine PhV.	Precaution SPC section 4.4 will state that there is limited information concerning use of vildagliptin in patients ≥ 75 years of age and that caution should be exercised when prescribing to this group (section 4.4)
Patients with moderate and severe renal impairment	Post marketing clinical studies in moderate and severe renal impairment. Routine PhV including targeted questionnaire.	Precaution SPC section 4.4.SPC will state that there is limited information concerning use of vildagliptin in patients with moderate and severe renal impairment and that vildagliptin should not be prescribed in these patients (section 4.4)
Patients with severe hepatic impairment	Routine PhV including targeted questionnaire..	Precaution SPC section 4.4 will state that there is limited information concerning use of vildagliptin in patients with severe hepatic impairment and that vildagliptin should not be prescribed to this group (section 4.4)
Patients with compromised cardiac function	Routine PhV The matched cohort observational study will monitor detailed concomitant treatments, in particular cardio-depressant drugs (including defetolide) in the cohort studies of the RMP.	Precaution SPC section 4.4 for NYHF classes III-IVwill state that there is limited information concerning use of vildagliptin in patients with heart failure class I-II and that therefore vildagliptin should be used cautiously in these patients. SPC will also state that there is no experience of vildagliptin use in patients with heart failure class III-IV and that therefore use of vildagliptin is not recommended in this group (section 4.4)

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

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

Overall, the primary pharmacodynamic studies provided adequate evidence of a glucose-lowering effect of vildagliptin in animal models of diabetes. Vildagliptin was shown to act in vitro and in vivo as an inhibitor of the enzyme DPP-4, thus modulating glucose metabolism. The general pharmacology studies showed little safety concerns. Cardiovascular changes at high concentrations in dogs were further investigated in humans and are taken into account within the RMP. From the pharmacokinetic point of view, vildagliptin showed high bioavailability and similar kinetics in all species and in man.
Overall, the toxicology programme raised little concern; there were, however, skin-lesions observed in vildagliptin-treated cynomolgus monkeys. The clinical relevance of these findings is unknown, but no equivalent was found in clinical safety studies. Nevertheless, this issue is addressed in the SPC, as well as in follow-up measures.

Efficacy

Vildagliptin belongs to a new class of oral anti-diabetic drugs and acts as an inhibitor of DPP-4, thus increasing the levels of incretin hormones which is thought to be the principal mechanism of improvement of glucose homeostasis by vildagliptin. Data establishing the clinical efficacy of vildagliptin are based on a series of sufficiently large core studies:

Studies with vildagliptin given alone in T2DM patients showed a reduction of HbA1c (~1%) and FPG (~1 mmol/l) after 24 weeks. In comparator monotherapy studies, vildagliptin was not non-inferior (using a non-inferiority margin of 0.40%) to metformin 1000 mg bid . Statistical non-inferiority to rosiglitazone 8 mg qd was shown in an ITT analysis, but failed in a per-protocol analysis. Vildagliptin treatment as monotherapy was largely lipid and weight neutral.
A second line monotherapy indication, as initially sought by the applicant, was of concern to the CHMP with regard to the fact, that contraindications for metformin, which is the first line monotherapy, largely overlap with contraindications for vildagliptin, i.e. impaired cardiac and renal function. This would have limited the usage of vildagliptin with regard to this second-line monotherapy indication largely to patients intolerant to metformin, representing presumably a small subgroup. The applicant withdrew this part of the proposed indication on 5 July 2007.

The usage as approved is largely based on 3 pivotal add-on placebo-controlled studies each with metformin, pioglitazone, and glimepiride as a base treatment. The populations studied hereby reflected sufficiently the populations indicated for use, i.e. for an add-on therapy with vildagliptin in patients with: insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin, or: in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance, or: in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.
Add-on therapy of vildagliptin to insulin was also studied by the applicant. Upon concerns by the CHMP, among them the relatively small decrease of HbA1C values (mean reduction of 0.27%), the applicant withdrew the indication of a combined usage of vildagliptin and insulin during the evaluation of the MAA.
The 3 add-on therapy studies included patients with inadequate glucose control on monotherapy and achieved clinically relevant reductions of HbA1c (mean reductions of 0.51 – 0.97 % on the 50 mg bid dose) and FPG (mean reductions of 0.44-1.13 mmol/l) compared to placebo, when vildagliptin was added to either metformin, pioglitazone, or glimepiride.

Vildagliptin was largely weight neutral in combination with metformin and glimepiride, but the combination with pioglitazone resulted in a dose-dependent increase in weight. No comparisons have been made with other often used add-on alternatives such as metformin combined with a sulfonylurea.

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 for use in combination with metformin or a thiazolidinedione. The proportion of hypoglycaemic events in the vildagliptin plus glimepiride group was higher in a dose-dependent manner compared to placebo plus glimepiride. Because there was also no additional efficacy demonstrated for vildagliptin 100mg daily in combination with glimepiride, a limitation of the dose of vildagliptin to 50 mg once daily is therefore recommended for this indication.
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.

Safety

Safety data was based on a sufficiently large number of 3784 patients with T2DM exposed for ≥ 12 weeks, both as monotherapy or in combination with another antidiabetic product. 274 patients have been exposed to vildagliptin for ≥52 weeks as monotherapy which was considered as sufficient according to guidelines.

The overall incidences of AEs for monotherapy with vildagliptin were largely comparable to placebo. Adverse drug reactions reported at an increased frequency compared to placebo included dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia..
In combination with metformin, adverse drug reactions were reported to include tremor, headache, dizziness, fatigue and nausea.
Similarly, tremor, headache, dizziness, asthenia, nasopharyngitis and constipation were more common when glimepiride was combined with vildagliptin, compared to placebo.
Combined with pioglitazone 45 mg daily, the frequency of peripheral oedema was higher compared to pioglitazone alone (7.0% versus 2.5%). There was also a dose-dependent weight increases of 1.4, 1.5, and 2.7 kg, with placebo, Galvus 50 mg daily, and Galvus 100 mg daily, and headache and asthenia were more common. The applicant has commited to further characterize the cardiac safety of the combination of vildagliptin and TZD as part of the post-marketing follow-up measures.

Rare cases of angioedema and a small numerical imbalance of reports of elevated transaminases have been reported, both of which have been adressed appropriately in the SPC.

Since early studies had shown sudden deaths in dogs at high doses of vildagliptin, special focus was placed on the potential for conduction disturbances in human subjects. ECG measurements during exposure to high doses in healthy volunteers showed no effect, however, in the clinical studies, there was a higher incidence of first degree AV block in patients treated with vildagliptin. Thus, an association between vildagliptin and first degree AV block can neither be confirmed nor excluded, and the Applicant has committed to perform appropriate follow-up measures.

In the monotherapy studies the number of patients with hypoglycaemic events was low in all treatment groups. The proportion of patients reporting hypoglycemia was 0.4% in the vildagliptin 100mg daily group, and similar to some active controls. With the exception of vildagliptin plus insulin combination and vildagliptin plus pioglitazone combination, this was also the case with vildagliptin add-on therapy
In particular, the proportion of hypoglycaemic events in the vildagliptin plus glimepiride group was higher in a dose-dependent manner compared to placebo plus glimepiride. Consequently, a dose of vildagliptin limited to 50 mg once daily is recommended for this latter indication.

Preclinical studies with vildagliptin found skin lesions in monkeys. No clinical equivalent has been detected in the clinical studies, however. Awareness for possible skin alterations is raised by a warning

in the SPC. Additional follow-up measures, including planned mechanistic preclinical studies, address these concerns.

SAE were uncommon in all studies and there was no clustering of specific advents associated with vildagliptin treatment.

From vildagliptin monotherapy studies came some evidence of an increased incidence of overall AE in patients with moderate renal insufficiency, with inconclusive results from add-on studies. Therefore, vildagliptin should not be recommended in patients with moderate and severe renal impairment until more data is available, which is expected from a post-approval study.

Vildagliptin safety is not sufficiently assessed in patients with CHF. Therefore, caution is urged for patients with CHF class NYHA I-II, and the use is not recommended at all for those in NYHA class III-IV, as advised in the SPC. To resolve these uncertainties, the applicant has committed to undertake appropriate follow up measure.

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 Applicant performed a user consultation testing on the package leaflet. The design of the test formed the basis of an adequate and competent testing of the PIL in regard to finding, diagnosing and amending possible weaknesses. The present readability test was well designed to meet its main objectives. The results of the user testing described in the user testing report support the changes made to the PIL.

Risk-benefit assessment

Benefits of vildagliptin as add-on therapy to metformin, glimepiride and pioglitazone include clinically relevant and significant reductions of HbA1c and FPG compared to placebo. Vildagliptin treatment is also largely lipid and weight neutral in combination with metformin and glimepiride, and efficacy (as monotherapy) has been shown for up to 2 years treatment. However, the vildagliptin add-on therapy to metformin, pioglitazone and glimepiride has not been compared to other add-on alternatives and long-term efficacy data for vildagliptin (as add-on therapy) is limited. Both uncertainties are addressed in ongoing studies, the results of which will be evaluated as follow-up-measures.
Risks of the use of vildagliptin are an increase in weight and peripheral oedema when used with pioglitazone (45 mg per day). Combined with sulfonylureas, the risk of hypoglycemia is increased. Rare cases of angioedema, and elevations of transaminases have been reported. The findings of skin lesions in monkeys had no clinical equivalent so far and is addressed in follow-up measures.
For populations with CHF and renal insufficiency, there is insufficient safety data, or the possibility of an increased rate of AE, respectively. For both populations, the use of vildagliptin is either restricted or not recommended. Both populations are investigated with this regard in studies as post-approval commitments.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Routine pharmacovigilance was adequate to monitor the safety of the product.
- No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Galvus in the type 2 diabetes was favourable and therefore recommended the granting of the marketing authorisation.