London, 26 May 2005
Product name : **AVANDIA**
Product no: **EMEA/H/C/000268/II/0023**

SCIENTIFIC DISCUSSION

1. Introduction

Avandia (rosiglitazone) is an antihyperglycaemic agent of the thiazolidinedione chemical class. Its action is through binding to and activating the nuclear peroxisome proliferator activated receptor-gamma (PPARγ) and modifying transcriptional regulation of factors involved in the regulation of insulin action.

Avandia was first approved in the EU on 11 July 2000. Avandia is currently approved for monotherapy and combination therapy with metformin (MET) or sulphonylurea (SU). In this Type II application the MAH applied to add a triple oral combination indication for RSG with MET and SU. To this end, efficacy and safety data from 3 clinical studies are provided. These studies include use at the higher 8mg dose of RSG.

A Summary details of other, more minor, amendments to the SPC are provided in tabular format in EPAR module 8b.

2. Clinical efficacy

2.1. Triple therapy

Three clinical studies are proposed to support triple combination therapy of RSG with SU and MET (Table 4). Study 134 was conducted by GSK, whereas studies CV138055 and CV138055OL TCE were conducted by BMS in support of their triple combination indication for the addition of a TZD to the combination product Glucovance™ (Metformin Hydrochloride+Glibenclamide fixed-dose combination, MET/Glib), which has been approved in the US. Data from these three studies were not integrated due to the different data format and coding dictionaries utilised by the two companies. A total of 1,202 patients were included. This number does not include patients from Study CV138055OL TCE, since these are already counted in the core double-blind study CV138055. A total of 900 patients were treated with RSG, comprising of 561 patients from Study 134, 181 patients from Study CV138055 and a further 158 patients treated in the OL extension who were previously treated with placebo.

Table 4: Triple Therapy Studies

Study Number	Duration	RSG Total Daily Dose (Regimen)	Treatment Groups[1]	Patient Numbers[2]	Report Location
134	26 weeks	4mg (bd) 8mg (bd)	RSG+MET+SU MET+SU	837 (826)	m5.3.5.1
CV138055	24 weeks	4mg (od) - 8mg (bd)	RSG+MET+SU MET+SU	365 (365)	m5.3.5.1
CV138055 OL TCE	20 weeks	4mg (od) - 8mg (bd)	RSG+MET+SU	313 (313)	m5.3.5.2

1. Studies 134 and CV138055 were double-blind, placebo-controlled, i.e. placebo was added-on to background SU+MET. In the BMS studies CV138055 and CV138055OL TCE, MET+SU refers to the fixed-dose combination product Glucovance™.
2. Indicates all randomised patients, and in brackets intent-to-treat (ITT) population (i.e., all randomised patients who had a baseline and at least one on-therapy efficacy assessment).
3. Abbreviations: RSG = rosiglitazone; MET = metformin; SU = sulphonylurea (including glibenclamide, gliclazide, glipizide and glimepiride); TCE = triple combination extension; OL= open-label; DB = double-blind; bd = twice daily, od = once daily

2.1.1. Main studies

GSK Study **134** was a 26-week DB, PG study in patients with T2DM. Men and women diagnosed with T2DM and aged between 35 and 75 years were eligible. Fasting C-peptide had to be ≥1.0ng/mL. Prior use of RSG, insulin or anorectic agents was excluded. Patients were taking SU+MET for at least 3 months prior to screening. Following titration to protocol-specified doses of SU (maximal labelled glibenclamide, 20mg/day) and MET (maximally effective doses of 2,000mg/day) combination therapy, patients entered a four-week single-blind placebo run-in/maintenance period of four weeks. At the end of this period, patients inadequately controlled on combination therapy (FPG ≥140mg/dL and ≤ 270mg/dL)

were randomised to receive placebo, 4mg/day RSG, or 8mg/day RSG for 26 weeks, in addition to SU+MET. Doses of SU and MET remained at the protocol-specified doses.

Study **CV138055** was a 24-week DB, PG study in patients with T2DM. Men and women diagnosed with T2DM and aged between 20 and 78 years with BMI ≥23 and ≤40kg/m^2were eligible. Prior to study entry, patients were taking either MET+SU combination therapy, or monotherapy with SU, MET or a TZD, for at least 8 weeks, at doses specified in the protocol. During a 2 to12-week open-label lead-in phase, all patients were administered MET/Glib fixed-dose combination and titrated up to doses of at least 1,500mg/7.5mg daily, and a maximum of 2,000mg/10mg daily. Following the lead-in phase, patients who remained inadequately controlled (HbA1c >7.0% and ≤ 10.0%), were randomised to 4mg/day RSG or matching placebo, in addition to continuing open-label MET/Glib at the same dose, for 24 weeks. During the double-blind RSG treatment phase, patients who had HbA1c ≥7.0 % or FPG ≥126mg/dL, had the RSG dose increased to 8mg/day.

Study **CV138055OL TCE** was a 20-week OLE of Study CV138055. The study was designed to allow patient rescue from the DB treatment phase for lack of glycaemic control and to collect additional safety and efficacy information on triple combination therapy. Patients who either completed the double-blind RSG treatment phase in Study CV138055, or who were discontinued from CV138055 due to lack of glycaemic control, were eligible. All patients maintained their lead-in MET HCl/Glib dose. Patients taking 4mg/day RSG triple combination therapy, with HbA1c ≥7.0% or FPG ≥126mg/dL, had their RSG dose increased to 8mg/day.

From the above it is obvious that study 134 is pivotal to the application.

2.1.2. Methods

Mean change from baseline in HbA1c (ITT, LOCF) was the primary efficacy variable.

2.1.3. Results

2.1.3.1. 6-month glycaemic efficacy

Patient disposition for 134 is given in Table 5. There were no remarkable findings.

Table 5: Study 134 Reasons for Withdrawal Post-Randomisation (All Randomised Patients)

	SU + MET+PBO N = 276	8mg RSG+MET+SU N = 280	4mg RSG+MET+SU N = 281
Completed Study, n (%)	226 (81.9)	239 (85.4)	238 (84.7)
Total withdrawn, n (%)	50 (18.1)	41 (14.6)	43 (15.3)
Adverse Experience[1]	12 (4.3)	13 (4.6)	12 (4.3)
Lack of efficacy	26 (9.4)	1 (0.4)	9 (3.2)
Other[2]	12 (4.3)	27 (9.6)	22 (7.8)

1. AE onset may have occurred either before or after randomisation.
2. Other category includes lost to follow-up and protocol deviations
3. Data Source: Section 13, Table 13.3.1 from Study 134 CSR.

Six-month efficacy results for HbA1c and FPG changes from baseline in trial 134 are given in Table 6.

Table 6: Study 134 Glycaemic Efficacy Parameters at Week 26 Compared to Baseline and Placebo(ITT with LOCF)

	Treatment Group		
HbA1c (%)[2]	**PBO+MET+SU**	**8mg RSG+MET+SU**	**4mg RSG+MET+SU**
N [1]	272	277	275
Baseline (mean ± SD)	8.7 ± 1.28	8.7 ± 1.17	8.6 ± 1.14
Week 26 (mean ± SD)	8.9 ± 1.49	7.8 ± 1.24	8.2 ± 1.31
Change from Baseline (mean ± SD)	0.2 ± 1.04	-0.9 ± 1.15	-0.4 ± 1.05
95% CI	(0.1, 0.3)	(-1.1, -0.8)	(-0.6, -0.3)
p-value [3]	0.0054	<0.0001	<0.0001
Comparison with MET+SU	-		
(adjusted mean)		-1.1	-0.6
95% CI [4]		(-1.3, -0.9)	(-0.8, -0.4)
p-value [5]		<0.0001	<0.0001
Fasting Plasma Glucose (mg/dL)[2]			
N[1]	273	277	276
Baseline (mean ± SD)	189.3 ± 45.83	191.5 ± 46.57	190.4 ± 45.86
Week 26 (mean ± SD)	202.9 ± 51.29	151.4 ± 53.48	171.8 ± 55.88
Change from Baseline (mean ± SD)	13.6 ± 50.78	-40.1 ± 54.33	-18.6 ± 53.89
95% CI	(7.6, 19.7)	(-46.5, -33.7)	(-24.9, -12.2)
p-value [3]	<0.0001	<0.0001	<0.0001
Comparison with MET+SU			
(adjusted mean)		-51.6	-30.1
95% CI [4]		(-60.8, -42.5)	(-39.2, -20.9)
p-value [5]		<0.0001	<0.0001

1. N = number of patients with values at baseline and week 26 (using LOCF).
2. Reference range for HbA1c <6.5%; reference range for FPG: 13-50 years, 70-115mg/dL; ≥51 years, 70-125mg/dL
3. From paired t-test.
4. From Dunnett's procedure using standard error from estimate statements within GLM model.
5. 1. From comparisons of LS means within GLM model; significance level: 0.0270.
6. Data Source: Section 14, Table 14.2 and Table 14.3A from Study 134 CSR.

In Study 134, HbA1c responders were defined as patients who achieved a reduction in HbA1c of ≥0.7% from baseline to week 26. Of the patients treated with PBO+MET+SU, 15.8% met the definition of responder compared to 38.9 % of patients on 4mg RSG+MET+SU and 62.8% of patients on 8mg RSG+MET+SU therapy.

In CV130855 there was a significant reduction in HbA1c in the RSG+MET+SU group when compared with those treated with PBO+MET+SU only, with a difference of -1.02% between groups (p<0.001).

Subgroup data
Subgroup analyses for sex, age, baseline BMI and baseline HbA1c were performed in trial 134 and are summarised in Table 7. Generally, the findings are consistent with the overall analysis. Lower efficacy of RSG in males *vs.* females and in lower BMI strata *vs.* higher BMI strata have been seen in other trials with RSG and may be expected from the pharmacology. Of some interest is the observation that efficacy of RSG add-on seemed enhanced in patients with higher baseline C-peptide and in patients who reduced the SU dose during triple therapy (not shown in table).

Table 7: Study 134 Change from Baseline at Week 26 in HbA1c by Gender, Age, Baseline BMI and Baseline HbA1c (ITT with LOCF)

	Treatment Group		
	PBO+MET+SU	**8mg RSG+MET+SU**	**4mg RSG+MET+SU**
Gender			
Males, n[1]	165	171	161
mean ± SD	0.18 ± 1.13	-0.84 ± 1.06	-0.28 ± 0.96
Females, n[1]	107	106	114
mean ± SD	0.18 ± 0.91	-1.09 ± 1.26	-0.64 ± 1.13
Age			
<65 years, n[1]	215	228	219
mean ± SD	0.21 ± 1.09	-0.92 ± 1.18	-0.39 ± 1.11
≥65 years, n[1]	57	49	56
mean ± SD	0.07 ± 0.87	-0.97 ± 0.96	-0.59 ± 0.71
Baseline BMI			
<27kg/m^2, n[1]	46	42	40
mean ± SD	0.09 ± 1.01	-0.70 ± 1.07	-0.12 ± 0.8
≥27kg/m^2, n[1]	226	235	235
mean ± SD	0.20± 1.05	-0.97 ± 1.16	-0.48 ± 1.08
Baseline HbA1c			
<9%, n[1]	173	170	172
mean ± SD	0.30 ± 0.92	-0.57 ± 0.98	-0.26 ± 0.84
≥9%, n[1]	99	107	103
mean ± SD	-0.03 ± 1.21	-1.50 ± 1.17	-0.71 ± 1.27

1. n= those patients who had both a baseline and a week 26 value.
2. Data Source: Section 14, Table 14.4.1, Table 14.4.2, Table 14.4.3 and Table 14.4.4 from Study 134 CSR.

2.1.3.2. Long-term glycaemic efficacy

Study CV138055OL TCE provided a limited amount of data from 20W OLE. The findings do not contradict maintained glycaemic efficacy of RSG+MET+SU during that period.

2.1.3.3. Other efficacy data

Lipids

As anticipated, RSG as add-on to MET+SU was associated with moderate increases in TC (due to some rise in both HDL-C and LDL-C), essentially neutral effects on HDL:LDL and TG, and reductions of FFA. No strict dose-response was seen. Use of lipid-lowering agents was similarly distributed between treatment groups.

2.1.4. CHMP Position

The CHMP acknowledged that the addition of a third OHA to patients having exhausted maximal/optimal insulin secretagogue (SU) plus insulin sensitiser (MET) would appear contrary to current practice, where these patients would be switched to insulin or insulin plus MET. While it is conceded that trial 134 showed clear and dose-ordered add-on effect on glycaemic control of RSG to background maximal/optimal SU+MET in the study population, the CHMP opinion is that the following points are to be taken into account:

- The trial enrolled patients on stable SU (at least half maximal dose) plus MET ≥1,000 mg, who were then rapidly (during 1-4 weeks) titrated to maximal glibenclamide plus MET 2,000 mg. Failure was declared after four weeks' maintenance on this combination. To what extent the randomised population would be representative of patients seen in clinical practice should be better discussed.
- Subgroup analyses indicated enhanced efficacy of RSG add-on in patients who reduced the SU dose during the study period. Generally, the role of maintained maximal SU in the triple combination (other than increasing the risk of hypoglycaemia, and fluid retention see safety assessment) is unclear and the CHMP considered that this should be discussed further. It may be that, as briefly discussed in the clinical overview, better use of RSG within a triple therapy would be in (obese and insulin resistant) patients failing on MET+RSG and then having a (low) dose of insulin secretagogue added. This has not been tested, however. The validity of the arguments that

what has been tested is a worst-case scenario for hypoglycaemic safety and that efficacy outcomes of a triple combination would be independent of the order of dosing of the individual components appears rather thin and should be substantiated further.

- The great majority of randomised patients were obese and subgroup analyses indicated enhanced efficacy of RSG add-on at higher BMI and among patients with higher baseline C-peptide. This provides further arguments that any triple therapy indication should focus on the overweight and insulin resistant, as for the currently approved RSG+MET dual therapy indication.
- Given the fact that the efficacy of SU is relatively less pronounced in obese patients with higher C-peptide levels and that great majority of randomised patients in the trials fell within this particular group, the CHMP considered that the value of continuing SU therapy in the triple group vs. replacement of SU by RSG should be discussed.

The MAH was requested through an RSI (adopted at September 2004 CHMP meeting) to address the different concerns from the CHMP regarding the tripe therapy. In the RSI the MAH was requested to answer the following questions:

Question

The proposed addition of a third OHA to patients having exhausted maximal/optimal insulin secretagogue (SU) plus insulin sensitiser (MET) would appear contrary to established practice, where these patients would be switched to insulin or insulin plus MET. The MAH should justify why an insulin-comparative trial was not performed and provide any external data to illustrate how triple therapy with RSG+MET+SU would compare with a switch to insulin in patients failing on MET+SU.

Further, the practical clinical implications of the results are questioned. In most cases adding RSG to MET+SU would be of little help to failing patients taking the slow onset of antiglycaemic activity of RSG into consideration. On the contrary, patients on RSG+MET might benefit of the add-on of a SU. These issues should be discussed by the MAH.

Summary of MAH response

- C-peptide data from 134 and CV130855 demonstrate that the majority of patients who fail to achieve control on MET+SU are insulin-resistant rather than insulin-deficient. This is considered representative of a real-world scenario in T2DM. Those T2DM patients who still have an adequate insulin response with SU may benefit from RSG triple combination.
- An insulin comparator study was not performed as RSG triple oral therapy is not viewed by the MAH as a treatment strategy that replaces insulin. It should be seen as a therapeutic option for those patients who are insulin-resistant and still have some pancreatic reserve.
- Reference is made to a presentation at EASD 2004 of a 24-week study in patients failing MET+SU being randomised to RSG or insulin glargine as the third agent. The MAH interprets the findings as indicative of similar glycaemic control in the two groups. Further, a small 16-week study comparing PIO (pioglitazone) triple therapy with bedtime NPH in patients failing MET+SU gave similar results.
- The MAH acknowledges the slow onset of effect of RSG, but points out that in both 134 and CV130855 maximal effect on glycaemia was reached by 18 weeks. Similar findings were made in a published trial.
- The MAH concludes that the body of evidence clearly demonstrates that RSG triple combination therapy provides a useful addition to the established therapeutic options and may delay the need for insulin therapy in patients who are taking OAD, the majority of whom are insulin resistant rather than insulin deficient.

CHMP Comment:

A comprehensive comment on efficacy of triple RSG therapy is given below after question 6 of the RSI. Suffice it here to say that the EASD abstract referred to in the response (Rosenstock J *et al.*) referred to an open label study (n=217) that randomised patients failing on MET+SU to RSG 4-8 mg or insulin glargine (titrated to FPG ≤5.5mmol/l) as add-on. At 24 weeks change from baseline in HbA_{1c} was not different between groups, but insulin glargine had better efficacy in patients with baseline HbA_{1c} ≥9.5,

had better effect on FPG (at the price of more nocturnal hypoglycaemia), had less effect on weight gain, and was associated with fewer AEs than RSG triple therapy.

Question

The trial enrolled patients on stable SU (at least half maximal dose) plus MET ≥1,000 mg, who were then rapidly (during 1-4 weeks) titrated to maximal glibenclamide plus MET 2,000 mg. Failure was declared after four weeks' maintenance on this combination. To what extent the randomised population would be representative of patients seen in clinical practice should be better discussed. Data should be provided on randomised patients on maximal SU+MET already at enrolment.

There is also a concern that, during the titration period, patients treated with MET >2,000 mg at enrolment may have been down-titrated to MET 2,000 mg. The question arises whether this could have made previously sufficiently controlled patients eligible for triple therapy. The MAH should clarify and present efficacy analyses with any such patients excluded.

Summary of MAH response

- Reanalysis indicated that 43% of patients in 134 were on max MET + max SU at screening. Demographic characteristics were similar to those in the FAS.
- A *post hoc* analysis of effects on glycaemia was performed in this subset. Data for HbA_{1c} are given in the table below. The effect size was essentially identical to that seen in FAS.

Table 3. 4 Change in HbA1c at Week 26 Compared to Baseline (ITT Population with LOCF; Patients receiving max. MET + max. SU at Screening)

	Treatment Group		
HbA1c (%)	PBO	RSG 2mg bd	RSG 4mg bd
N	121	121	120
Baseline (mean ± SD)	8.84 ± 1.25	8.76 ± 1.17	8.88 ± 1.09
Week 26 (mean ± SD)	9.06 ± 1.46	8.31 ± 1.26	7.83 ± 1.24
Change from Baseline (mean ± SD)	0.23 ± 1.11	-0.42 ± 0.96	-1.05 ± 1.22
Median	0.2	-0.5	-1.0
Range	-4.1 – 2.9	-3.6 – 3.2	-4.1 – 4.4

Data Source: AdHoc 1294.2.2

- In total, there were 175 patients who took MET >2,000 mg at screening ((PLA 62, 4 mg RSG 52, 8 mg RSG 61). Data on HbA_{1c} in patients who received submaximal MET (≤2,000 mg) at baseline are given in the table below. Again, the response in this subset was very similar to that seen overall.

Table 3. 6 Change in HbA1c at Week 26 Compared to Baseline in Patients Taking ≤2000 mg Metformin at Screening (Intent-to-Treat Population with LOCF; Patients on ≤ MET at Screening)

	Treatment Group		
HbA1c (%)	**PBO**	**RSG 2mg bd**	**RSG 4mg bd**
N	210	223	216
Baseline (mean ± SD)	8.70±1.29	8.59±1.15	8.68±1.18
Week 26 (mean ± SD)	8.80±1.49	8.14±1.35	7.74±1.24
Change from Baseline (mean ± SD)	0.11±1.09	-0.45±1.075	-0.94±1.098
Comparison with Baseline Mean (95% CI), p value	0.12 (-0.02 to 0.26) p=0.1036	-0.47 (-0.61 to -0.39) p<0.0001	-0.93 (-1.07 to -0.79) p<0.0001
Comparison with Placebo Mean (95% CI), p value		-0.59 (-0.78 to -0.39) p<0.0001	-1.05 (-1.25 to -0.85) p<0.0001

Data Source: AdHoc 1340

Question

Subgroup analyses indicated enhanced efficacy of RSG add-on among patients who reduced the SU dose during the study period. Generally, the role of maintained maximal SU in the triple combination (other than increasing the risks of hypoglycaemia and fluid retention, see safety assessment) is unclear and should be discussed further. It may be that, as briefly discussed in the clinical overview, better use of RSG within a triple therapy would be in (obese and insulin resistant) patients failing on MET+RSG and then having a (low) dose of insulin secretagogue added. This has not been tested, however. The validity of the arguments that what has been tested is a worst-case scenario for hypoglycaemic safety and that efficacy outcomes of a triple combination would be independent of the order of dosing of the individual components appears rather thin and should be substantiated further.

Summary of MAH response

- Regarding patients who reduced the dose of SU during the study, it is noted that this happened in 19% of patients in 134. In all but four cases, the dose reduction was necessitated by an AE of hypoglycaemia.
- The MAH discusses the role of maintained maximal SU mainly from a safety perspective. It is noted that 134 had a forced titration design, which may not reflect clinical practice, where RSG would be introduced slowly, taking into account any tendency to hypoglycaemia and down-titrating the dose of SU as needed. The MAH also brings forward arguments against the reasoning that maximal dose SU may contribute to increased risk of oedema. In the 8 mg RSG+SU dataset, there were no differences in oedema rates between studies exploring add-on of RSG to maximal *vs.* submaximal doses of SU. The risks of hypoglycaemia and oedema are considered most likely correlated with the introduction and dose of RSG with consequent insulin sensitisation.
- As regards the order of dosing and "worst case scenario" issues, the MAH maintains that adding RSG to existing MET+SU is most likely to cause hypoglycaemia due to insulin sensitisation. As the insulin-sensitisation effect of RSG takes some weeks to achieve maximal effect, hypoglycaemia may be difficult to predict. If SU were to be added to MET+RSG (a combination that does not increase fasting insulin levels), the starting dose of SU should probably be low. In conclusion, the MAH reiterates that study data from 134 and CV138055 provide clear evidence regarding efficacy and manageable safety of adding RSG in triple therapy, in a worst-case scenario for hypoglycaemic risk. The MAH acknowledges that, from a theoretical viewpoint, better use of RSG within a triple combination could be to add a low dose of SU to (overweight and presumably insulin-resistant) patients failing on MET+RSG. There is limited support from RECORD interim for this approach.

Question

Given the fact that the efficacy of SU is relatively less pronounced in obese patients with higher C-peptide levels and that great majority of randomised patients in the trials fell within this particular group, the value of continuing SU therapy in the triple group vs. replacement of SU by RSG should be discussed.

Summary of MAH response

- The majority of patients in 134 were overweight and had higher C-peptide levels and were, thus, likely to be insulin-resistant, rather than insulin-deficient. In such populations, the combination of SU+RSG has been shown to improve insulin sensitivity and markers of β-cell function.
- There are no available data on switching from MET+SU to MET+RSG in failing patients. Given the efficacy data obtained in 134, which showed add-on efficacy of RSG irrespective of baseline BMI or C-peptide stratum, the MAH would consider it inappropriate to withdraw SU when initiating RSG as a general measure.

Table 5. 1 Mean change from baseline in HbA1c and FPG according to baseline BMI and C-peptide concentration

	Treatment Group		
HbA1c (mean change from baseline)	**PBO+MET+SU**	**8mg RSG+MET+SU**	**4mg RSG+MET+SU**
Baseline BMI			
<27 kg/m^2 (n)	46	42	40
mean ± SD	0.1 ± 1.01	-0.7 ± 1.07	-0.1 ± 0.80
≥27 kg/m^2 (n)	226	235	235
mean ± SD	0.2 ± 1.05	-1.0 ± 1.16	-0.5 ± 1.08
C-peptide*			
<0.66 nmol/L (n)	33	41	39
mean ± SD	0.1 ± 1.41	-0.7 ± 1.11	-0.6 ± 0.86
≥0.66 nmol/L (n)	239	236	236
mean ± SD	0.2 ± 0.99	-1.0 ± 1.15	-0.4 ± 1.07
Fasting Plasma Glucose (mean change from baseline)	**PBO+MET+SU**	**8mg RSG+MET+SU**	**4mg RSG+MET+SU**
Baseline BMI			
<27 kg/m^2 (n)	46	42	40
mean ± SD	11.7 ± 54.06	-28.5 ± 54.64	-5.8 ± 50.42
≥27 kg/m^2 (n)	227	235	236
mean ± SD	14.0 ± 50.20	-42.1 ± 54.13	-20.7 ± 54.26
C-peptide*			
<0.66 nmol/L (n)	33	41	39
mean ± SD	20.1 ± 54.79	-18.2 ± 52.84	-23.6 ± 52.99
≥0.66 nmol/L (n)	240	236	237
mean ± SD	12.8 ± 50.26	-43.9 ± 53.79	-17.7 ± 54.11

* 0.66 nmol/L = 2 ng/mL

Question

The great majority of randomised patients were obese and subgroup analyses indicated enhanced efficacy of RSG add-on at higher BMI and in patients with higher baseline C-peptide. This provides further arguments that any triple therapy indication should focus on the overweight and insulin resistant, as for the currently approved RSG+MET dual therapy indication.

Summary of MAH response

- The MAH acknowledges that the therapeutic value of RSG could be expected to be greatest in the overweight, insulin-resistant patients, who made up the great majority of the study population in 134.

- A revised indication is proposed:
  Rosiglitazone is indicated in the treatment of type 2 diabetes mellitus:
  As triple oral therapy in combination with metformin and a sulphonylurea in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

2.1.5. CHMP Conclusion

Taking into account the data originally presented in the dossier and the argumentation in the response, the following appears relevant:

There is clear efficacy on HbA_{1c} and FPG at group-level when RSG is added to failing MET+SU in a T2DM population dominated by overweight and insulin-resistant patients. The methodological concerns raised regarding trial 134 appear acceptably resolved.

No comparative trial *vs.* insulin as add-on or alternative therapy in patients failing on MET+SU has been performed by MAH and there is little peer-reviewed data available. From what is available, it appears likely that RSG may be less effective than insulin, at least in patients with poor control, and very likely that the onset of effect is slower with RSG, compared with insulin. Whether the delay in glycaemic effect with RSG corresponds to a loss of chance for the patient may be speculative.

As stated by MAH, it appears likely that the test of RSG as add-on to maximal MET+SU represents an unfavourable scenario for risk of hypoglycaemia and that more rational and better tolerated use of RSG within a triple combination could be when SU is added as the third component. Taking into account the different modes of action of MET, SU and RSG, the CHMP do not consider the lack of specific study data for this approach as a critical deficiency.

From an efficacy perspective it does not appear reasonable to exclude that RSG could be used within triple OAD and that a therapeutic indication could be granted, especially if limited to overweight patients. However, the SPC should be strengthened in order to highlight that in the decision to start triple OAD, the alternative to introduce insulin therapy should be taken into consideration. The CHMP proposed a more strengthened wording for section 4.4 which has been accepted by the MAH (see Annex 5).

3. Clinical safety

The safety profile of RSG has been well delineated within MAA, multiple variation procedures and continuous follow-up of extensive post-marketing data, as described in detailed PSUR assessments. The current assessment will focus entirely on adverse reactions of known interest and how these are affected by the proposed use of RSG 8 mg in combination with SU and use of RSG within a triple combination containing also SU and MET. The adverse reactions of interest are considered to be:

- Fluid retention (oedema) and congestive heart failure (CHF)
- Weight gain
- Anaemia
- Hypoglycaemia
- Dyslipidaemia
- Hepatobiliary events

3.1. Oedema and CHF

TZD including RSG have dose-related effects to fluid retention with oedema. Oedema is also more common in females and in the elderly. It is incontrovertible that fluid retention can cause or aggravate CHF in predisposed patients. This is adequately described in the current SPC.

3.1.1. Triple therapy

In trial 134, oedema AEs were reported in 4.0%, 10.0% and 14.3% in the PBO+MET+SU, 4 mg RSG+MET+SU and 8 mg RSG+MET+SU, respectively. CHF events were over-represented with RSG+MET+SU (1.1% and 1.8% in RSG 8 mg and 4 mg, respectively), compared with PBO+MET+SU (0.4%). No reports of CHF were noted in CV138055.

3.1.2. CHMP Position

No qualitatively new signal is generated. The clear dose relationship for risk of oedema is well known. However the CHMP considered that this should be reflected in the SPC (section 4.4) knowing that the increased dosage of RSG with SU may be accepted. The information in the SPC is otherwise generally adequate but percentages given in section 4.8 should be checked and justified by MAH. The reporting rate for CHF in trial 134 appears to be the highest recorded outside RSG+insulin combo trials. Even though the observations are few, the CHMP considers that this creates a concern that full insulin sensitisation with RSG+MET together with maximum-dose insulin secretagogue may not be such a good idea. The MAH was requested to comment on this through question 9 of the RSI.

The MAH was requested to answer the following question (RSI September 2004):

Question

No qualitatively new signal is generated. The clear dose relationship for risk of oedema should be reflected in the SPC (section 4.4). The information in the SPC is otherwise generally adequate but percentages given in section 4.8 should be checked and justified by MAH. The reporting rate for CHF in triple therapy trial 134 appears to be the highest recorded outside RSG+insulin combo trials. Even though the observations are few, this creates a concern that full insulin sensitisation with RSG+MET together with maximum-dose insulin secretagogue may not be such a good idea. The MAH should comment.

Summary of MAH response

- The dose-relatedness of oedema has been highlighted in the revised SPC, section 4.4. Percentages for oedema AEs in different RSG combinations have been recalculated, taking into account the integrated databases, including the Avandamet database for MET+RSG, see SPC section 4.8 (See Annex 5).
- Regarding the incidence of CHF-related AEs in 134, the MAH wishes to point out that the population enrolled had a long mean duration of T2DM and a high incidence of cardiovascular risk factors, and that the incidence of CHF in the control group was also higher than in control groups of SU+RSG trials. The incidence of CHF in 134 did not appear to be dose-dependent. There were no fatal cases of CHF and none of the CHF events were independently adjudicated as true CHF events. The notion that maximal SU in combination with RSG should be a specific risk factor for CHF is considered contradicted by findings from SU+RSG trials using submaximal and maximal doses of SU, respectively.
- The MAH emphasises that an individualised approach to triple combination therapy is necessary in order to achieve appropriate glycaemic control while minimising the risk of adverse events. The revised Product Information is considered appropriate to alert the prescriber to this.

3.1.3. CHMP Conclusion

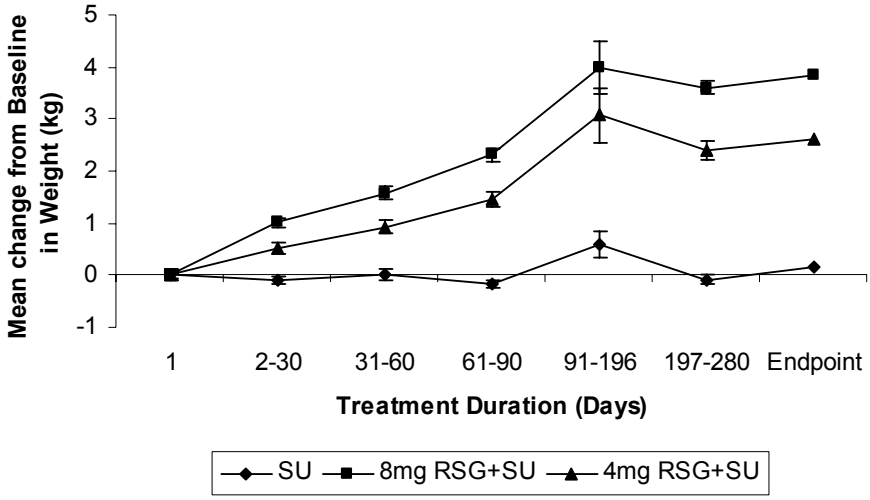
The CHMP is of the opinion that the SPC amendments regarding dose-relatedness and incidence of oedema are considered acceptable. The concerns regarding tolerability of RSG triple therapy from viewpoints of fluid retention and risk of CHF remain. As noted by the MAH, triple therapy would be an option in a patient population with long duration of T2DM and high accumulated incidence of cardiovascular risk factors. Even in the absence of peer-reviewed, insulin-comparative data, the contributory role of RSG appears obvious. In the above-mentioned (Q2-6) abstract from EASD 2004, the incidence of oedema was 12.5% on MET+SU+RSG, compared with 0% on MET+SU+Insulin glargine. Weight gain was significantly greater on the triple OAD combination. This must be taken into account in the overall risk-benefit assessment. Indeed, an individualised approach to triple RSG therapy appears

necessary. Possibly, this could be managed through further strengthening of the SPC. The CHMP requests the MAH to make the changes accordingly, as presented in Annex 5. The MAH is in agreement with the proposed wording of the CHMP, for section 4.8 of the SPC.

3.2. Weight gain

Weight gain is a well-described feature of treatment with TZD, particularly in combination with SU. It may be due in part to fluid retention, but more importantly to (mainly subcutaneous) fat deposition. Weight gain during treatment with TZD has not been shown to affect metabolic control or BP control negatively, or to be a specific risk factor for dyslipidaemia during such treatment. The eventual impact on (cardiovascular and other) outcomes remains to be determined. Weight evolution during RSG+SU studies is illustrated below.

Figure: Mean (SE) Change from Baseline in Weight (Kg) at Defined Intervals and Study Endpoint (Week 24 or 26) in the RSG+SU DB Dataset (Randomised Population)



CHMP Position:

No new signal is generated by submitted data. Acceptable analyses have been provided for relationship between degree of weight gain and metabolic control, BP control, lipids. The MAH was requested to give background on the percentages for weight gain given in section 4.8 through a RSI.

The MAH was requested to answer the following question (RSI September 2004):

Question
Percentages for weight gain given in section 4.8 of the SPC should be explained and justified.

Summary of MAH response
The MAH has updated the percentages in section 4.8 of the SPC, focusing on available long-term data. This takes into account the Avandamet database for MET+RSG, 24-month trial 135 for SU+RSG, and extension data for CV138055 OL TCE for RSG triple therapy.

CHMP Conclusion:

The justifications for these amendments appear appropriate to the CHMP and the MAH proposal in section 4.8 of the SPC has been considered acceptable for the CHMP.

3.3. Hypoglycaemia

RSG when used in combination with SU will increase the risk of hypoglycaemia in parallel with improvement of glycaemic control. In the current data-base hypoglycaemia AEs were, expectedly, most commonly reported in trial 134, which tested RSG as add-on to full-dose SU and MET (Table 13).

Table 13: Overview of Hypoglycaemia in the Triple Therapy Study 134 (Randomised Population)

Parameter	Study 134		
	PBO+MET+SU N=276 n (%)	8mg RSG+MET+SU N=280 n (%)	4mg RSG+MET+SU N=281 n (%)
Hypoglycaemia	27 (9.8)	97 (34.6)	75 (26.7)
Hypoglycaemia with FPG <50mg/dL	0	2 (0.7)	1 (0.4)
Hypoglycaemia with corrective therapy[1]	7 (2.5)	62 (22.1)	37 (13.2)
Hypoglycaemia SAEs	0	0	1 (0.4)
Hypoglycaemia AE withdrawals	0	2 (0.7)	0

In the 8 mg RSG+SU DB set (representing mostly trials with submaximal SU), hypoglycaemia was reported at 11.1%.

CHMP Position:

Even though there were no hypoglycaemia SAEs, the high reporting rate in triple combination may create some concern. It is reasonably related to the full-dose SU used. As mentioned in the efficacy assessment, the MAH was requested to further expand on the overall suitability of combining RSG with full-dose SU in triple combination.

The MAH was requested to answer the following question (RSI September 2004):

Question

Even though there were no hypoglycaemia SAEs, the high reporting rate in triple combination may create some concern. It is reasonably related to the full-dose SU used. The overall suitability of combining RSG with full-dose SU in triple combination should be better discussed by MAH. The SPC should also highlight the risk of hypoglycaemia increases in dose-related manner when RSG is used in combination with SU (dual or triple).

Summary of MAH response

- The MAH notes that a very conservative approach to monitoring of hypoglycaemia was used in the triple RSG trials, especially in CV130855.
- The hypothesis that maximal dose of SU contributed is not supported by findings in trials CV130855 and 134. Hypoglycaemia was recorded more frequently in CV130855, despite the use of submaximal SU in this trial. Further, data from SU+RSG studies do not support that the risk of hypoglycaemia is primarily related to SU dose level.
- The MAH does not believe that hypoglycaemia seen in RSG triple therapy is any worse than that seen with insulin.
- In the revised SPC, a precautionary statement regarding risk of hypoglycaemia when RSG is used in combination has been introduced in section 4.4 (see Annex 5).

CHMP Conclusion:

Proposed amendments to the SPC are acceptable to the CHMP (see Annex 5).

3.4. Need for change of concomitant medications

In the RSI The MAH was requested to provide further data concerning concomitant medication in each treatment group for the trial 134.

The MAH was requested to answer the following question (RSI September 2004):

Question

For trial 134, the MAH is asked to provide detailed data concerning concomitant medication in each treatment group:
How many patients started therapies with diuretics, lipid-lowering agents, anti-hypertensives or weight-reducing agents during the study?
In how many patients with pre-existing therapies with diuretics, lipid-lowering agents, anti-hypertensive agents or weight-reducing agents, were these doses increased?

Summary of MAH response

- The proportion of patients in 134 who initiated a diuretic, an antihypertensive or a lipid-lowering agent during the study and who remained on this medication at study end is given in the table below. It is noted that use of RSG necessitated increased introduction mainly of diuretic therapy.

Table 12. 1 Patients who initiated diuretic, antihypertensive or lipid lowering agents during study

	Placebo	RSG 4mg	RSG 8mg
	N = 276 n (%)	N = 281 n (%)	N = 280 n (%)
Diuretic	1 (0.36)	4 (1.42)	13 (4.64)
Antihypertensive	4 (1.45)	11 (3.91)	8 (2.86)
Lipid lowering	9 (3.26)	16 (5.69)	8 (2.86)

- For patients who were on diuretic, antihypertensive or lipid-lowering agents already at study start, no relevant between-group differences were noted.

CHMP Conclusion:

The requested information has been provided. Findings were as expected. The CHMP considers the response satisfactory.

3.5. Anaemia

RSG dual and triple combination therapy was associated with a dose-related increase in events of anaemia. The highest incidences were reported in triple combination, *i.e.* when RSG was used in combination with MET. This is in line with what has been previously described and has not been fully explained. There were no anaemia SAEs with 8mg RSG combination therapy. Furthermore, the majority of reported anaemia AEs did not correspond to a decrease in Hb and/or Hct to a value predefined as of potential clinical concern.

CHMP Conclusion:

Anaemia, interpreted as (mainly) dilutional is a well-described feature of RSG and other TZD. There is still no definite signal of myelotoxicity of this class of agents. No new signal is generated by the submitted data.

3.6. Dyslipidaemia

As described in the efficacy section, RSG was associated with expected and dose-related changes of the lipid pattern in submitted trials. Dyslipidaemia AEs were reported more frequently with RSG than control both in dual and triple therapy combinations.

CHMP Conclusion:

No new signal is created. The eventual clinical impact of RSG on cardiovascular risk will hopefully be better illustrated after finalisation of the RECORD outcome trial.

3.7. Hepatobiliary events

It should be noted that the hepatic safety of RSG is being discussed in more detail within the variation EMEA/H/C/268/II/26. The currently submitted data did not provide signals of dose-related or other hepatotoxicity of RSG in excess of that seen with comparators.

4. Overall conclusion: Clinical efficacy and safety

4.1 RSG in triple combination with SU and MET

Pivotal trial 134 showed clear and dose-ordered add-on effect on glycaemic control of RSG 4-8 mg to failing background maximal/optimal SU+MET in a study population dominated by overweight and presumably insulin-resistant T2DM patients. Findings from an additional trial were supportive of efficacy and limited OLE data do not contradict sustainability of response up to approximately one year. Responses to RSI give reasonable reassurance regarding methodological issues raised.

The MAH has not performed a comparative trial *vs.* add-on of or switch to insulin, which would be the accepted therapeutic option in this situation. Preliminary external data indicate that antiglycaemic efficacy of RSG may be inferior to that of add-on insulin, at least in patients with poor glycaemic control. The time action profile of RSG also suggests that onset of effect would be delayed, compared with that of insulin, indicating a potential loss of chance for the patient. The mode of use of RSG tested, *i.e.* as third component of the triple combination is probably not optimal from the pharmacological point of view. The lack of data for other modes of use, *i.e.* triple therapy with SU added to a failing combination of MET+RSG is, however, not considered a major issue.
The safety profile of triple RSG therapy as tested creates concerns regarding increased fluid retention with risk for CHF, and hypoglycaemia. Partly, these problems may be explained by longer duration of T2DM and higher accumulated baseline risk for cardiovascular events in the population studied, but the contributory role of RSG seems clear. Again, preliminary external data suggest an inferior safety profile in comparison with that of add-on insulin.
Considering the above, triple therapy with MET+SU+RSG should not be brought forward as a first-line alternative in patients failing dual OAD. At the same time, it might be a relevant option in some patients, particularly overweight patients where insulin resistance may be considered an important reason for failure on dual OAD. Treatment needs to be individualised carefully, as also suggested by MAH.

The MAH agreed with comments from the CHMP and made the appropriate changes accordingly in the SPC and PL (cf. Annex 5). Therefore the therapeutic indication could be granted.

4.2 Benefit/risk

The overall benefit/risk assessment is considered acceptable.

CONCLUSION

The CHMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics and reflected into the Package Leaflet, based on the observations and the appropriate conclusions.

The CHMP adopted on 18 November 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.