European Medicines Agency

London, 14 December 2006
EMEA/CHMP/511689/2006

Withdrawal Public Assessment Report
Of a Type II variation for a new indication

NovoNorm
(repaglinide)

EMEA/H/C/187/II/65

MAH:
Novo Nordisk A/S

This Withdrawal Public Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the application. It may not include all available information on the product in the case where the CHMP assessment of latest submitted information was still ongoing.

It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the application for this new indication, which provides an overview on all available information at the time of the Applicant's withdrawal.

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I. CHMP RECOMMENDATION PRIOR TO THE WITHDRAWAL

Based on the CHMP review of the data and the MAH's response to the CHMP Requests of Supplementary Information (RSI) on safety and efficacy, the CHMP considered that the application for NovoNorm for the proposed extension of the indication for the use of repaglinide in combination with a thiazolidinedione (TZD) was not approvable, since major objections still remained, which preclude a recommendation for the variation to extend the indication at the present time. The details of these major objections and other concerns are provided in section III.

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II. SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Not applicable

Non-clinical aspects

Not applicable

Clinical aspects

II.3.1 Clinical Pharmacology

No pharmacokinetic interaction studies have been submitted with this variation application. Repaglinide, rosiglitazone, and pioglitazone are predominantly metabolised by the following cytochrome P450 (CYP) subfamilies:

Repaglinide (CYP3A4 and CYP2C8)
Rosiglitazone (CYP2C8)
Pioglitazone (CYP3A4 and CYP2C9)

In vitro inhibition data and *in vivo* C_{max} data for the respective drugs are summarised below.

	IC_{50} CYP2C8	IC_{50} CYP3A4	C_{max}
Repaglinide	15 µM	>>5.5 µM	0.07 µM
Pioglitazone	>> 25 µM	>>5.5 µM	0.4 µM
Rosiglitazone	12.5 µM	>>5.5 µM	0.4 µM

Considering the plasma C_{max} obtained and the in vitro IC_{50} values for CYP2C8 and 3A4 of the respective drugs, the possibility of a pharmacokinetic interaction between repaglinide and pioglitazone as well as between repaglinide and rosiglitazone appears remote, with a ratio C_{max}/IC_{50} <0.1 in all cases. Moreover, data from Study 2053 and Study 2064 indicate no safety issues suggestive of a pharmacokinetic interaction.

The CHMP considered that for troglitazone, induction of CYP3A4 has been observed in vivo. However, in vitro data indicate that rosiglitazone and pioglitazone are less potent inducers than troglitazone, and in vivo no indication for induction by these drugs has been observed.

Therefore, on the grounds that pharmacokinetic interactions between repaglinide and registered thiazolidinediones appear remote, the CHMP considered the absence of pharmacokinetic interaction studies as part of this application to be acceptable.

II.3.2 Clinical efficacy

In support of their application, results from two clinical trials were submitted by the MAH, in which the efficacy and safety of repaglinide monotherapy, thiazolidinedione monotherapy and combination therapy (repaglinide + thiazolidinedione) were compared. The aim of the studies was to test whether the combination treatment with repaglinide and thiazolidinedione achieved significantly better glycaemic control than either treatment used alone.

Other comparisons (i.e. with sulphonylurea and metformin monotherapy, sulphonylurea/metformin combination therapy, repaglinide/metformin combination therapy) were beyond the scope of these studies. As this application seeks approval of repaglinide/thiazolidinedione combination therapy in patients for whom metformin is unsuitable, it was the MAH's view that comparisons with metformin treatment arms are not applicable.

II.3.2.1 Methodology

The trials were identical in design: 24-weeks, randomised, multicentre, open-label, parallel-group, with the exception of the choice of thiazolidinedione (rosiglitazone in AGEE-2053 and pioglitazone in AGEE-2064) used concomitantly with repaglinide.

Key characteristics of the study population of both trials were: type 2 diabetes for at least one year; age above 18 years; unsatisfactory glycaemic control with sulphonylurea or metformin (given as ≥ 50% maximal dose) with HbA1c values > 7.0%. This widely available and poorly controlled study population was considered by the MAH the most appropriate to compare the relative potencies of combination and monotherapy with repaglinide and thiazolidinediones. The MAH recognised that since subjects failed to achieve suitable glycaemic control using 50% or more of maximum recommended doses (rather than maximal doses) they may not be true treatment failures. However, as approval is not being sought for use of repaglinide plus thiazolidinedione the MAH's position was that combination treatment in patients who have failed on sulphonylurea or metformin monotherapy, the inclusion of genuine treatment failures is not considered necessary.

Main exclusion criteria were: treatment with insulin, repaglinide, thiazolidinediones, alpha-glucosidase inhibitors, or combination treatment with more than one antidiabetic medication, within the past 3 months; body mass index> 45.0 kg/m^2; HbA1c > 12%; heart failure (NYHA class III and IV), unstable angina pectoris and/or myocardial infarction within the past 12 months.

In the rosiglitazone study a total of 252 subjects were enrolled and in the pioglitazone study a total of 246 subjects were enrolled. Prior therapy was withdrawn for 2 weeks, followed by randomisation, a 12-week dose optimisation period (doses were optimised according to each of the drugs respective labelling), and a 12-week maintenance period.

For these studies an open-label trial design was chosen, since repaglinide and rosiglitazone/pioglitazone tablets are visually distinguishable from each other. A double-dummy technique was considered impractical since the subjects would self-administer their medications throughout the clinical trial, and multiple dose adjustments could be anticipated during the dose-adjustment period of the trial.

Primary endpoint was the difference in changes from baseline HbA1c values between study groups at the end of the trial period, and secondary endpoint was fasting plasma glucose. A difference of 0.7%

in HbA1c was considered clinically meaningful. Assuming a drop out rate of 20%, a sample size of 240 patients was calculated to be sufficient (power 80%, 2-sided t-test, alpha = 0.05). An interim analysis was planned to be conducted when half of the targeted number of completers would be available. Significance levels of 0.005 and 0.04806 were applied to the interim analysis and final tests, respectively. As results, 242 subjects were randomised to provide 194 completers, assuming a dropout rate of 20%. The interim analysis was planned for the time when 97 patients had completed the trial.

In case of patient withdrawal or missing data at times after baseline, the missing values of HbA1c and FPG were substituted by imputed data. Two methods of imputation were used, i.e. the incremental mean imputation (IMI) method and the last observation carried forward (LOCF) method. The IMI was utilised as the primary method of imputation, and the LOCF was used to provide supportive information.

Criteria for evaluation of safety included hypoglycaemic episodes, adverse events, laboratory assessments (haematology, biochemistry and lipids), physical examination, vital signs and body weight during the course of the trial.

In the light of the data submitted, the CHMP considered that for the indication 'addition to TZD', efficacy and safety of the combination should be demonstrated in patients insufficiently controlled by TZD monotherapy. However, inclusion criteria comprised patients who were insufficiently controlled by SU or MET and not TZD. Therefore, it is not known whether the subjects were TZD failures.

In addition, according to the indication of TZD, patients who cannot be treated with metformin should have been included. The studies did not use such patients exclusively, but included a wider range of patients. In general, patients who can't be treated with metformin are those with renal insufficiency or patients who can't tolerate metformin because of gastrointestinal side effects. It is not expected that these subjects will differ from other diabetic patients in their glycaemic controllability. Therefore, the CHMP considered that the wider range of patients should have been selected with respect to this item.

According to the MAH, other comparisons than repaglinide+TZD versus two monotherapy arms were beyond the scope of the studies. However, TZD+SU is another possible comparison. TZDs are also registered as dual therapy in combination with SU, and therefore an active controlled study comparing TZD+Repaglinide with TZD+SU would be a logical requirement.

In their responses to the April 06 RSI, the MAH claimed that the CHMP guideline on diabetes mellitus advises to perform an active controlled study, depending on the results of placebo-controlled studies, but does not specify that this is a mandatory requirement. The MAH also referred to literature where it is stated that most classes of drugs are equally efficacious in reducing HbA1c, with the exception of the α-Glucosidase Inhibitors and nateglinide (both less efficacious). Finally, the MAH did not believe that a trial comparing TZD + SU with TZD + repaglinide was essential for an evaluation of the risk/benefit of TZD + repaglinide combination therapy. Furthermore, the MAH considered that such a trial would likely just confirm that repaglinide and SUs were equally efficacious, not only in monotherapy but also in combination with another OAD (in this case a TZD).

The CHMP considers that all arguments of the MAH are indirect. Study populations could differ, and that will have consequences for efficacy. The trial that compared metformin+repaglinide with metformin+SU (AGEE-2025) was not a non-inferiority or equivalence trial. Primary endpoint was mean blood glucose during hypoglycaemia. Efficacy by HbA1c was a secondary endpoint. For an evaluation of the benefit/risk of TZD+repaglinide a comparison with TZD+SU is still requested.

In their original submission, the MAH stated that the reason why a double-dummy technique was impractical was the potential for multiple dose adjustments by subjects themselves. The CHMP considered this argument not acceptable. Therefore, in their April 06 assessment of the original dossier, the CHMP considered the open-label design a weakness of the studies, and a major deficiency.

In their responses to the April 06 RSI, the MAH recognised that there was a higher risk of bias in an open-label trial compared to a double-blind, double-dummy trial. However, the primary efficacy endpoint (reduction in HbA1c) would have been blinded to both the patient and investigator throughout the 24 weeks of the trial. Therefore, although the trials were open-label, they were of sufficient size and quality and demonstrated that TZD + repaglinide combination treatment was safe and more efficacious than repaglinide and TZD monotherapy.

The CHMP still considers the design of the studies to be insufficient, although the fact that it was an open-label design was not the major point. In addition, the CHMP strongly advises to consider a double-blind study when the MAH thinks over planning an active comparator study.

II.3.2.2 Subject disposition

Subject disposition of both trials are summarised in Table 1 and Table 2. A total of 252 and 246 patients were enrolled in trial 2053 and 2064, respectively. In both trials, the percentage of patients who discontinued therapy was higher in the monotherapy groups (40-60%) compared to combination treatment groups (15-17%). The most important reason for discontinuation was ineffective therapy.

Table 1: Study AGEE-2053, subject disposition

	Combination N (%)	Repaglinide N (%)	Rosiglitazone N (%)
Patients treated	127 (100)	63 (100)	62 (100)
Completed Study	106 (84)	38 (60)	37 (60)
Discontinued	21 (17)	25 (40)	25 (40)
Reasons for not completing:			
AE - Hyperglycaemia	0	2 (3)	1 (2)
AE - Other	4 (3)	2 (3)	5 (8)
Non-compliance	4 (3)	1 (2)	3 (5)
Ineffective therapy	3 (2)	13 (21)	13 (21)
Other	10 (8)	7 (11)	3 (5)

Table 2: Study AGEE-2064, subject disposition

	Combination N (%)	Repaglinide N (%)	Pioglitazone N (%)
Patients treated	123 (100)	61 (100)	62 (100)
Completed Study	105 (85)	36 (59)	26 (42)
Discontinued	18 (15)	25 (41)	36 (58)
Reasons for not completing:			
Adverse event	5 (4)	3 (5)	1 (2)
Non-compliance	3 (2)	1 (2)	1 (2)
Ineffective therapy	6 (5)	13 (21)	31 (50)
Other	4 (3)	8 (13)	3 (5)

With respect to the higher rate of dropouts which occurred in the monotherapy group, it is important to emphasize that the withdrawal criterion for ineffective therapy was the same for all treatment groups (unacceptable hyperglycemia in the absence of a treatable concurrent illness [FPG above 270 mg/dL on 2 or more consecutive occasions] in spite of proper dose escalations to the maximum allowed dose(s)). The average duration of treatment for such dropouts (due to ineffective therapy) in monotherapy groups was approximately 8 weeks, compared to approximately 14 weeks for the combination therapy.

For both clinical trials, the rate of discontinuation did not differ notably between groups for any reasons but lack of efficacy. The principal concern of a high dropout rate in one group would be whether it materially altered the response that would be expected for the subjects remaining in that treatment group. Since the rate of discontinued subjects for lack of efficacy was highest in the monotherapy groups, such dropouts would be expected to leave only the most responsive subjects in

the monotherapy groups by the end of the study. According to the MAH, such a high dropout rate would therefore be expected to exaggerate the response of the monotherapy, resulting in a lower apparent difference between monotherapy and combination therapy. Thus, the MAH's interpretation was that if the differential dropout rates have affected the results of the study, the expected outcome of any bias would be that the effect of the combination therapy is underestimated.

In Study AGEE-2053, 60% of the patients treated completed the study as compared to only 42% in Study AGEE-2064. The CHMP therefore requests that the MAH comment further on this seemingly otherwise extraordinarily high rate of non-compliance in Study AGEE-2064.

Additionally, given that pioglitazone monotherapy in Study AGEE-2064 was associated with an increase in HbA1c over the course of the trial of 0.32 % (see Table 4), which seems an inherently odd finding, the CHMP requested that the MAH commented further, in particular with respect to the relative use of imputed data in this arm of the trial in response to the high number of patient withdrawals (58%) and the appropriateness of the methods of imputation used.

In their responses to the April 06 RSI, the MAH responded that the imputation method (IMI) used in AGEE-2064 was outlined in the statistical analysis plan (SAP) for this trial and was further described in a paper by Khutoryansky and Huang (2001). As there was no universally recommended method of handling missing values, results of the IMI analysis were compared with those calculated using LOCF (as specified in the SAP). Furthermore, a *post-hoc* analysis of completers only was performed. Due to the high proportion of dropouts in the monotherapy arms, an analysis of completers could be expected to be biased upwards (i.e. the decrease in HbA_{1c} is overestimated since completers are patients reacting most favourably to the treatment). Since the LOCF method will carry forward data for dropouts before they had potentially reached full treatment effect, this method could result in results being biased downwards (i.e. decreases in HbA_{1c} are underestimated). The IMI imputation method was expected to give results that are less biased than the LOCF method because the IMI method also takes into account the trend in mean increment shown per treatment. All three methods (IMI, LOCF, post-hoc completers) showed that combination therapy was associated with significantly greater decreases in HbA_{1c} over 24 weeks compared with the corresponding monotherapy treatment arms. Thus, although a large number of withdrawals were observed for the two monotherapy treatment arms, this consistency between the three methods of analysis was indicative of the robustness of the MAH's findings. As outlined above, all patients were receiving the maximal dose of pioglitazone (30 mg, once daily) at the time of drop out and therefore it was likely that these patients were similar to true TZD monotherapy failures. Moreover, for many patients, their diabetes was so advanced (the mean duration of type 2 diabetes since diagnosis was 6 to 7 years) that monotherapy *per se* could have been insufficient to achieve satisfactory glycaemic control. The MAH therefore considered that the poor response to pioglitazone monotherapy (i.e. a mean increase in HbA_{1c} of 0.32 % points) to be reflective of this.

The CHMP considered that the consistency between the three methods of analysis was in support of the efficacy of the combination of TZD+repaglinide. The poor rate of optimal control in the TZD (and repaglinide) monotherapy arms was indeed indicative that monotherapy in these patients was insufficient to achieve satisfactory glycaemic control. However, patients did not receive the maximum permitted doses. The maximum permitted dose for pioglitazone was 45 mg daily and for rosiglitazone 8 mg daily. Therefore, many of the patients cannot be regarded as true TZD failures. The issue is therefore not completely resolved and further information is still requested (See section III).

II.3.2.3 HbA1c and FPG

Results on HbA1c and FPG are shown in Table 3 and Table 4. Data are shown for IMI-method. Results with LOCF were similar.

Table 3: Study AGEE-2053. HbA1c (%) (IMI-method) and FPG (m/dL) during 24 weeks of therapy.

		Baseline	EOS	Change ±	P-value for comparison vs.	
HbA1c	N	Mean	Mean	SEM	Rep Mono	Rosi Mono
Combination	126	9.1	7.7	-1.43 ± 0.10	<0.001	<0.001
Repaglinide	59	9.3	9.1	-0.17 ± 0.14	-	0.057
Rosiglitazone	55	9.0	8.5	-0.56 ± 0.14	-	-
FPG						
Combination	122	257.2	163.8	-94.4 ± 4.55	<0.001	0.001
Repaglinide	57	268.9	208.0	-54.2 ± 6.67	-	0.193
Rosiglitazone	56	251.8	189.7	-66.6 ± 6.72	-	-

Table 4: Study AGEE-2064. HbA1c (%) (IMI-method) and FPG (mg/dL) during 24 weeks of therapy.

		Baseline	EOS	Change ±	P-value for comparison vs.	
HbA1c	N	Mean	Mean	SEM	Rep Mono	Pio Mono
Combination	123	9.3	7.5	-1.76 ± 0.11	<0.001	<0.001
Repaglinide	54	9.0	8.9	-0.18 ± 0.17	-	0.033
Pioglitazone	57	9.1	9.5	+0.32 ± 0.16	-	-
FPG						
Combination	119	252.8	169.4	-82.0 ± 5.08	<0.001	<0.001
Repaglinide	54	248.2	215.2	-33.9 ± 7.54	-	0.146
Pioglitazone	56	245.6	229.2	-18.5 ± 7.40	-	-

In study AGEE-2053, at 24 weeks, combination treatment was more effective than monotherapy in both studies. With combination treatment a reduction in HbA1c was measured of –1.43 ± 0.10%. For repaglinide monotherapy a reduction was found of -0.17 ± 0.14%, and for rosiglitazone monotherapy resulted in a reduction in HbA1c of –0.56 ± 0.14%. The mean difference in reductions of HbA1c values between the combination therapy and repaglinide monotherapy groups was 1.26%, and the difference with rosiglitazone monotherapy was 0.87%.

In study AGEE-2064, combination treatment resulted in a decrease in HbA1c of -1.76%, versus -0.18% with repaglinide monotherapy. With pioglitazone monotherapy HbA1c increased with +0.32%. The mean difference in reductions of HbA1c values between the combination therapy and repaglinide monotherapy groups was 1.58%, and the difference with pioglitazone monotherapy was 2.08%.

Those patients who completed 24 weeks of treatment, were categorised by final HbA1c levels to produce a "responder" analysis (3). In study AGEE-2053, the percentage of patients who achieved optimal control (HbA1c≤7.0%) was 39% for the repaglinide + rosiglitazone combination versus 5% and 16% for repaglinide monotherapy and rosiglitazone monotherapy groups respectively. In study AGEE-2064 percentages were respectively 52% for the repaglinide + pioglitazone group versus 9% and 8% for the repaglinide monotherapy and pioglitazone monotherapy groups.

Table 5: Study AGEE-2053 and 2064. Proportion of subjects within categorised values of HbA1c at baseline and at end of study - completers only

Time	**Treatment**	**N**	**HbA1c ≤ 7% n (%)**	**7% < HbA1c ≤ 8% n (%)**	**HbA1c > 8% n (%)**
Study 2053					
Baseline	Combination	106	1 (1)	23 (22)	82 (77)
	Repaglinide	37	0	6 (17)	30 (83)
	Rosiglitazone	37	1 (3)	8 (22)	27 (75)
Week 24	Combination	106	41 (39)	32 (30)	33 (31)
	Repaglinide	37	2 (5)	11 (30)	24 (65)
	Rosiglitazone	37	6 (16)	12 (32)	19 (51)

Time	Treatment	N	HbA1c ≤ 7% n (%)	7% < HbA1c ≤ 8% n (%)	HbA1c > 8% n (%)
Study 2064					
Baseline	Combination	101	1 (1)	22 (22)	78 (77)
	Repaglinide	35	0	12 (34)	23 (66)
	Pioglitazone	26	0	9 (35)	17 (65)
Week 24	Combination	101	53 (52)	24 (24)	24 (24)
	Repaglinide	35	5 (9)	10 (29)	22 (63)
	Pioglitazone	26	2 (8)	8 (31)	16 (62)

The CHMP considered that the figures of responders given by the MAH are misleading, as they are based on completers only. It would have been more useful to analyse the responder percentages for the total number of patients who started treatment, as the percentages of withdrawals due to lack of efficacy was high. For the total population the following figures were calculated. In study AGEE-2053 optimal control was achieved in 32% (41/127) of patients receiving repaglinide + rosiglitazone, versus 3% (2/63) of the repaglinide monotherapy group and 9.6% (6/62) of the rosiglitazone monotherapy group. In study AGEE-2064 percentages were respectively 43% (53/123) for the repaglinide + pioglitazone group versus 8% (5/61) and 3% (2/63) for the repaglinide and pioglitazone monotherapy groups.

As shown in Table 5, there were 9 fewer patients in the rosiglitazone monotherapy arm (of those who completed Study AGEE-2053) with a HbA1c > 8%, compared with 1 fewer in the pioglitazone monotherapy arm of Study AGEE-2064. Also, there were 5 and 2 more patients in Study AGEE-2053 and AGEE-2064, respectively with an HbA1c ≤ 7% among those who completed the trials. Optimal control was therefore achieved in only 9.6% (6 completers / 62 patients with intention to treat) and 3.0% (2 completers / 63 patients with intention to treat) in the rosiglitazone and pioglitazone monotherapy arms of these studies. The CHMP therefore requested that the MAH commented, not only on these very poor rates of optimal control under study conditions, but also on the apparently weaker efficacy of pioglitazone as compared to rosiglitazone, albeit in separate studies.

The MAH responded that the poor rate of optimal control in the TZD (and repaglinide) monotherapy arms could be partially explained by the selection of patients for these trials who were not optimally controlled with metformin or SU monotherapy. They considered it likely that, for many patients, their diabetes was so advanced (the mean duration of type 2 diabetes since diagnosis was 6 to 7 years) that monotherapy per se was insufficient to achieve satisfactory glycaemic control. They considered the apparent weaker efficacy of pioglitazone versus rosiglitazone monotherapy to be a coincidental finding that might be partly explained by the slightly different baseline and demographic characteristics of the two trial populations, and the different sites at which these trials were conducted. Based on published clinical trials of rosiglitazone and pioglitazone, it was the MAH's view that the two drugs had a similar efficacy. This is also the conclusion of the recent comprehensive review of marketed OADs in which it was concluded that "most classes of drugs are equally efficacious in reducing HbA1c, with the exceptions of the α-Glucosidase Inhibitors (AGIs) and nateglinide" (both being less efficacious; Kimmel and Inzucchi, 2005).

II.3.2.4 Dosage

The dosage regimen was recorded for each patient. Due to the fact that the final daily doses of dropouts could be smaller than those of patients who completed therapy, the median values of total daily dosage were considered more representative for purposes of between-group comparisons. The median total daily doses of repaglinide and rosiglitazone in the combination group were 6.0 (range 0-15) and 4.0 (range 0-8) respectively. In the monotherapy groups median dosages were 12.0 (range 1-16) for repaglinide and 8.0 (range 2-8) for rosiglitazone. So, in the combination group median total daily doses were approximately half as great as the median total daily doses used in the monotherapy groups. In the trial with pioglitazone, median total daily doses of repaglinide and pioglitazone in the combination group were 6.0 (range 1-16) and 30.0 (range 3-30) respectively. In the monotherapy groups median dosages were 10.0 (range 1-16) for repaglinide and 30.0 (range 3-30) for pioglitazone.

Here, the median total daily dose of repaglinide was lower in the combination group than in the monotherapy group. Pioglitazone dosage was not adjusted.

In their April 06 assessment of the original dossier, the CHMP considered that, due to the high number of dropouts in the monotherapy groups, it is hard to compare dosages between groups. For the indication applied for, it is important to know whether subjects who withdrew from the studies were at their maximum dosage of monotherapy. The MAH was asked to submit these data..

The MAH accepted that the patients included in the two TZD + repaglinide studies were not true TZD failures in the sense that they were previous non-responders on maximal tolerated doses of TZD.

For AGEE-2064, all patients were receiving the maximal dose of pioglitazone (30 mg, once daily) at the time of drop out and therefore it is likely that these patients are similar to true TZD monotherapy failures. For AGEE-2053, the median daily dose of rosiglitazone received at the time of study drop out was 4 mg (range 2 to 8 mg). Since the maximum permitted daily dose of rosiglitazone was 8 mg, many of patients cannot therefore be regarded as true TZD failures.

The CHMP agrees that recruitment would be difficult if a population of patients is utilized who can be considered as failures on TZD. However, a run-in period of TZD monotherapy could have been included in the design of the study before randomisation. Patients who are still insufficiently controlled after that period could enter the study and be randomised. Such a period should be long enough reach maximum effect of TZD. Such a run-in period is often employed in clinical trials used for submissions to Regulatory Authorities. The question is whether the patients from the two trials can be expected to be failures on TZD monotherapy. By inclusion criteria they were failures on SU or MET, although this has not been formally established by a run-in period. However, it is unlikely that failures on one monotherapy will get sufficiently controlled by switching to another monotherapy. Results in the monotherapy arms were poor. TZD+repaglinide combination was more efficacious than the individual drugs. However, TZDs were not given at their maximum dose (see also question 1d). Median dose for dropouts in the monotherapy arms due to insufficient efficacy was 30mg for pioglitazone (45 mg is maximum recommended dose) and 4 mg for rosiglitazone (8mg maximum recommended dose). Therefore, these patients cannot be considered as true failures on TZD monotherapy.

The CHMP also considers that both pioglitazone and rosiglitazone were not given in maximum permitted doses. The maximum permitted dose for pioglitazone is 45 mg daily and for rosiglitazone 8 mg daily. Therefore, many of the patients cannot be regarded as true TZD failures. The issue is therefore still not resolved (see Section III).

In addition to the above points, the CHMP considered that the SPC submitted mentioned (section 4.2) that in case repaglinide is added to TZD, patients should maintain their dosage of TZD and repaglinide should be started at 0.5mg before main meals. This posology has not been studied, as in the trials subjects started with low dosages of both medications.

II.3.2.5 Summary of assessment of the clinical efficacy

Data from two trials were submitted in support of this application, comparing combination treatment of repaglinide+TZD with repaglinide and TZD monotherapy.

Inclusion criteria comprised patients who were insufficiently controlled by SU or MET and not subjects failing on TZD, as is required for the claimed indication. Therefore, it is not known whether the subjects in the trial were TZD failures. The high numbers of dropouts in the monotherapy arms due to insufficient efficacy are in support of the claimed indication. However, the dosages used by patients who withdrew from the study were not presented.

In addition, according to the indication of TZD, patients should have been included who can't be treated with metformin. The studies did not use such patients exclusively, but included a wider range

of patients. In general, patients who can't be treated with metformin are patients with renal insufficiency or patients who can't tolerate metformin because of gastrointestinal side effects. It is not expected that these subjects will differ from other diabetic patients in their glycaemic controllability. Therefore, the wider range of patients can be accepted with respect to this item.

In their original submission dossier, the MAH stated that other comparisons than repaglinide+TZD versus two monotherapy arms were beyond the scope of the studies. However, TZD+SU is another possible comparison. TZDs are registered as dual therapy in combination with SU, and therefore an active controlled study comparing TZD+Repaglinide with TZD+SU is a logical requirement. However, in their April 06 assessment of the original dossier, the CHMP considered the open-label design a weakness of the studies, and the argumentation of the MAH for this design was not acceptable.

In both studies combination treatment appeared to be more effective than repaglinide and TZD monotherapy. This was the case for the primary endpoint HbA1c and for FPG. In the monotherapy arms there was a higher percentage of dropouts due to ineffective therapy (21-50%) compared to combination treatment (2-5%), supporting the efficacy of combination therapy. A post hoc responder analysis was performed upon values of HbA1c and FPG at baseline and at end of treatment. However, this analysis was only performed for subjects who completed the 24-week treatment period, and therefore figures are somewhat misleading.

The SPC proposed with the application mentions in section 4.2 that in case of adding repaglinide to TZD, patients should maintain their dosage of TZD and repaglinide should be started at 0.5mg before main meals. This posology has not been studied, as in the trials subjects started with low dosages of both medications.

For troglitazone, induction of CYP3A4 has been observed in vivo. However, in vitro data indicate that rosiglitazone and pioglitazone are less potent inducers than troglitazone, and in vivo no indication for induction by these drugs has been observed.

In conclusion:
- pharmacokinetic interactions between repaglinide and registered thiazolidinediones appear remote, and the absence of pharmacokinetic interaction studies is considered acceptable.
- lack of a study that compares TZD+repaglinide with TZD+SU is still seen as a major objection
- the patients included in the two trials were not true failures on TZDs
- The open-label design of the studies can be criticised.

Therefore, because of the multiple deficiencies in the submitted studies, in their April 06 assessment of the original dossier, it was the opinion of the CHMP that the indication *"NovoNorm is also indicated in combination with thiazolidinediones in patients (particularly overweight patients) who, due to contra-indications or intolerance to metformin, are using rosiglitazone or pioglitazone monotherapy but have insufficient glycaemic control with these products"* could not be granted.

II.3.3 Clinical safety

Patient exposure

The overall safety population for this application comprised 498 subjects with type 2 diabetes, 250 of whom were exposed to repaglinide/thiazolidinedione combination therapy and 248 to monotherapy with either repaglinide or thiazolidinedione (rosiglitazone or pioglitazone). Particular focus was given to assessing the safety in the areas of hypoglycaemia, liver function, weight gain and fluid retention. These will be covered individually below.

Adverse events

For both studies, the overall proportion of subjects with adverse events (serious and non-serious) was generally comparable across treatment groups (ranging from 56 to 73% of subjects). For all treatment groups, the majority of adverse events (89 to 96%) were mild or moderate in severity and were judged

by the Investigator as being unlikely to be related to the trial product. No unexpected adverse events were observed in connection with Study 2053 or Study 2064.

The TEAE occurring in ≥ 5% of subjects of any treatment group – by body system, differed between the two studies. The different efficacies and safety profiles demonstrated between the two studies AGEE-2053 and AGEE-2064 suggest that a further study is needed on the effects of combination therapy with repaglinide and rosiglitazone as compared to repaglinide and pioglitazone. The MAH was asked to comment.

To address this issue, the MAH responded that the observed difference in the TEAE may be coincidental, reflecting the low number of TEAEs reported for a particular body system and the fact that although the two studies had the same design, the trials were performed at different sites and had trial populations that differed slightly with respect to baseline and demographic characteristics. The CHMP agrees that the difference in TEAE profiles may be coincidental and that from literature no difference in efficacy and safety between rosiglitazone and pioglitazone has been described. The issue is resolved.

The most common adverse events reported across the two studies were 'upper respiratory tract infection', 'infection viral', and 'headache'. A higher incidence of 'weight increase' was reported for combination therapy (5.7 to 6.3%) than monotherapy with repaglinide (1.6%), rosiglitazone (1.6%), or pioglitazone (1.6%). For Study 2064, combination therapy was associated with a higher incidence of 'peripheral oedema' than pioglitazone monotherapy (5.7% vs. 1.6% of subjects). However, the incidence of 'peripheral oedema' was similar for combination therapy and rosiglitazone monotherapy in Study 2053 (3.9% and 3.2% of subjects, respectively). No cases of 'peripheral oedema' were reported for repaglinide monotherapy in either study.

- *Hypoglycaemia*

For both Study 2053 and Study 2064, the vast majority of reported hypoglycaemic episodes were classified as 'minor' or 'symptoms only'. Among the 250 subjects treated with repaglinide/rosiglitazone or repaglinide/pioglitazone combination therapy, there was one major hypoglycaemic episode (reported for a subject in the repaglinide/rosiglitazone group). This episode was considered by the Investigator to be possibly related to the study product. No major hypoglycaemic events were reported for subjects on repaglinide or thiazolidinedione monotherapy.

The overall percentage of subjects having minor hypoglycaemic events in the repaglinide/rosiglitazone or repaglinide/pioglitazone combination therapy groups was equivalent to that reported for repaglinide monotherapy (7% of subjects in each group).

In total, 26% of subjects treated with repaglinide/rosiglitazone or repaglinide/pioglitazone had symptomatic hypoglycemia (defined as symptoms that were considered to be related to hypoglycaemia but not confirmed by blood glucose measurement) compared with 14% and 6% of subjects on repaglinide or thiazolidinedione monotherapy, respectively. The higher risk of symptomatic hypoglycemia during repaglinide/thiazolidinedione combination therapy was generally consistent with the improved glycaemic control observed for this regimen.

- *Hepatic safety*

For both Study 2053 and Study 2064, no clinically relevant changes in mean plasma ALT levels were observed for any treatment group during the 24 weeks of study treatment.
Only one subject (in the repaglinide monotherapy group of Study 2053) had elevated ALT levels that reached 3 times the upper limit of normal: this episode was resolved upon cessation of therapy.

- *Body weight*

For repaglinide/rosiglitazone or repaglinide/pioglitazone combination therapy, there was a trend toward greater weight gains than that observed for repaglinide or thiazolidinedione monotherapy. Such gains averaged 4.9 kg for combination therapy, compared with 1.0 kg and 2.2 kg for repaglinide and thiazolidinedione monotherapy, respectively. The greater weight gain associated with combination therapy is thought to be related to the larger improvements in glycaemic control observed with this

treatment regimen. Weight gain for repaglinide/rosiglitazone or repaglinide/pioglitazone combination therapy was significantly correlated with improved glycaemic control: there was a statistically significant trend toward greater weight gains for greater reductions in HbA1c values. By contrast, no statistically significant correlation between weight gain and increased glycaemic control was found for repaglinide or thiazolidinedione monotherapy.

- *Peripheral Oedema*

Peripheral oedema was reported as an adverse event for 3.9% and 5.7% of subjects receiving repaglinide/rosiglitazone and repaglinide/pioglitazone combination therapy, respectively, compared with 3.2% of subjects on rosiglitazone monotherapy and 1.6% of subjects on pioglitazone monotherapy. No cases of peripheral oedema were reported for repaglinide monotherapy.
Of the 17 cases of peripheral oedema reported, one was rated as a serious adverse event. This event, which occurred in a subject receiving repaglinide/rosiglitazone combination therapy, was associated with a diabetic ulcer of the foot, and was considered unlikely to be related to the trial product by the Investigator.

Two subjects discontinued study treatment because of oedema; one subject on rosiglitazone monotherapy and one subject on repaglinide/pioglitazone combination therapy.

- *Other safety variables*

For both studies, small decreases in mean haemoglobin values were observed for all treatment groups from baseline to end of study. Reductions in haemoglobin were similar for combination therapy and thiazolidinedione monotherapy (ranging from -0.5 to -0.8 g/dL) and were greater than those observed with repaglinide monotherapy. Minor changes in mean leukocyte or thrombocyte counts were also observed for all treatment groups in studies 2053 and 2064.

For both studies, median changes in values of VLDL cholesterol, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, or free fatty acids were generally similar for repaglinide/thiazolidinedione combination therapy and thiazolidinedione monotherapy.

No clinically relevant differences with respect to other laboratory assessments (i.e. biochemistry), physical examination, vital signs or ECG assessments were observed for Study 2053 and Study 2064.

- *Serious adverse events and deaths*

No deaths occurred in either studies. For both studies, the frequency of serious adverse events was generally low (Study 2053: 4.8 to 9.5% of subjects; Study 2064: 1.6 to 6.5% of subjects) and similar across treatment groups; no particular treatment-dependent pattern emerged.

Of the 35 serious adverse events reported for the two studies, two events were considered by the Investigator to be possibly related to the trial product; one case of hypoglycaemia with repaglinide/rosiglitazone combination therapy and a cerebrovascular disorder reported for a subject on pioglitazone monotherapy. All other events were considered unlikely to be related to the trial product.

- *Discontinuation due to AES*

Although more subjects discontinued monotherapy than combination therapy due to insufficient efficacy, the percentage of subjects who discontinued therapy due to adverse events other than hyperglycaemia was similar in the combination therapy (3.6% [9/250] of subjects) and monotherapy (4.4% [11/248] of subjects) groups.

Conclusions on Clinical Safety

In their April 06 assessment, the CHMP concluded that a greater weight increase was seen with combination treatment. This could be the result of improvement of glycaemic control, as also suggested by the significant correlation between HbA1c reduction and weight gain. However, the decreases in haemoglobin and the incidence of peripheral oedema in the combination treatment and TZD monotherapy groups are also suggestive for haemodilution due to fluid retention, a known side effect of TZDs.

The MAH's response to this issue made reference to the addition of repaglinide, which appears to increase the frequency of certain TZD-related adverse events (oedema, lowering of haemoglobin values). This could be partly related to the fact that, since a higher proportion of patients in the combination treatment arms completed the trials, the average duration of treatment (and hence exposure to TZDs) was longer. In AGEE-2053, 84% of the patients completed the combination treatment versus 60% in both the repaglinide and the rosiglitazone treatment arms. Similarly in AGEE-2064, 85% of the patients completed the combination treatment versus 59% in the repaglinide and 42% in the pioglitazone treatment arms. Although some TZD-related AEs increased in the combination therapy arms, the safety profile was acceptable, comparable with studies assessing TZD + SU combination therapy (Horton et al., 1998; Kipnes et al., 2001), and the percentage of patients discontinuing treatment due to adverse events was not greater in the combination treatment arms compared to the monotherapy arms. In the studies submitted with this application, no increase in cardiovascular adverse events has been observed.

The CHMP considered that no unexpected adverse events were reported. A greater weight increase was seen with combination treatment, possibly due to improvement of glycaemic control, but also to fluid retention. An increase in hypoglycaemia can be expected in the group having improved glycaemic control. The CHMP concluded therefore that there is no proof that average duration of treatment could be a reason for the difference in certain AES. Furthermore, although the comparison with data from literature was reassuring, it is not a proof of safety. The issue is still not resolved (See Section III).

III. CHMP MAIN CONCERNS AT THE TIME OF THE WITHDRAWAL

The CHMP has assessed the MAH's answers to their questions. In summary, the following points remain outstanding.

Due to the multiple deficiencies in the submitted studies, it is the opinion of the CHMP that the indication *"NovoNorm is also indicated in combination with thiazolidinediones in patients (particularly overweight patients) who, due to contra-indications or intolerance to metformin, are using rosiglitazone or pioglitazone monotherapy but have insufficient glycaemic control with these products"* can not be granted.

With respect to the design of the studies, the issue is considered not resolved. Patients in the trial were not true failures on TZD, as they were not treated with the maximum permitted dose. In addition, lacking a direct comparison with TZD+SU, the MAH relates the results of the studies to literature and other clinical trials. However, such an indirect comparison is not acceptable, as study populations might differ and can affect the results.

With respect to the greater weight increase with combination treatment, the MAH states that this difference may be partly related to the difference in average duration of treatment. This might be the case, but there is no proof of this argument. Comparison with data from literature is reassuring, but constitutes no proof of safety.

The MAH proposed, should the indication not be acceptable for the CHMP, to add a paragraph to section 5.1 (Pharmacodynamic properties) of the SPC, as follows:
"Repaglinide and thiazolidinediones have been used in combination in two open randomised, controlled clinical trials. The combination therapy provided improved glycaemic control compared to monotherapy. If repaglinide is added to a thiazolidinediones the starting dose of repaglinide should be 0.5 mg before main meals and the thiazolidinedione dose may have to be lowered temporarily. The combination treatment may be associated with increased weight gain and fluid retention".

The CHMP considered that the wording proposed constitutes a hidden indication. It would be inappropriate to have data included in the SPC having failed to sufficiently demonstrate efficacy in the applied indication.

The MAH is requested to respond to the below major objections and other concerns in writing and in an oral explanation.

III.1 MAJOR OBJECTIONS

1. The efficacy and safety of repaglinide added to TZD in the proposed patient population has not been sufficiently demonstrated. Patients in the two trials cannot be considered as true failures on rosiglitazone or pioglitazone monotherapy, as they were not treated with the maximum permitted dose. Considering the quality of the study the open-label design of the studies is a major deficiency. Furthermore, indirect comparisons were made to indicate that repaglinide is as efficacious as SUs, but these arguments are not convincing. A direct comparison between TZD+repaglinide and TZD+SU is requested for approval of the indication.

III.2 OTHER CONCERNS

1. In the response to the Major Objection 2 of the 1st RSI adopted in April (greater weight increase with combination treatment), the MAH states that this difference in weight increase may be partly be related to the difference in average duration of treatment. This might be the case, but there is no proof of this argument. Comparison with data from literature is reassuring, but also forms no proof of safety.

This Withdrawal Public Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the application. It may not include all available information on the product in the case where the CHMP assessment of latest submitted information was still ongoing.

It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the application for this new indication, which provides an overview on all available information at the time of the Applicant's withdrawal.

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
BMI	Body mass index
CYP	Cytochrome P450
ECG	Electrocardiogram
FPG	Fasting plasma glucose
HbA1c	Glycosilated haemoglobin A1 (subfraction C)
ITT	Intent to treat
OAD	Oral antidiabetic drug
PSUR	Periodic Safety Update Report
Rep	Repaglinide
Rosi	Rosiglitazone
SAE	Serious adverse event
SD	Standard deviation
SU	Sulphonylurea
TEAE	Treatment emergent adverse event
TZD	Thiazolidinediones