European Medicines Agency

London,21 November 2007
Product name: **Avandia**
Procedure No: **EMEA/H/C/268/II/52**

SCIENTIFIC DISCUSSION

1. INTRODUCTION

Rosiglitazone (RSG) is a member of the thiazolidinedione (TZD) class of antidiabetic agents. It improves glycaemic control by improving insulin (INS) sensitivity. RSG, as Avandia, was approved in the European Union (EU) in 2000. It is approved for use as monotherapy in patients, particularly overweight patients, who cannot take metformin (MET), dual therapy in combination with MET or a sulphonylurea (SU), or triple therapy in combination with MET and an SU.

The combination use of RSG and INS has been approved in parts of the world. In the European Union (EU), the Avandia Summary of Product Characteristics (SPC) currently has a contraindication statement for use in combination with INS due to the dose-dependent fluid retention effects described in studies of RSG use with INS.

The Marketing Authorisation Holder (MAH) applied in this variation for an extended indication for Avandia including the combination with INS. Consequently, the MAH applied as well for the removal of the contraindication with INS.

2. Clinical aspects

2.1 Clinical Efficacy

The MAH in support of this extension of indication variation has submitted five double-blind, 26-week studies (Study 082, Study 085, Study 095, Study 136 and Study 347) and an open-label study OLE (Study 114) which have been conducted to evaluate RSG in combination with INS, where the sequence of treatment was the addition of RSG to existing INS therapy. Additionally, the MAH has submitted a clinical study (009) using Avandamet (RSG+MET) in combination with insulin as supportive of this extension of indication – in contrast to the aforementioned studies, the sequence of treatment was the addition of INS therapy to RSG.

All five of the double-blind studies were randomised and placebo-controlled. Four of the double-blind studies were 26 weeks in treatment duration (Study 082, Study 095, Study 085 and Study 136) and one was 24 weeks in treatment duration (Study 347). A single-blind placebo run-in period prior to randomisation was used in the double-blind studies to establish a routine and to ensure adequate compliance. Study 082 and Study 095 also had an optional 4-week insulin standardisation period (prior to the run-in period) where the insulin dose was adjusted and standardised to twice daily injections. The open-label study, OLE (Study 114), was designed as a 48-month study but was terminated when sufficient safety data became available (at 33 months), by the sponsor.

In total 1809 subjects participated in the five RSG and insulin double-blind studies and 410 entered subsequent long term treatment (Study 114) for up to 33 months. The RSG and insulin double-blind studies investigated total daily doses of RSG of 2mg/day, 4mg/day and 8mg/day; Study 095 assessed RSG administered once daily (od), Study 082 and Study 085 assessed RSG given twice daily (bd) and in Study 136 and Study 347 subjects received RSG either od or bd. All subjects entering the open label extension (OLE) study received RSG at a total daily dose (tdd) of 8mg/day, plus insulin, regardless of prior treatment or adequacy of glycaemic control in the double-blind study; subjects were maintained on the dosing regimen they received in the double-blind study. An 8mg tdd for RSG was chosen for the extension study to optimise glycaemic benefit and to obtain additional safety data at the higher dose.

In Table 1 below there is a summary of the submitted studies.

Table 1 Clinical studies utilising Rosiglitazone in combination with insulin

Study No.	Location	Study Design	No. Subjects Randomised/ Intent-to-Treat	Dose/Duration
Rosiglitazone and Insulin Double-blind Studies				
082	US	Randomised, double-blind, multi-centre study to evaluate the safety and efficacy of RSG when administered bd to subjects with T2D inadequately controlled on INS monotherapy	**Total: 319/313** 107/106 2mg bd RSG 105/103 4mg bd RSG 107/104 PBO	RSG 2mg, 4mg (bd)/ 26 weeks
085	Europe	Randomised, double-blind, multi-centre study to investigate the effects of RSG on INS requirements in INS treated T2D subjects	**Total: 277/276** 138/137 RSG 139/139 PBO	RSG 2mg, 4mg (bd)/ 26 weeks
095	US	Randomised, double-blind, multi-centre study to evaluate the safety and efficacy of RSG when administered od to subjects with T2D inadequately controlled on INS monotherapy	**Total: 292/287** 99/97 4mg od RSG 97/95 8mg od RSG 96/95 PBO	RSG 4mg, 8mg (od)/26 weeks
136	Europe	Randomised, double-blind, multi-centre, placebo controlled study to evaluate the efficacy and safety of RSG with concurrent INS therapy and/or a sulphonylurea in T2D subjects with chronic renal failure (not on dialysis)	**Total: 291/288** 148/145 RSG 143/143 PBO	RSG 4mg (od, bd)/ 26 weeks
347	US	Randomised, double-blind, multi-centre study to evaluate the safety and efficacy of RSG when administered od or bd to subjects with T2D inadequately controlled on INS monotherapy	**Total: 630/568** 209/193 2mg od RSG 209/189 2mg bd RSG 212/186 PBO	RSG 2mg (od, bd)/ 24 weeks
Rosiglitazone and Insulin Open Label Study				
114	US	An open-label extension study to assess the long term safety and efficacy of RSG when administered od or bd in combination with INS to subjects with T2D who successfully completed Studies 082 or 095	**Total: 410** 213 4mg bd RSG 197 8mg od RSG	4mg (bd), 8mg (od)/ 33 months

Key: RSG = rosiglitazone; INS = insulin; PBO = placebo; T2D = type 2 diabetes; bd = twice daily; od = once daily

In addition, the AVANDAMET Study 009 was a randomised, double-blind and placebo-controlled study with a 24-week treatment duration. The study design and entry criteria are given in detail later in this report.

In the RSG+INS studies, RSG was added to established insulin therapy whereas in AVANDAMET Study 009 insulin was added to established AVANDAMET therapy and titrated according to glycaemic status. An 8-week run-in period was used in AVANDAMET Study 009 to change prior oral anti-hyperglycaemic treatment to AVANDAMET and to identify subjects requiring additional glycaemic control.

In total 324 subjects participated in the AVANDAMET and insulin study (009), which assessed AVANDAMET administered at the maximum daily dose of RSG 8mg/MET 2000mg given in two 4mg/1000mg doses bd.

The following table, Table 2, presents information on the Study 009 conducted with Avandamet and insulin.

Table 2 Clinical study using Avandamet in combination with insulin

Study No.	Location	Objectives/ Main Inclusion Criteria	No. Subjects Randomised/ Intent-to-Treat	Dose/Regimen/ Duration
AVANDAMET and Insulin Double-blind Study				
009	Europe	Randomised, double-blind, multi-centre study to evaluate the safety and efficacy of addition of INS in subjects inadequately controlled on maximum dose AVANDAMET	**Total: 324/319** 163/161 AVANDAMET 161/158 PBO	AVANDAMET (RSG/MET) 4mg/1000mg, bd/ 24 weeks

The primary efficacy parameter for studies 009 and 347 was mean change from baseline in glycosylated haemoglobin (HbA1c) at 24 weeks, for Study 082, Study 095 and Study 136 mean change from baseline in HbA1c at 26 weeks and for Study 085 percent change from baseline in total daily insulin at 26 weeks.

The primary objective of the open label extension (OLE) study 114, was the evaluation of the safety and tolerability of RSG 8mg/day + INS combination therapy.

Further information on the studies for each one of them is presented and discussed below.

I. Study 082

Methods

Study design and entry criteria

Subjects were on insulin at a total daily dose ≥30 units (U) prior to screening and had HbA1c ≥ 7.5 %. The insulin regimen was standardised to twice-daily injections and the insulin dose was adjusted according to the investigator's discretion during a four week standardisation period. The standardisation period was followed by a four week run-in period.

Those subjects who were inadequately controlled (Fasting Plasma Glucose (FPG) ≥ 7.8mmol/L) at the end of the run-in period were eligible for randomisation to one of three treatment groups (INS, RSG 2mg bd + INS, RSG 4mg bd + INS). The study permitted changes in INS dose only for safety reasons.

The main exclusion criteria included subjects with hepatic disease, renal disease, cardiovascular disease, or anaemia as well as subjects with heart failure.

There was no titration of the RSG dose in this study while insulin could be titrated in the case of hypoglycaemia. Baseline mean insulin dose was higher in the RSG 4 mg bid group but otherwise there were no relevant differences in baseline characteristics or withdrawal rates.

In this study the target population (patients intolerant or with contraindications to MET) is not adequately represented.

Results

Glycaemic Efficacy

i. HbA1c

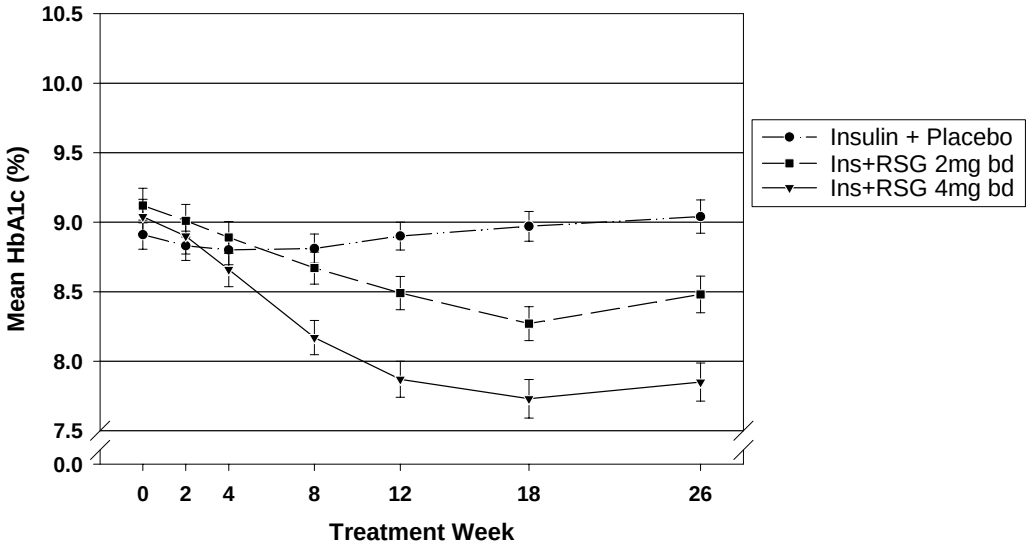
The table 3 below shows the change in HbA1c from baseline after 26 weeks of treatment.

Table 3 Change from Baseline in HbA1c at Week 26 (Intend-to-Treat (ITT) population)

HbA1c (%)	**INS+RSG 2mg bd (N=106)**	**INS+RSG 4mg bd (N=103)**	**INS (N=103)**
Baseline (mean±SD)	9.1±1.28	9.0±1.27	8.9±1.07
Week 26 (mean±SD)	8.5±1.36	7.9±1.39	9.0±1.21
Change From Baseline (mean ± SD)	-0.6±1.07	-1.2±1.06	0.1±0.98
95% CI	(-0.9, -0.4)	(-1.4, -1.0)	(-0.1, 0.3)
p-value	<0.0001	<0.0001	0.2032
Pairwise Comparison:	**INS+RSG 2mg bd vs INS**	**INS+RSG 4mg bd vs INS**	**INS+RSG 4mg bd vs INS+RSG 2mg bd**
Adjusted Mean Difference	-0.7	-1.3	-0.6
95% CI	(-1.0, -0.4)	(-1.6, -1.0)	(-0.9, -0.3)
Significance Level	0.050	0.050	0.050
p-value	<0.0001	<0.0001	<0.0001

The mean HbA1c during this 26 weeks period for the three arms of the study is presented in the diagram below.

Figure 1 Mean HbA1c over Time (ITT Population)



(ROSIGLITAZONE/082 - ITT Population) (Error Bars = SE)

ii. Fasting plasma glucose (FPG)

The mean decrease in FPG was statistically ($p<0.0001$) significantly greater in both INS+RSG treated groups than in the INS group, with adjusted mean differences of -2.23mmol/L and -2.56 mmol/L in the RSG 2mg bd + INS and RSG 4mg bd + INS groups, respectively .

Change in Insulin Dose

The total daily insulin dose was decreased for significantly ($p\leq0.001$) more subjects in both INS+RSG groups (34.0% and 43.7% in the 2mg bd and 4mg bd groups, respectively) compared to the INS group (13.5%).

Decreases from baseline to week 26 in HbA1c were comparable or greater in subjects who ultimately had decreases in insulin dose compared to subjects who had no change in insulin dose

Lipids

Compared to baseline, there was an increase in total cholesterol in all three treatment groups, with a larger increase in the INS+RSG treated subjects (9%, 14% and 3% for the RSG 2mg bd + INS, RSG 4mg bd + INS and INS groups, respectively). This was reflected in an increase in low-density lipoprotein (LDL)-cholesterol of 8% in the RSG 2mg bd + INS group and 16% in the RSG 4mg bd + INS group and a decrease in LDL in the INS alone group of 1%.

The addition of RSG 4mg bid resulted in a more pronounced reduction of glycaemic parameters compared to the other groups and was at the same time associated with a higher proportion of patients with reduced INS doses. However, the baseline mean INS dose was higher for the RSG 4mg bd + INS group compared to the other two groups which may have affected the reduction of the INS doses.

It is surprising that there was practically no reduction of HbA1c in the INS group since it is stated that the INS dose was adjusted according to the investigator's discretion during a four week standardisation period. Furthermore, since the INS dose was to be changed only for safety reasons during the remainder of the study, the effect of the addition of RSG to INS can not be compared to the effect of increasing the dose of INS. The combination of RSG and INS has not been compared to the combination of MET and INS. However, since the proposed indication includes patients intolerant to MET, such a comparison is not adequate.

As seen previously with TZD treatment there was an increase in total and LDL cholesterol associated with the treatment.

I. Study 085

Methods

Study Design and Entry Criteria

Subjects had FPG ≤ 10.0 mmol/L and had received continuous treatment with ≥30 U INS for at least 3 months prior to baseline. Subjects entered a four- to six-week run-in period during which the investigator was only permitted to increase the daily insulin dose (or perform no change); any subjects who required a decrease were withdrawn. Subjects were randomised at baseline to receive 2mg bd RSG or placebo in addition to insulin. At week 8 or 12, the dose of RSG given to subjects receiving INS+RSG was increased to 4mg bd for the remainder of the 26 week double-blind treatment period. The lower dose of RSG could be reinstated if symptoms warranted it.

The main exclusion criteria included subjects with hepatic disease, renal disease, cardiovascular disease, or anaemia as well as subjects with congestive heart failure (CHF).

The primary objective in this study was to examine the change in INS doses associated with the addition of an up-titrated dose of RSG. The baseline INS doses were somewhat higher in the RSG+INS group compared to the INS group. The withdrawal rate was considerably higher in the RSG+INS group compared to the INS group, mainly due to adverse events.

Results

Change in Insulin Dose

Table 4 Change from Baseline and Number (%) of Subjects with Changes in total Daily Insulin Dose (ITT population)

	INS+RSG (N=137)	**INS (N=139)**
Baseline (Geometric mean; units)	60.9 (58.60, 63.28)	57.4 (55.42, 59.48)
Week 26 (Geometric mean; units)	46.6 (44.59, 48.66)	52.1 (50.09, 54.13)
% Change from Baseline		
Geometric mean ± SE (units)	-23.5 (-25.23, -21.75)	-9.3 (-10.38, -8.23)
95% CI	-26.9, -20.0	-11.4, -7.2
p-value	<0.0001	<0.0001
Difference from placebo		
Adjusted mean difference (units)	-16.5	-
95% CI	-20.5, -12.2	-
p-value	0.0001	-
Reduction in dose, n (%)		
No Reduction	32 (23.4)	62 (44.6)
Reduction <10%	15 (10.9)	27 (19.4)
Reduction 10 - <20%	24 (17.5)	28 (20.1)
Reduction 20 - <30%	22 (16.1)	14 (10.1)
Reduction 30 - <40%	20 (14.6)	4 (2.9)
Reduction 40 - <50%	14 (10.2)	4 (2.9)
Reduction ≥50%	10 (7.3)	0
Number of Subjects with Reduction ≥30%	44 (32.1)	8 (5.8)

A total of 36.7% of subjects treated with RSG achieved an insulin dose reduction of ≥30% and also maintained glycaemic control at Week 26 which was significantly higher compared to 6.5% of subjects treated with INS alone (p=0.0001). Maintenance of glycaemic control was defined as an FPG value ≤ baseline value.

Glycaemic Efficacy

i HbA1c

Table 5 Change from Baseline in HbA1c at Week 26 (ITT Population with Last Observation Carried Forward (LOCF))

HbA1c (%)	**INS+RSG (N=126)**	**INS (N=135)**
Baseline (mean ± SD)	8.1 ± 1.02	8.1 ± 1.23
Week 26 (mean ± SD)	8.1 ± 1.35	8.6 ± 1.56
Change From Baseline (mean±SD)	-0.1 ± 1.26	0.5 ± 1.09

The INS doses were reduced more in the group with RSG addition compared to the group receiving only INS which is not surprising since this group achieved an additional antidiabetic drug while the other group did not. However, it is surprising that the HbA1c did not change during the study. The patients still had a suboptimal HbA1c after 26 week treatment and thus the clinical relevance of the algorithm for INS dosing is questionable.

III. Study 095

Methods

Study Design and Entry Criteria

Study 095 was identical to Study 082 in design and entry criteria except that subjects received od treatment with RSG or placebo. Subjects were randomised to 26 weeks of double-blind treatment with INS, RSG 4mg od + INS or RSG 8mg od + INS.

The baseline INS doses were considerably higher in the RSG add-on groups compared to the INS group. As in the previous study the withdrawal rates were highest in the RSG+INS groups

Results

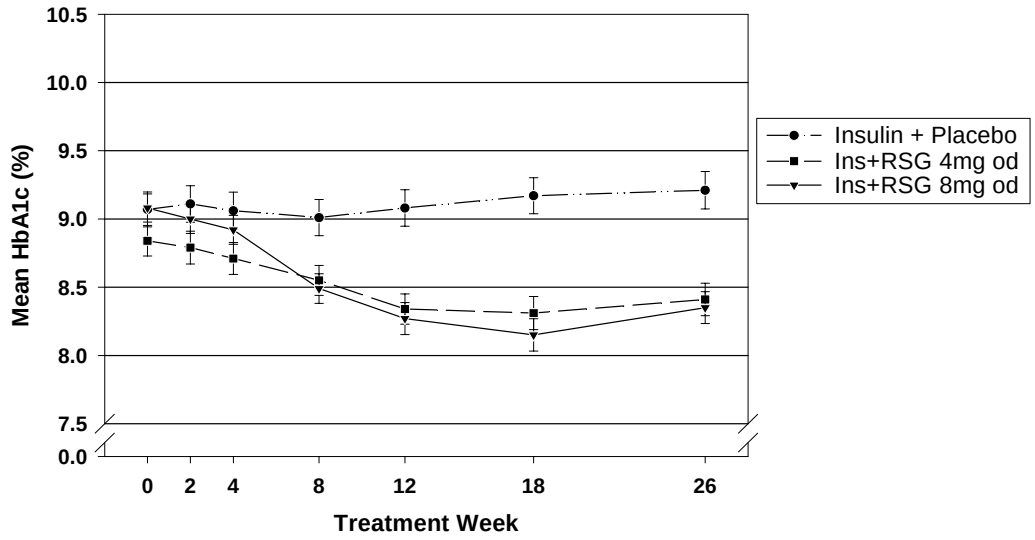
Glycaemic Efficacy

i. HbA1c

Table 6 Change From Baseline in HbA1c at Week 26 (ITT Population)

HbA1c (%)	INS+RSG 4mg od (N=97)	INS+RSG 8mg od (N=95)	INS (N=95)
Baseline (mean ± SD)	8.8 ± 1.10	9.1 ± 1.01	9.1 ± 1.24
Week 26 (mean ± SD)	8.4 ± 1.17	8.4 ± 1.14	9.2 ± 1.34
Change From Baseline (mean±SD)	-0.4 ± 0.96	-0.7 ± 0.96	0.1 ± 0.95
95% CI	(-0.6, -0.2)	(-0.9, -0.5)	(-0.1, 0.3)
p-value2	<0.0001	<0.0001	0.1738
Pairwise Comparison:	INS+RSG 4mg od vs INS	INS+RSG 8mg od vs INS	INS+RSG 8mg od vs INS+RSG 4mg od
Adjusted Mean Difference	-0.6	-0.9	-0.3
95% Confidence Interval3	(-0.9,-0.3)	(-1.2, -0.6)	(-0.5, <0.1)
Significance Level3	0.025	0.025	0.050
p-value4	<0.0001	<0.0001	0.0656

Figure 2 Mean HbA1c over time (ITT Population)



(ROSIGLITAZONE/095 - ITT Population) (Error Bars = SE)

ii. Fasting Plasma Glucose

The mean decrease in FPG was statistically ($p \leq 0.0001$) significantly greater in both INS+RSG treated groups than in the INS group, with adjusted mean differences of -1.77 mmol/L and-2.32 mmol/L in the RSG 4mg od + INS and RSG 8mg od + INS groups, respectively

Change in insulin dose

The total daily insulin dose was decreased for significantly ($p \leq 0.001$) more subjects in both INS+RSG groups (47.4% and 52.6% for 4mg od and 8mg od groups, respectively) than in the INS group (15.8%).

Decreases from baseline to Week 26 in HbA1c were comparable or greater in subjects who ultimately had decreases in insulin dose compared to subjects who had no change in insulin dose.

Lipids

Compared to baseline, there was an increase in total cholesterol in both the INS+RSG treatment groups (9% and 12% for the 4mg od and 8mg od INS+RSG groups, respectively) whereas there was a decrease of 3% in total cholesterol in the group treated with INS alone. This was reflected in an increase in LDL-cholesterol of 6% in the RSG 4mg od + INS group and 14% in the RSG 8mg od + INS group and a decrease in LDL-cholesterol in the INS group of 5%.

IV. Study 136

Methods

Study Design and Entry Criteria

Subjects had T2D (FPG ≥ 7.0mmol/L and ≤ 12.0mmol/L), were receiving treatment with insulin and/or a sulphonylurea and had chronic renal failure but were not on dialysis. Subjects were stratified according to severity of renal failure (Creatinine clearance CrCl), mild (CrCl 60-79mL/min), moderate (CrCl 30-59mL/min) or severe (CrCl ≤ 29mL/min).

Subjects entered a 4 week, single blind placebo run-in period during which they continued treatment, at constant doses, with any INS and/or SU they were taking prior to visit 1. Following the run-in period, eligible subjects were randomised to receive 4mg od RSG (titrated to 4mg bd at 8 or 12 weeks to optimise glycaemic control) or placebo for 26 weeks in addition to their existing antihyperglycaemic medication. Investigators were to reduce the dose of either INS or SU during the study if hypoglycaemia occurred, according to a set algorithm.

The main exclusion criteria included subjects with hepatic disease, cardiovascular disease, Congestive Heart Failure (CHF) (New York Heart Association, NYHA class I-IV) or unstable or severe angina requiring continual nitrate treatment for symptomatic relief.

The Baseline characteristics were largely similar between the groups, but the withdrawal rate was higher in the group receiving RSG. No up-titration of SU or INS doses was performed while RSG could be up-titrated to optimize blood glucose control. This strategy does not facilitate the comparison between the treatments.

Results

Glycaemic Efficacy

i. HbA1c

Decreases in mean HbA1c at Week 26 were similar irrespective of the final on-therapy dose of RSG and irrespective of the degree of renal impairment/failure (Table 7). These decreases from baseline were 0.6%, 0.4% and 0.6% greater than seen with INS &/or SU for subjects with mild, moderate and severe renal failure, respectively ($p < 0.05$ for all comparisons).

Table 7 Mean Change from Baseline in HbA1c at Week 26 (ITT Population)

HbA1c (%)	**INS &/or SU+RSG (N=137)**	**INS &/or SU (N=140)**
Baseline (mean ± SD)	8.2±1.23	8.3±1.24
Week 26 (mean ± SD)	7.7±1.08	8.3±1.22
Change from baseline		
Mean ± SD	-0.5±0.92	-<0.1±0.88
95% CI	(-0.7, -0.4)	(-0.2, 0.1)
p-value	<0.0001	0.6397
Difference from INS &/or SU		
Adjusted mean difference	-0.5	-
95% CI	(-0.7, -0.3)	-
p-value	0.0001	

ii. Fasting plasma glucose

RSG in combination with INS and/or a SU produced a significant ($p<0.0001$) decrease from baseline of 1.81mmol/L in mean FPG after 26 weeks of treatment and was significantly more effective than INS &/or SU ($p=0.0004$).

In general it is not surprising that HbA1c and FPG did not change in the control group since no optimisation of the doses in this group was permitted. Thus, even though the addition of RSG resulted in reductions in HbA1c in patients with renal dysfunction, the efficacy can not be compared to the control group.

Lipids
In the INS &/or SU+RSG group mean increases were observed in total cholesterol (10.2%), LDL-cholesterol (9.7%) and triglycerides (15.9%)

V. Study 347

Methods

Study Design and Entry Criteria

Subjects with HbA1c level >7.5% who had to have received INS monotherapy continuously for at least 8 Weeks prior to screening with a minimum dose of 30 units per day.

Subjects who completed a 2-Week Run-In period were randomised to INS+RSG 2mg od, INS+RSG 2mg od, titrating to 2mg bd at Week 8, and INS+PBO.

All subjects underwent a blinded titration of study medication at Week 8, with the exception of subjects with new oedema, significant weight gain, or other signs or symptoms of fluid retention such as shortness of breath. The INS dosage may have been reduced at the investigator's discretion for subjects who recorded hypoglycaemia. Subjects who in the opinion of the investigator required additional glycaemic control may have had their INS dose increased according to the investigator's discretion.

The main exclusion criteria included hepatic disease, renal disease, cardiovascular disease or anaemia, ongoing CHF or history of CHF, ongoing oedema or history of peripheral oedema requiring pharmacological treatment in the 12 months prior to screening.

The design of this study is more clinically adequate (compared to 082, 085 and 095) since the INS dose in the comparator group could be up-titrated during the study and the up-titration of the RSG dose was only performed in patients without fluid-related adverse events. Furthermore, patients with ongoing oedema or history of peripheral oedema were excluded. Baseline INS doses were highest in the INS group. This may indicate that these subject were more INS resistant compared to the other groups. Withdrawal rates did not differ between the groups in any relevant manner, but the proportions of patients that were lost to follow-up were surprisingly high.

Results

Glycaemic Efficacy

i. HbA1c

Table 8 Change from Baseline to Week 24 in HbA1c (ITT Population with LOCF)

HbA1c (%)	INS+RSG 2mg od (N=193)	INS+RSG 2mg bd (N=189)	INS (N=186)
N	193	188	185
Baseline (mean ± SD)	8.9±1.10	9.0±1.24	9.1±1.33
Week 24 (mean ± SD)	8.3±1.25	8.2±1.32	8.7±1.37
Change from baseline to Week 24			
Mean ± SD	-0.6±1.14	-0.78±1.13	-0.44±1.21
95% CI	(-0.8, -0.5)	(-1.0, -0.6)	(-0.6, -0.3)
p-value	<0.0001	<0.0001	<0.0001
Comparison with INS			
Adjusted mean difference	-0.3	-0.4	
95% CI	(-0.5, <-0.1)	(-0.6, -0.1)	
p-value	0.0165	0.0007	

ii. Fasting plasma glucose

There were no statistically significant differences in FPG for either of the INS+RSG groups compared with the INS group at Week 24. There was, however, a statistically significant reduction from baseline to Week 24 in FPG for the INS+RSG 2mg bd group but not for the other two groups.

Change in insulin dose

Table 9 Summary Change from Baseline to Week 24 in Total Daily Insulin Dose (ITT with LOCF)

Total Daily Insulin dose	INS+RSG 2mg od N=193	INS+RSG 2mg bd N=189	INS N = 186
N	193	189	186
Baseline (mean ± SD)	77.9±44.10	73.5±41.25	80.3±46.91
Week 24 (mean ± SD)	79.2±45.20	73.4±41.73	81.8±49.37
Change from baseline to Week 24			
Mean ± SD	1.4±13.84	-0.1±15.55	1.5±26.61
95% CI	(-0.6, 3.3)	(-2.4, 2.1)	(-2.4, 5.3)
p-value	0.1682	0.9107	0.4566
Comparison with INS			
Adjusted mean difference	-0.2	-2.0	
95% CI	(-4.6, 4.1)	(-6.4, 2.4)	
p-value	0.9055	0.3095	

Lipids

There were increases in total and HDL-cholesterol and triglycerides in the INS+RSG groups that were more pronounced compared to the INS group.

The HbA1c declined mostly in the RSG+INS groups. The insulin doses did not change compared to baseline. However, the mean insulin dose in the RSG 2mg bid group was considerably lower compared to the INS group. Thus, a lower HbA1c was achieved with a lower insulin dose which probably is a result of increased insulin sensitivity.

VI. Study 114 (OLE study)

Methods

Study Design and Entry Criteria

Following completion of Study 082 and Study 095, subjects were eligible to enter the OLE Study 114. All subjects were treated with INS+8mg RSG. Subjects continued on the same dose of INS they took in the previous study but after a period of two weeks, the total dose of INS could be decreased by 20-30% in subjects who achieved a glucose level ≤5.6mmol/L.

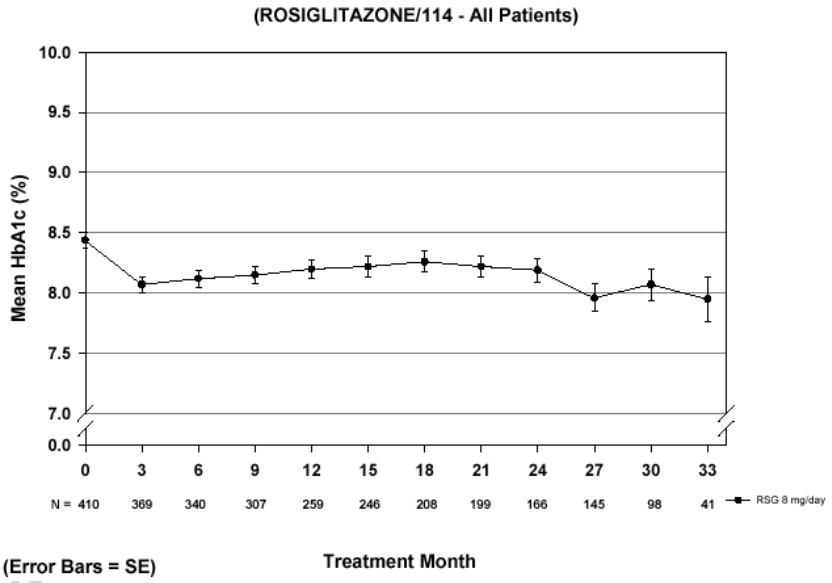
At the discretion of the investigator for safety reasons the dose of INS could be discontinued during the study and the subject maintained on RSG monotherapy at a total daily dose of 8mg for the duration of the study. Subjects were not permitted to take any other antidiabetic medications for the duration of the study.

Results

Glycaemic Efficacy

i. HbA1c

Figure 3 Mean HbA1c over Time

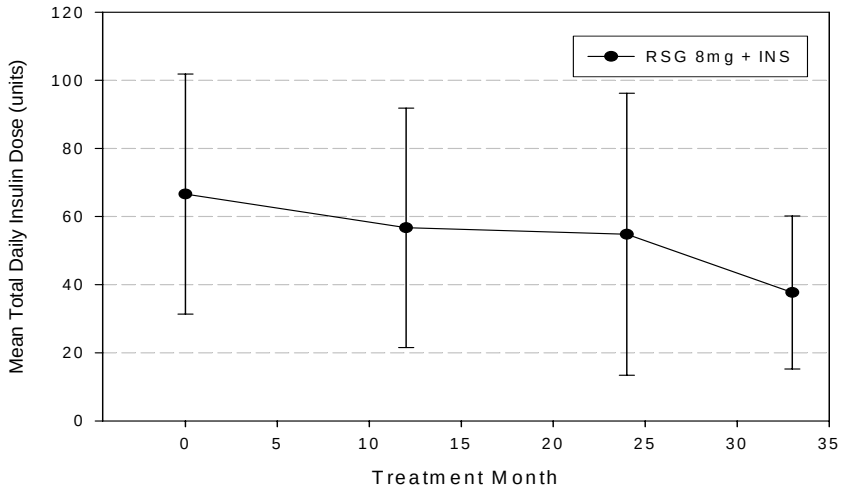


The initial decrease in HbA1c in the extension study was likely attributable to subjects who had an increase in RSG dose during open-label therapy or were switched from INS alone in the prior study to INS+RSG.

The HbA1c appears deteriorating up to week 24 and is on an unsatisfying level above 8%. HbA1c is lower between week 27 and 33, but many patients had been withdrawn at this stage and there is probably a selection of patients with good treatment results.

Change in insulin dose

Figure 4 Mean (± SD) Total Daily Insulin Dose over Time



The same discussion as per the HbA1c can be applied to the development of mean insulin doses as it is shown in the figure 4, above. Thus, long term efficacy can not be considered as fully evaluated.

VII. Study 009

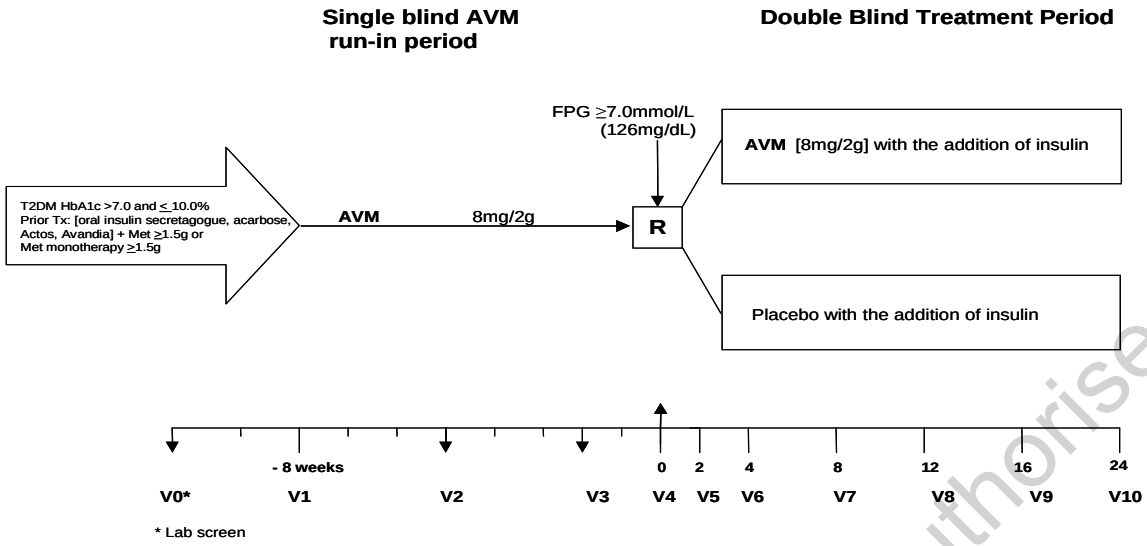
Methods

Study Design and Entry Criteria

Subjects were aged 18–70 years and were receiving ≥1.5g of metformin alone or in combination with an oral insulin secretagogue, Avandia, acarbose or pioglitazone, at constant doses for at least eight weeks prior to Visit 1 and had HbA1c >7.0% and ≤10.0% from a pre-screening sample.

Eligible subjects entered an 8-week single-blind run-in period during which prior oral anti-hyperglycaemic therapy was changed to AVANDAMET at the maximum daily dose of 8mg/2000mg. Subjects requiring additional glycaemic control after completing the run-in period (i.e., FPG ≥7.0mmol/L) were randomised to either continue on AVANDAMET and start INS or switch from AVANDAMET to placebo and start INS. Double-blind study treatment was administered at a constant dose throughout the 24 week double-blind period. The dose of open-label insulin could be adjusted in response to the subject's daily capillary blood glucose levels by following study-specific INS dosing algorithms. The starting dose of INS was 24 U (12U injected before breakfast and 12U before the evening meal).

Figure 5 Study Design (AMV Study 009)



The main exclusion criteria included subjects with hepatic disease, renal disease, cardiovascular disease, anaemia or Congestive Heart Failure (CHF) (New York Heart Association, NYHA class I-IV) as well as subjects with ongoing oedema requiring pharmacological treatment, subjects with ongoing oedema not currently requiring pharmacological treatment who experienced an exacerbation of symptoms during run-in and subjects who developed new oedema prior to randomisation.

In AVANDAMET study 009, patients who were likely to be at risk of fluid-related events were excluded, such as patients who developed oedema on AVANDAMET during run-in. This can be expected to reduce the incidence of fluid-related AEs when INS is added. Duration of T2D in this trial was shorter than in the previous studies and withdrawal rates were lower compared to other studies. This is the only study in which INS is added to optimised RSG treatment.

Results

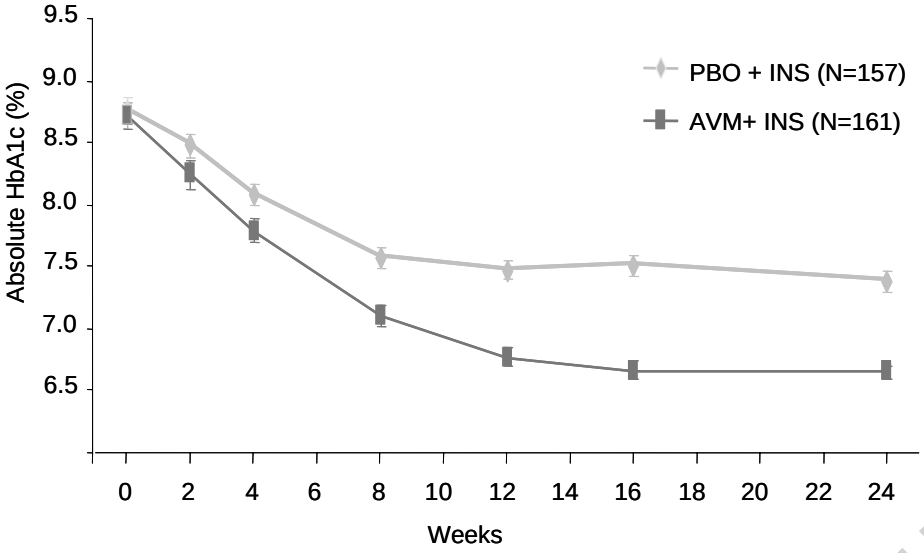
Glycaemic Efficacy

i. HbA1

Table 10 Change from Baseline in HbA1c at Week 24 (ITT population with LOCF)

HbA1c (%)	**AVANDAMET+INS (N=161)**	**INS (N=158)**
No. of subjects with values at Baseline and Week 24	161	157
Baseline (mean ± SD)	8.7 ± 1.40	8.8 ± 1.23
Week 24 (mean ± SD)	6.8 ± 0.90	7.5 ± 1.04
Change from Baseline (mean ± SD)	-2.0 ± 1.33	-1.3 ± 1.31
Model Adjusted Change from Baseline (mean ± SE)	-1.7 ± 0.10	-1.0 ± 0.09
Difference from INS		
Mean (95% CI)	-0.7 (-0.84, -0.45)	
p-value	<0.0001	

Figure 6 Mean (±SE) HbA1c (%) by Visit (ITT population with LOCF)



ii. Fasting plasma glucose

At Week 24 there were decreases from baseline in mean FPG in both groups: 3.4mmol/L in the insulin add-on group and 1.90mmol/L in the insulin switch group. Adjusting for baseline, gender and country, the mean treatment difference of 1.4mmol/L was statistically significant ($p<0.0001$).

Change in insulin dose

The mean final total daily insulin dose at Week 24 was lower in the insulin add-on group than the insulin switch group (33.2U vs. 58.6U). Adjusting for baseline HbA1c, gender and country, the mean treatment difference of 25.4U in final total daily insulin dose at Week 24 was statistically significant ($p<0.0001$).

AVANDAMET Study 009 has demonstrated that adding INS to AVANDAMET can significantly reduce HbA1c compared with INS monotherapy. Secondary endpoints supported glycaemic efficacy. FPG was reduced and INS doses were lower in the AVANDAMET+INS group compared with the INS group. However, the clinically relevant treatment alternative to AVANDAMET+INS would be MET+insulin rather than insulin alone. Such a comparison would have had a potential to show the additional effect of RSG.

Since this study evaluated Avandamet instead of Avandia it is not pivotal for the current application.

VIII. Clinical studies in special populations

Subgroup analyses were carried out for Study 082 and Study 095 only, as these studies were very similar with respect to entry criteria and study design.

Table 11 Summary of Baseline Demographic Characteristics for Studies 082 and 095 (ITT Population)

Baseline Characteristics	Study 082 (% of subjects)	Study 095 (% of subjects)
Gender (male)	56	56
Age (<65 years)	78	70
Race (white)	70	71
BMI (≥ 27 kg/m^2)	87	84

Glycaemic Efficacy - HbA1c

When HbA1c was analysed by gender with the exception of the RSG 4mg od + INS group, all doses and regimens tested produced greater reductions from baseline in females than males.

The combination of INS+RSG was similarly effective in the elderly (≥65 years of age) and non-elderly (<65 years of age) in reducing HbA1c.

The magnitude of reduction in HbA1c was greater for subjects with a baseline BMI ≥ 27kg/m^2 compared to subjects with a baseline BMI < 27kg/m^2.

Subjects with higher baseline HbA1c values (≥ 9%) showed greater decreases from baseline in HbA1c in the INS+RSG treatment groups than subjects with lower baseline HbA1c values.

Efficacy in subgroups was only evaluated for 2 studies. Efficacy was more pronounced in females compared to men, in subjects with higher BMI and HbA1c compared to those with lower values. Some of these findings may be explained by increased insulin resistance.

Discussion on Clinical Efficacy

As described above, data from seven studies have been provided in support of this type II variation application to extend the Avandia indications to include combination use with INS in patients who cannot take MET due to contraindication or intolerance.

Studies 082 and 095 had similar designs and included inadequately controlled patients with T2D treated with insulin. The addition of RSG 8mg daily resulted in a more pronounced reduction of glycaemic parameters compared to RSG 4mg daily and INS only, and was at the same time associated with a higher proportion of patients with reduced insulin doses. However, since the insulin dose was to be changed only for safety reasons during the remainder of the study, the effect of the addition of RSG to INS can not be compared to the effect of increasing the dose of insulin. As seen previously with TZD treatment there was an increase in total and LDL cholesterol. Concerning the OLE study (study 114) it should be remarked that the number of patients reaching month 33 was very limited, and therefore data from this study have limited value.

In Study 085 the insulin doses were reduced more in the group with RSG addition compared to the group receiving only insulin which is not unexpected since this group achieved an additional anti-diabetic drug while the other group did not. However, the HbA1c did not change during the study. The patients still had a suboptimal HbA1c after 26-week treatment and thus the clinical relevance of the algorithm for insulin dosing must be questioned. The results of this study are not supportive of the applied indication.

Study 136 included patients with reduced renal function and showed a reduction in HbA1c in patients treated with RSG but not in the control group. However, this is expected since no optimisation of the doses in the control group was permitted.

Study 347 had a clinically more adequate design since the insulin dose could be up-titrated during the study and the up-titration of the RSG dose was only performed in patients without fluid-related adverse events. Furthermore, patients with ongoing oedema or history of peripheral oedema were excluded. HbA1c declined most in the RSG+INS groups while the insulin doses did not change compared to baseline. However, the mean insulin dose in the RSG 2mg bid group was considerably lower compared to the INS group. Thus, a lower HbA1c was achieved with a lower insulin dose which probably is a result of increased insulin sensitivity. Similar results were found in study 009 in which Avandamet + insulin was compared to insulin only.

In conclusion, despite a somewhat inadequate design of the presented studies, the CHMP agreed that RSG added to the ongoing insulin treatment reduces HbA1c. At the same time, the insulin doses are reduced or unchanged which probably is a result of increased insulin sensitivity. However, the target population (patients intolerant or with contraindications to MET) is not adequately represented in the presented studies since patients with cardiac diseases were excluded to a large extent (see Discussion on Clinical Safety).

2.2 Clinical Safety

The main safety issue concerning the combination of insulin and rosiglitazone is the dose-dependent fluid retention effect that has been seen in previous studies.

I. Patient exposure

Safety data are available from a total of 1809 subjects from INS+RSG studies (24-26 weeks), and from 410 subjects who entered the INS+RSG open label extension study (Study 114), who received treatment for up to a further 33 months.

Safety data are available from a total of 322 subjects from the double-blind AVANDAMET+INS Study 009, which was of 24 weeks treatment duration (for description of studies see table 1 and 2).

Data presentation

Safety results from the INS+RSG studies and from the AVANDAMET+INS study, are presented in the following order:

1. By INS+RSG treatment group:
    - Integrated data from the double-blind (DB) Studies 082, 085 and 095
    - Integrated data from the DB studies plus OL Study 114
2. By INS+RSG daily dose:
    - Integrated data from the DB Studies 082 and 095
3. Individually reported INS+RSG studies:
    - Data from Study 136 in T2D subjects with chronic renal failure
    - Data from Study 347
4. Individually reported AVANDAMET Study 009.

Overall exposure

Table 12 Cumulative Exposure by Treatment Group in DB and OL Studies (All Randomised Population)

Subject exposure	DB				DB+OL	
	INS+RSG (N=546)		INS (N=342)		INS+RSG (N=687)	
	n	%	n	%	n	%
≥ 1 month	531	97.3	334	97.7	669	97.4
≥ 3 months	496	90.8	321	93.9	624	90.8
≥ 6 months	436	79.9	289	84.5	556	80.9
≥ 9 months	0	0	0	0	353	51.4
≥ 12 months	0	0	0	0	313	45.6
≥ 15 months	0	0	0	0	280	40.8
≥ 18 months	0	0	0	0	257	37.4
≥ 21 months	0	0	0	0	220	32.0
≥ 24 months	0	0	0	0	203	29.5
≥ 27 months	0	0	0	0	170	24.7
≥ 30 months	0	0	0	0	156	22.7
≥ 33 months	0	0	0	0	114	16.6
≥ 36 months	0	0	0	0	83	12.1
≥ 39 months	0	0	0	0	51	7.4
≥ 42 months	0	0	0	0	12	1.7

More than 500 patients have been exposed to the INS+RSG combination for 6 months and 313 patients for one year. The CHMP considers that this is sufficient.

II. Adverse events

Common Adverse events

Double Blind (DB) and Open Label (OL) studies

Hypoglycaemia was the most frequent AE reported, occurring in 51.5% of subjects treated with INS+RSG compared with 30.1% of subjects treated with INS alone in the DB studies. Hypoglycaemia will be discussed more fully in the relevant section further below in this report. Overall, there was a slightly higher AE rate for those treated with INS+RSG (85.5%) as compared with INS (74.9%) in the DB group. The overall incidence of AEs was similar irrespective of the RSG tdd used (91.6% for 4mg tdd, 93.3% for 8mg tdd). However, anaemia, oedema dependent, hyperlipaemia and urinary tract infection were dose dependent.

The types of AEs reported in the INS+RSG studies were consistent with those previously seen with RSG monotherapy, or in combination with MET or SU, as reflected in the current labelling.

A higher overall incidence of AEs was reported in subjects receiving INS+RSG compared with INS alone which was mainly due to a higher incidence of hypoglycaemia, anaemia and upper respiratory tract infection (URTI) .

Table 13 AEs by Preferred Term (Incidence Greater Than 6.0%) by Treatment Group (All Randomised Population)

	DB				DB+OL	
	INS+RSG (N=546, 246.4SY)		INS (N=342, 159.2SY)		INS+RSG (N=687, 845.3SY)	
Preferred term	**n (%)**	**SY**	**n (%)**	**SY**	**n (%)**	**SY**
Any AE	467 (85.5)	189.53	256 (74.9)	160.80	615 (89.5)	72.76
Hypoglycaemia	281 (51.5)	114.04	103 (30.1)	64.70	376 (54.7)	44.48
URTI	98 (17.9)	39.77	49 (14.3)	30.78	176 (25.6)	20.82
Anaemia	46 (8.4)	18.67	8 (2.3)	5.03	107 (15.6)	12.66
Infection viral	44 (8.1)	17.86	20 (5.8)	12.56	88 (12.8)	10.41
Injury	41 (7.5)	16.64	30 (8.8)	18.84	101 (14.7)	11.95
Oedema legs	30 (5.5)	12.18	9 (2.6)	5.65	78 (11.4)	9.23
UTI	28 (5.1)	11.36	23 (6.7)	14.45	64 (9.3)	7.57
Arthralgia	27 (4.9)	10.96	10 (2.9)	6.28	69 (10.0)	8.16
Headache	25 (4.6)	10.15	20 (5.8)	12.56	47 (6.8)	5.56
Sinusitis	25 (4.6)	10.15	18 (5.3)	11.31	64 (9.3)	7.57
Oedema dependent	25 (4.6)	10.15	7 (2.0)	4.40	58 (8.4)	6.86
Pain	22 (4.0)	8.93	17 (5.0)	10.68	53 (7.7)	6.27
Hyperlipaemia	22 (4.0)	8.93	6 (1.8)	3.77	66 (9.6)	7.81
Coughing	20 (3.7)	8.12	8 (2.3)	5.03	45 (6.6)	5.32
Weight increase	20 (3.7)	8.12	3 (0.9)	1.88	68 (9.9)	8.04
Hypercholesterolaemia	18 (3.3)	7.31	1 (0.3)	0.63	56 (8.2)	6.62
Dyspnoea	15 (2.7)	6.09	3 (0.9)	1.88	42 (6.1)	4.97
Hypertension aggravated	12 (2.2)	4.87	15 (4.4)	9.42	51 (7.4)	6.03

The overall incidence of AEs was similar in the 4mg and 8mg total daily dose (tdd) groups (91.6% vs 93.3%). AEs occurring with a higher frequency in the 8mg tdd group compared with 4mg tdd included hypoglycaemia (66.7% vs 53.3%), anaemia (12.4% vs 3.7%), injury (11.4% vs 3.7%), oedema dependent (9.5% vs 2.8%), hyperlipaemia (8.6% vs 3.7%) and UTI (7.6% vs 1.9%).

Study 136

Table 14 AEs by Preferred Term (Incidence Greater Than 5.0%) by Treatment Group (All Randomised Population)

Preferred Term	**INS &/or SU+RSG (N=148) n (%)**	**INS &/or SU (N=143) n (%)**
Any AE	111 (75.0)	97 (67.8)
Hypoglycaemia	33 (22.3)	17 (11.9)
Oedema	16 (10.8)	5 (3.5)
Respiratory disorder	9 (6.1)	3 (2.1)
Anaemia	8 (5.4)	7 (4.9)
Infection viral	8 (5.4)	3 (2.1)
Injury	8 (5.4)	3 (2.1)
URTI	6 (4.1)	9 (6.3)
Hyperglycaemia	5 (3.4)	12 (8.4)
Hypertension	1 (0.7)	8 (5.6)

Study 347

For the all randomised population in Study 347, the percentage of subjects reporting at least one AE on therapy was similar among all treatment groups (INS+PBO: 77.4%; INS+RSG 2mg od: 76.6%; INS+RSG 2mg bd: 70.3%). There were no unexpected differences between treatment groups in the incidence of treatment emergent AEs. The most common AEs reported were hypoglycaemia, tremor, peripheral oedema, upper respiratory tract infection and nasopharnygitis. Most AEs of tremor and dizziness were reported as symptoms of hypoglycaemia and so were recorded both as the symptom and as hypoglycaemia. The most frequently reported AEs for all treatment groups considered related or possibly related to the study medication by the investigator were hypoglycaemia, tremor, oedema, dizziness, and weight increase.

Table 15 Treatment-Emergent Adverse Events by Preferred Term (Incidence Greater Than or Equal to 5.0%) (All Randomised Population)

• Preferred Term	INS+RSG 2mg od N=209	INS+RSG 2mg bd N = 209	INS N = 212
Any AE	160 (76.6)	147 (70.3)	164 (77.4)
Hypoglycaemia	91 (43.5)	92 (44.0)	87 (41.0)
Tremor	14 (6.7)	18 (8.6)	12 (5.7)
Peripheral Oedema	6 (2.9)	15 (7.2)	18 (8.5)
Upper Respiratory Tract Infection	9 (4.3)	10 (4.8)	11 (5.2)
Dizziness	9 (4.3)	9 (4.3)	13 (6.1)
Nasopharyngitis	11 (5.3)	8 (3.8)	9 (4.2)
Influenza	11 (5.3)	8 (3.8)	6 (2.8)

Study 009

A total of 69 subjects (43%) who had INS added to maximal AVANDAMET therapy reported on therapy AEs compared with 60 subjects (38%) who were switched from maximal AVANDAMET therapy to INS monotherapy. The most commonly occurring on-therapy AEs (i.e. those that occurred in at least 2% of subjects in either treatment group) are summarised in Table 16 below. Hypoglycaemic events are not included in this table, but are discussed in the relevant section further in this report.

The most frequently occurring AEs in the INS add-on (AVANDAMET+INS) group were oedema and nasopharyngitis, with the proportions of subjects higher in the INS add-on (AVANDAMET+INS) group than the INS switch (INS) group. In the INS switch (INS) group, the most commonly occurring events were oedema and bronchitis, the latter being reported for the same proportion of subjects in both groups.

Most events were of mild or moderate intensity. The proportion of subjects reporting severe AEs was slightly higher in the INS add-on (AVANDAMET+INS) group (7%) compared with the INS switch (INS) group (3%). The only event of severe intensity and which was fluid-related was an event of anaemia reported by one subject in the INS add-on (AVANDAMET+INS) group.

Twelve subjects (7%) in the INS add-on (AVANDAMET+INS) group reported on-therapy AEs considered by the investigator to be suspected/probably related to study medication compared with six subjects (4%) in the INS switch (INS) group. The only related event occurring in at least 2% of subjects in either treatment group was oedema (including peripheral oedema): eight subjects (5%) in the INS add-on (AVANDAMET+INS) group and two subjects (1%) in the INS switch (INS) group.

The AE profile reported in AVANDAMET Study 009 was similar to that seen in previous AVANDAMET studies and is generally consistent with the known effects of concomitant administration of RSG and MET. Additionally, when comparing against the current AE profile of

concomitant RSG and INS administration, an improved AE profile was reported in AVANDAMET Study 009. It is of note that there were no cases of CHF reported in Study 009.

Table 16 On-Therapy AEs Reported by at Least 2% of Subjects in Either Treatment Group (Safety population)

Preferred Term	AVANDAMET+INS (N=162) n (%)	INS (N=160) n (%)
Any AE	69 (43)	60 (38)
Oedema	12 (7)	4 (3)
Nasopharyngitis	9 (6)	3 (2)
Bronchitis	5 (3)	4 (3)
Urinary tract infection	5 (3)	2 (1)
Back pain	4 (2)	3 (2)
Osteoarthritis	4 (2)	0
Gastroenteritis	3 (2)	2 (1)
Arthralgia	2 (1)	3 (2)
Pain in extremity	2 (1)	3 (2)
Vertigo	1 (1)	3 (2)
Spinal disorder	0	3 (2)

There was a dose-dependent increase in oedema compared to the INS group in all studies (except in study 347) in which RSG was added to an established insulin dose. The overall incidence of AEs was lower in study 009 in which insulin was added to established oral therapy.

Adverse events for additional safety considerations

Anaemia

RSG combination therapy was associated with a dose related increase in events of anaemia. The anaemia was mostly mild to moderate and lead to few withdrawals.

Table 17 Summary of Anaemia-Related AEs Across the Studies

	Treatment	Anaemia-Related AE %
Insulin +Rosiglitazone Studies 082, 095, 085	INS+RSG 8mg tdd (N=202)[1]	14.4
	INS+RSG (N=546)[2]	8.6
	INS (N=342)[2]	2.3
Insulin + Rosiglitazone Study 136	INS &/or SU + RSG (N=148)	5.4
	INS &/or SU (N=143)	4.9
Insulin + Rosiglitazone Study 347	INS+RSG 2mg od (N=193)	1.0
	INS+RSG 2mg bd (N=189)	2.4
	INS+PBO (N=186)	0
AVANDAMET + Insulin Study 009	AVANDAMET+INS (N=161)	2.0
	PBO+INS (N=158)	1.0

1. Integrated data from double-blind Study 082 and Study 095
2. Integrated data from double-blind Study 082, Study 085 and Study 095

It is well known that TZD are associated with anemia probably caused by hemodilution. This was confirmed in the presented studies. The incidences were lower in studies 347 and 009 in which patients prone to fluid related events were excluded and RSG and insulin doses were more carefully titrated.

Oedema

DB and OL population

INS+RSG was associated with a dose related increase in oedema-related AEs compared with INS alone. Events classified as serious or severe or which led to withdrawal were rare.

In Study 085 the proportion of subjects experiencing oedema-related AEs was similar in the INS+RSG combination group (14.5%) and INS alone group (11.5%).

Study 347

The proportion of subjects experiencing oedema-related AEs was comparable between the INS+RSG 2mg bd group (11.0%) and INS group (10.8%), and was lower in the INS+RSG 2mg od group (5.7%).

Study 136

INS+RSG was associated with an increase in oedema-related AEs compared with INS alone in renally impaired subjects. There was a trend towards an increase in oedema events with severity of renal failure in subjects receiving INS+RSG combination therapy.

Study 009

Oedema occurred more frequently in the insulin add-on group compared with the insulin switch group. All of the events were mild to moderate in intensity and few subjects withdrew due to oedema.

Table 18 Summary of Oedema-Related AEs Across the Studies

	Treatment	Oedema-Related AE %
Insulin +Rosiglitazone Studies 082, 095, 085	INS+RSG 8mg tdd (N=202)[1]	17.8
	INS+RSG (N=546)[2]	14.7
	INS (N=342)[2]	8.2
Insulin + Rosiglitazone Study 136	INS &/or SU + RSG (N=148)	18.9
	INS &/or SU (N=143)	9.1
Insulin + Rosiglitazone Study 347	INS+RSG 2mg od (N=193)	5.7
	INS+RSG 2mg bd (N=189)	11.0
	INS+PBO (N=186)	10.8
AVANDAMET + Insulin Study 009	AVANDAMET+INS (N=161)	7.0
	PBO+INS (N=158)	3.0

1. Integrated data from double-blind Study 082 and Study 095
2. Integrated data from double-blind Study 082, Study 085 and Study 095

As for anaemia, the incidences of oedema were lower in studies 347 and 009 in which patients prone to fluid related events were excluded and RSG and insulin doses were more carefully titrated. It should be noted that in patients with reduced renal function, the incidence of oedema was doubled in the RSG group compared to patients without RSG.

CHF-related Adverse Events

In all INS+RSG studies, except Study 347, CHF included the terms cardiac failure, cardiac failure left, cardiac failure right and pulmonary oedema. In Study 347 and 009, CHF included the term cardiac failure congestive.

DB and OL population

A higher incidence of CHF-related events was observed in the INS+RSG group (2.4%) compared with the INS group (0.9%). A higher incidence of events occurred in the RSG 8mg tdd compared with the RSG 4mg tdd group (3.0% vs 1.9%). Following longer term treatment with INS+RSG in the DB+OL population, the rate of CHF events was 6.2%.

Seven serious AEs (SAE) related to CHF were reported in the INS+RSG group of the DB population compared with two in the INS group. A higher number of SAEs occurred in the RSG 8mg tdd group (n=4) than in the RSG 4mg tdd group (n=1).

Study 136

This was a population at risk for fluid-related events as illustrated by a high incidence of cardiovascular (CV) AEs prior to randomisation in the overall population. Four (2.7%) events of CHF and two (1.4%) events of pulmonary oedema were reported in the INS &/or SU+RSG combination group compared with four (2.8%) events of CHF in the INS &/or SU group.

Study 347

CHF was reported in three subjects in the INS+RSG combination treatment groups, but no subjects in the INS group. In this study CV AEs were independently reviewed by an Adjudication Committee.

Study 009
There were no reports of CHF in this study.

Table 19 Summary of CHF Events Across the Studies

	Treatment	CHF %
Insulin +Rosiglitazone Studies 082, 095, 085	INS+RSG 8mg tdd (N=202)[1]	3.0
	INS+RSG (N=546)[2]	2.4
	INS (N=342)[2]	0.9
Insulin + Rosiglitazone Study 136	INS &/or SU + RSG (N=148)	3.6
	INS &/or SU (N=143)	3.7
Insulin + Rosiglitazone Study 347	INS+RSG 2mg od (N=193)	1.0
	INS+RSG 2mg bd (N=189)	0.5
	INS+PBO (N=186)	0
AVANDAMET + Insulin Study 009	AVANDAMET+INS (N=161)	0
	PBO+INS (N=158)	0

1. Integrated data from double-blind Study 082 and Study 095
2. Integrated data from double-blind Study 082, Study 085 and Study 095

In all studies, 52 of the 57 subjects who experienced non-fatal CHF related AEs had a prior or current CV related condition, four subjects had no CV related condition and one subject had obesity as a risk factor at study baseline. In the five subjects with no prior history of CV related events, two events were considered to have a possible causal relationship to study medication.

Patients with diabetes are at an increased risk for the development of symptomatic heart failure due to both systolic and diastolic dysfunction. An incidence rate of 2-3 per 100 patient years has been shown in different studies. In the presented studies there was clearly a dose-dependent increase in CHF incidence, especially in the studies in which RSG was introduced at the highest dose. A majority of the patients who developed CHF had prior or current CV related conditions. This warrants for careful titration of both RSG and insulin doses and a warning against use in patients with risk factors for cardiac diseases.

Hypoglycaemia

DB and OL population

Hypoglycaemia events were reported more frequently in the INS+RSG group. A higher percentage of events occurred in the RSG 8mg tdd group compared to the RSG 4mg tdd group. One SAE related to hypoglycaemia was reported occurring in the INS+RSG group in the DB population.

Table 20 Reports of Hypoglycaemia by Treatment Group and Study (All Randomised Population)

Study	INS+RSG	INS
Total DB subjects with hypoglycaemia	281	104
082, n (%)	127 (59.9)	41 (38.3)
085, n (%)	24 (17.4)	20 (14.4)
095, n (%)	130 (66.3)	43 (44.8)

Study 136

More subjects in the INS &/or SU+RSG group reported hypoglycaemia than in the INS and/or SU group. These results were similar irrespective of the degree of renal impairment. Two subjects experienced SAEs of hypoglycaemia, both in the INS and/or SU+RSG combination group.

Study 347

The proportions of subjects reporting AEs of hypoglycaemia or blood glucose decreased were similar between INS+RSG combination treatment and INS monotherapy groups. The majority of the episodes of hypoglycaemia were mild to moderate in intensity. Severe hypoglycaemia was reported in a similar proportions of subjects in each treatment group (<3%).

Study 009

In AVANDAMET Study 009, 43% in the INS add-on group reported 535 on-therapy hypoglycaemic events compared with 45% with 365 hypoglycaemic events in the INS switch group. All hypoglycaemic events were mild or moderate intensity, and none was serious or led to withdrawal from the study.

Table 21 Summary of Hypoglycaemia Across the Studies

	Treatment	Hypoglycaemia %
Insulin +Rosiglitazone Studies 082, 095, 085	INS+RSG 8mg tdd (N=202)[1]	68.8
	INS+RSG (N=546)[2]	51.5
	INS (N=342)[2]	30.4
Insulin + Rosiglitazone Study 136	INS &/or SU + RSG (N=148)	22.3
	INS &/or SU (N=143)	11.9
Insulin + Rosiglitazone Study 347	INS+RSG 2mg od (N=193)	45.5
	INS+RSG 2mg bd (N=189)	45.0
	INS+PBO (N=186)	41.0
AVANDAMET + Insulin Study 009	AVANDAMET+INS (N=161)	43.0
	PBO+INS (N=158)	45.0

1. Integrated data from double-blind Study 082 and Study 095
2. Integrated data from double-blind Study 082, Study 085 and Study 095

The majority of hypoglycaemia AEs reported in the DB population came from Studies 082 and 095. The differences compared to the INS monotherapy groups reflect the fact that INS was not up-titrated in these studies.

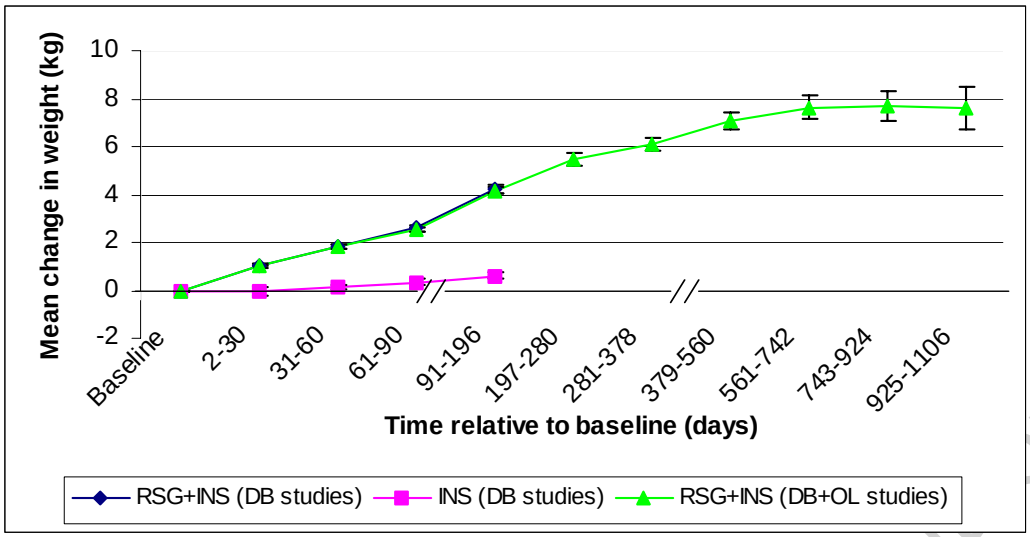
In studies 347 and 009 the addition of RSG was not associated with a marked increase in hypoglycaemia compared to INS monotherapy.

Weight Increase Adverse Events

DB and OL population

Mean weight increased in the INS+RSG group, with a maximum increase of +4.2kg. A larger increase in mean weight was observed in the RSG 8mg tdd group compared with the RSG 4mg tdd group (5.0kg and 3.8kg, respectively). Mean weight slightly increased over time in the INS only group, with a maximum increase of 0.6kg. Following longer term treatment in the DB+OL population, mean weight increased further, with a maximum increase of 7.7kg at approximately 24-30 months.

Figure 7 **Mean (Change from Baseline in Weight (kg) by Treatment Group in DB and OL Studies (All Randomised Population)**



Study 136

A statistically significant increase from baseline in mean weight was found in both treatment groups (0.6 kg in the INS &/or SU group and 2.7 kg in the INS &/or SU+RSG combination group). The increase in weight observed in the RSG combination group was progressive throughout the 26 week study period.

Study 347

Both INS+RSG groups showed statistically significant mean weight increases relative to INS monotherapy treatment. (1.1 kg, 2.3kg and 0.84 kg respectively in the RSG 2mg od, RSG 2mg bid and INS groups).

Study 009

There were increases in subject weight in both treatment groups, with a slightly larger increase in the INS add-on group. The mean treatment difference of 1.1kg (3.3kg vs 2.2 kg) was statistically significant (p=0.0206).

Weight increase, at least partly due to fluid retention, is a well known side effect associated with TZD treatment. As for other adverse events associated with fluid retention, the weight increase was most pronounced in the studies in which RSG was introduced at maximal doses without up titration of the dose. However, the mean weight increase was statistically larger compared to INS monotherapy in all studies. Weight gain should be carefully monitored since it may be a sign of fluid retention. This should be stated in the SPC.

Cardiovascular Adverse Events

In all INS+RSG studies except Study 347, CV events of interest were defined in consultation with the FDA, and comprise the following categories and preferred terms:

- Heart Failure

  Cardiac failure, pulmonary oedema and cardiac failure left

- Ischaemic Heart Disease

  Angina pectoris, angina pectoris aggravated, coronary artery disorder, myocardial infarction (MI), myocardial ischaemia, cardiac arrest and thrombosis coronary

- Arrhythmia

  Fibrillation atrial, fibrillation ventricular, sudden death, tachycardia ventricular and arrhythmia ventricular

- Cardiac Arrest.

In Study 347, CV events of interest included the terms: cardiac failure congestive, angina pectoris, myocardial infarction, coronary artery disease and coronary artery stenosis.
In AVANDAMET Study 009, CV events of interest included the terms: cardiac failure, ischaemic heart disease.

Table 22 Summary of CV-related Events Across the Studies

	Treatment	CV-related AE %
Insulin +Rosiglitazone Studies 082, 095, 085	INS+RSG 8mg tdd (N=202)[1]	6.4
	INS+RSG (N=546)[2]	6.8
	INS (N=342)[2]	3.2
Insulin + Rosiglitazone Study 136	INS &/or SU + RSG (N=148)	5.4
	INS &/or SU (N=143)	3.5
Insulin + Rosiglitazone Study 347	INS+RSG 2mg od (N=193)	2.4
	INS+RSG 2mg bd (N=189)	2.9
	INS+PBO (N=186)	1.9
AVANDAMET + Insulin Study 009	AVANDAMET+INS (N=161)	0.6
	PBO+INS (N=158)	0

1. Integrated data from double-blind Study 082 and Study 095
2. Integrated data from double-blind Study 082, Study 085 and Study 095

Baseline characteristics differed for those subjects with and without an on-therapy CV-related AE in the integrated INS+RSG population. In both treatment groups, subjects who experienced CV-related AEs were on average older (mean >64 years), had a longer mean duration of diabetes (≥15 years) and had a higher prevalence of prior CV disease (≥92%) than subjects who did not experience CV events (mean age >58 years, mean duration of diabetes 13 years, prior CV disease 77%).

As for adverse events associated with fluid retention, the incidences of CV adverse events in the currently submitted studies were highest in the studies in which RSG was introduced at maximal doses without up titration of the dose. Subjects who experienced CV adverse events seem to have had more

pre-existing risk factors. It was questioned whether patients with known prior cardiac diseases were in principal excluded from the studies, since these patients may be considered as a part of the target population for the intended indication and this could be a safety issue. The MAH responded that patients with known prior cardiac disease accounted for between 17 and 44% of the patient population in individual studies (see below).

Serious adverse events and deaths

Deaths

Table 23 Summary of Deaths in All RSG+INS Combination Studies

Subject ID	Preferred Term	Age	Gender	Cur [1]	Pri[1]	Rel[1]	Relationship
Double-blind Studies							
INS+RSG 2mg bd							
082.002.13523	Aneurysm	52	F	128	-	15	Unlikely
082.037.13931	Myocardial infarction	70	M	89	-	1	Unlikely
082.039.14299	Cerebrovascular disorder	74	F	49	-	1	Unlikely
INS+RSG 4mg bd							
085.813.76589	Myocardial infarction	66	F	95	-	6	Not related
INS+RSG 8mg od							
095.017.12304	Cardiac Arrest	54	F	33	-	1	Suspected
	Encephalopathy			33	-	1	Suspected
	Hypoglycaemia			33	-	1	Suspected
INS &/or SU+RSG							
136.701.74549[2]	Myocardial infarction	77	M	26		0	Unlikely
136.778.74643	Cardiac failure	72	M	122		7	Unlikely
	Pneumonia			122		7	Unlikely
INS							
085.751.76932	Cerebrovascular disorder	77	F	164		5	Unlikely
347.854.46762	Murder	45	M	56	-	32	Not related
Open label Study							
INS+RSG 4mg bd							
114.030.14030	Cardiac arrest	71	M	255	182	4	Unlikely
	Peritonitis			255	182	4	Unlikely
	Gall bladder disorder			255	182	4	Unlikely
114.056.14079	Cardiac failure	67	M	494	184	1	Unlikely
	Pericarditis						Unlikely
INS+RSG 8mg od							
114.042.12111	Hepatic neoplasm malignant	54	M	424	195	20	Not related
114.007.12291	Arrhythmia	78	F	327	182	17	Unlikely
114.017.12570	Cardiac failure	70	M	189	181	74	Not related
114.065.12397	Haemorrhage intracranial	74	F	392	189	65	Not related

1. Days on medication: cur = total days on medication in the protocol in which the event occurred relative to first dose date in that protocol; pri = total days on the prior protocol; rel = relative day of death compared to the last dosing date of last regimen
2. This subject was within the RSG+SU treatment group

Study 009
There was one death during the double-blind phase of study 009, a 70 year old male subject who died due to shock (circulatory arrest). The investigator considered there was no reasonable possibility that this event was related to study medication.

However it is considered that most deaths were probably not related to the study drug.

Other serious adverse events

DB and OL population
A higher overall frequency was reported in the INS+RSG group compared with INS only (9.0% vs 5.8%). The most frequently occurring SAEs in the INS+RSG group were cardiac failure (1.1%), cerebrovascular disorder (0.9%), pneumonia (0.9%), cellulitis (0.7%), anaemia (0.5%) and myocardial infarction (0.5%).

The incidences in the INS only group of cardiac failure (0.6%), pneumonia (0.0%), anaemia (0.0%) and MI (0.3%) were lower compared with the INS+RSG combination group in the DB population whereas cerebrovascular disorder (1.2%) and cellulitis (0.9%) occurred with a higher frequency.

Study 136
The incidence of SAEs was higher in the INS &/or SU+RSG combination group compared with the INS &/or SU group (13.5% vs 10.5%), however, the majority of these events were isolated occurrences (2 patients in each group with cardiac heart failure). On analysis of SAEs by severity of renal failure, the incidence of SAEs was higher in subjects with more severe renal failure, regardless of treatment group.

Study 347
The incidence of SAEs was comparable between the INS+RSG 2mg od (4.3%) and INS groups (4.2%), but was higher in the INS+RSG 2mg bd group (6.7%). The majority of SAEs reported were single events. Six SAEs occurred in more than one subject, of which two (angina pectoris and influenza) were in the INS+RSG 2mg bd group and three (hypoglycemia, cardiac failure congestive, myocardial infarction) were in the INS+RSG 2mg od group.

Study 009
In AVANDAMET Study 009, eight subjects (5%) in the insulin add-on group and six subjects (4%) in the insulin switch group had on-therapy non-fatal SAEs. No event occurred in more than one subject overall.

The overall incidence of SAE was higher in the RSG+INS groups compared to INS, but the incidences of each SAE were low. It should be noted that the proportion of patients with SAE was higher in study 136 (renally impaired patients) compared to the other studies.

Laboratory findings and vital signs

Haematology

In the integrated dataset, INS in combination with RSG resulted in a reduction in both Hb and Hct which appeared to reach a nadir by approximately 18.5-24.5 months of therapy, changing little over the subsequent 12 month assessment period. In subjects with renal impairment, the decreases in Hb and Hct observed with INS+RSG treatment were lower compared with subjects in the integrated dataset who did not have renal impairment.

Similarly, in Study 347 the decreases in Hb and Hct observed with INS+RSG treatment were lower compared with subjects in the integrated dataset.

In AVANDAMET Study 009, there were no apparent changes in Hb or Hct in the INS add on group.

Liver Function Tests

In the integrated dataset, no subjects receiving INS+RSG had values for ALT or AST greater than 3 times the upper limit of the reference range (ULRR) in the DB population. Following longer treatment duration, the incidence of ALT or AST between 3 and 5 times ULRR was rare, with no values increasing to greater than 5 times the ULRR. Similarly, in Study 347 no values for ALT and AST were within the ranges of potential clinical concern.
In renally impaired subjects, no values for ALT or AST were within the ranges of potential clinical concern.
There were no values for ALT and AST within the ranges of potential clinical concern in AVANDAMET Study 009.

Blood pressure and heart rate

DB and OL population
Following treatment for up to 280 days, mean SBP in the INS+RSG group was lower than baseline (change from baseline: range –1.9 to -0.3mmHg) for all time points with the exception of Days 61-90 (+0.2mmHg). In the INS only group, mean SBP was higher at all time points compared with baseline (change from baseline: range 1.4 to 4.1mmHg).

Mean DBP in the INS+RSG group was lower than baseline (change from baseline: range –0.2 to –2.1mmHg) for all time points up to 280 days. In the INS only group, mean DBP was the same or higher compared with baseline (change from baseline: range 0.0 to 1.4mmHg).

Mean heart rates in both the INS+RSG and INS groups were similar to baseline for up to 196 days of treatment.

Study 136, 347, 009
In these studies the proportions of subjects in both treatment groups with vital signs of potential clinical concern were low and there were no significant differences between treatment groups.

ECG

With respect to ECG parameters, safety was assessed by analysis of any AE related to an abnormal ECG parameter and by analysis of ECG value changes from baseline (PR, QRS and QTc intervals) or of potential clinical concern ranges (ventricular rate). The incidence of PR, QRS and QTc intervals of potential clinical concern in the DB population was low and similar between the INS+RSG and INS groups.
The incidence of new onset abnormal ECG values was similar (difference <2.0%) between the INS+RSG and INS groups in the DB study population.

In studies 136, 347 and 009 ECG was only registered at screening.

No safety signals concerning heamatholgy or liver function have emerged. Blood pressure was reduced and heart rate was unchanged in the INS+RSG population. No relevant ECG findings were registered.

III. Safety in special populations

The incidences of AEs in special population have been analysed for integrated INS+RSG Studies 082 and 095, but not Studies 085, 136 or 347 owing to differences in their designs. An analysis of AEs in special population has not been conducted for AVANDAMET Study 009 as the number of subjects involved was to low to allow meaningful analyses.

Age

DB and OL population

Table 24 AEs by Preferred Term and Age (Incidence Greater Than or Equal to 6.0% and More Than One Subject in Any Group) (All Randomised Population)

	INS+RSG			INS		
Preferred term	**<65 years (N=301) n (%)**	**65-75 years (N=95) n (%)**	**>75 years (N=12) n (%)**	**<65 years (N=149) n (%)**	**65-75 years (N=46) n (%)**	**>75 years (N=8) n (%)**
Total	274 (91.0)	90 (94.7)	11 (91.7)	124 (83.2)	43 (93.5)	8 (100)
Hypoglycaemia	187 (62.1)	63 (66.3)	7 (58.3)	65 (43.6)	14 (30.4)	5 (62.5)
URTI	67 (22.3)	21 (22.1)	0 (0.0)	34 (22.8)	6 (13.0)	1 (12.5)
Anaemia	25 (8.3)	18 (18.9)	1 (8.3)	6 (4.0)	1 (2.2)	0 (0.0)
Oedema dependent	13 (4.3)	9 (9.5)	2 (16.7)	3 (2.0)	1 (2.2)	0 (0.0)
Infection	5 (1.7)	8 (8.4)	0 (0.0)	5 (3.4)	3 (6.5)	0 (0.0)
Injury	29 (9.6)	7 (7.4)	1 (8.3)	14 (9.4)	5 (10.9)	0 (0.0)
Infection viral	29 (9.6)	7 (7.4)	0 (0.0)	15 (10.1)	1 (2.2)	0 (0.0)
UTI	17 (5.6)	6 (6.3)	2 (16.7)	9 (6.0)	9 (19.6)	2 (25.0)
Hyperlipaemia	14 (4.7)	6 (6.3)	1 (8.3)	5 (3.4)	1 (2.2)	0 (0.0)
Coughing	10 (3.3)	6 (6.3)	1 (8.3)	4 (2.7)	2 (4.3)	0 (0.0)
Cardiac failure	3 (1.0)	6 (6.3)	1 (8.3)	1 (0.7)	1 (2.2)	0 (0.0)
Bronchitis	15 (5.0)	5 (5.3)	0 (0.0)	4 (2.7)	3 (6.5)	0 (0.0)
Headache	18 (6.0)	3 (3.2)	0 (0.0)	12 (8.1)	2 (4.3)	1 (12.5)
Diarrhoea	9 (3.0)	3 (3.2)	0 (0.0)	6 (4.0)	6 (13.0)	2 (25.0)
Skin ulceration	2 (0.7)	3 (3.2)	0 (0.0)	1 (0.7)	0 (0.0)	2 (25.0)
Sinusitis	23 (7.6)	2 (2.1)	0 (0.0)	13 (8.7)	3 (6.5)	0 (0.0)
Pain	15 (5.0)	2 (2.1)	1 (8.3)	7 (4.7)	4 (8.7)	0 (0.0)
Hypertension aggravated	9 (3.0)	2 (2.1)	1 (8.3)	7 (4.7)	4 (8.7)	1 (12.5)
Arthralgia	20 (6.6)	1 (1.1)	0 (0.0)	5 (3.4)	2 (4.3)	0 (0.0)

It should be noted that only 12 patients older than 75 years have been exposed to the INS+RSG combination. There were increased incidences of anemia, oedema and cardiac failure among patients aged 65-75 years compared to younger patients.

Gender

The overall incidence of AE events was similar between male and female in the INS+RSG group while the incidence of oedema was higher in females compared to males (8.7% and 3.8% respectively).

BMI

The overall incidence of AEs in subjects with BMI ≥27kg/m^2 was higher than in subjects with BMI <27kg/m^2 in the INS group (87.9% vs 75.9%) but not in the RSG+INS group (91.4% vs 93.2%).
In the INS+RSG group, the only AE occurring with a notably higher incidence in the ≥27kg/m^2 group compared with the <27kg/m^2 group was oedema legs (6.0% vs 0.0%).

Race

In the INS+RSG group, no specific AE occurred more frequently in White subjects compared with both Black and Other subjects, however anaemia occurred with a lower frequency compared with Black and Other subjects (8.3% vs 15.2% vs 19.2%). Hypoglycaemia occurred with a lower incidence in Black subjects compared with White and Other subjects in both treatment groups.

IV. Post-marketing data

The GSK safety database contains reports of AEs worldwide from all sources, i.e., clinical trials, post marketing surveillance studies and spontaneous reporting (including literature and regulatory authorities). The safety database was examined to identify all cases reporting RSG in concomitant use with INS. A search of the database from launch until 25 May 2005 identified a total of 13449 reports from spontaneous sources and post marketing studies. Of these cases, 1835 reports noted concomitant use of INS. The majority of post marketing AE reports describing RSG in combination with INS has been received from spontaneous sources.

Of the 1835 spontaneous and post marketing study reports of RSG and concurrent INS, the majority were received from the USA (82%), Canada (6%), the UK (3%) and Germany (2%). Fifty-nine cases reported a fatal outcome. The majority of these cases described the death to be due to or in the presence of severe co-morbidity.

Serious Adverse Events (SAE) were reported in 669 cases. These SAEs included:

1) congestive heart failure, including pleural effusion, acute pulmonary oedema and pulmonary oedema (16% of RSG + INS vs 15% of all RSG)
2) oedema including peripheral oedema, pitting oedema, swelling, generalized oedema and fluid retention (7% of RSG + INS vs 5% of all RSG)
3) weight gain (5% of RSG + INS vs 3% of all RSG).

The proportion of the most frequently reported SAEs for RSG in combination with INS appears similar to the overall post marketing experience for RSG use in any diabetic treatment regimen. However, since data are mainly based on spontaneous reports, under-reporting may introduce a bias.

Discussion on clinical safety

In the studies presented in the current application more than 500 patients have been exposed to the INS+RSG combination for 6 months and 313 patients have been exposed for one year.

The main safety issue concerning the combination of INS and RSG is the dose-dependent fluid retention effect that has been seen in previous studies and the complications associated with this side effect.

There was a dose-dependent increase in anaemia in patients treated with INS+RSG compare to INS in all studies presented. The incidence of oedema was increased in the INS+RSG groups compared to insulin alone in all studies except for study 347. Mean weight increase in patients treated with RSG+INS was statistically larger compared to INS monotherapy in all studies. The CHMP was of the view that weight gain should be carefully monitored since it may be a sign of fluid retention, and therefore a warning to reflect this concern was added to section 4.4 of the SPC.

Compared to other studies, the incidences of anemia, oedema and weight increase were lower in studies 347 and 009 in which patients prone to fluid related events were excluded and RSG and insulin doses were more carefully titrated.

It should be noted that in patients with reduced renal function, the incidence of oedema was doubled in the RSG group compared to patients without RSG. A warning reflecting this information was included in section 4.4 of the SPC.

The CHMP also noted that only 12 patients older than 75 years have been exposed to the INS+RSG combination. There were increased incidences of anemia, oedema and cardiac failure among patients aged 65-75 years compared to younger patients. Therefore, a warning reflecting this information was included in section 4.4 of the SPC.

The majority of hypoglycaemia AEs reported in the double-blind studies population came from Studies 082 and 095. The differences compared to the INS monotherapy groups may reflect the fact that INS was not up-titrated in these studies. In studies 347 and 009 the addition of RSG was not associated with a marked increase in hypoglycaemia compared to INS monotherapy.

In the presented studies there was clearly a dose-dependent increase in CHF incidence, especially in the studies in which RSG was introduced at the highest dose. A majority of the patients who developed CHF had prior or current CV related conditions. This warrants for careful titration of both RSG and insulin doses and a warning against use in patients with risk factors for CHF.

As for adverse events associated with fluid retention, the incidence of CV adverse events was highest in the studies in which RSG was introduced at maximal doses without up titration of the dose. Subjects who experienced CV adverse events seem to have had more pre-existing risk factors. However, patients with known prior cardiac diseases were in principle excluded from the studies. The majority of the patients who developed CHF in the presented studies had prior or current CV related conditions. This was considered as a safety issue by the CHMP and, therefore, the MAH was requested to present separate safety data in patients with cardiac disease.

As requested, the MAH provided data in patients with pre-existing cardiac disease that were included in the studies. Unstable or severe angina was excluded in all studies. All classes of heart failure were excluded in the Avandia studies 136, 347 and 085 and Avandamet 009, whereas only CHF NYHA Classes 3 and 4 were excluded in studies 082, 095 and 114. In studies 082 and 095 patients were also excluded if they had ECG evidence of left ventricular hypertrophy. In all the Avandia studies, patients with CV diseases other than those above, and those with known prior cardiac diseases, were not excluded, and constituted between 17 and 44% of the study population in individual studies.

The CHMP agreed that the finding of an increased incidence of CHF in patients receiving insulin in addition to rosiglitazone is expected and could be handled with dosing recommendations and adequate warnings in the SPC. The results of Avandamet study 009 highlights the importance of careful selection of suitable patients as well as a careful dose titration.

The CHMP also noted that the presented studies, except study 009, were all performed in patients who received RSG as add-on treatment to prior insulin therapy. According to treatment guidelines this does not represent a clinically adequate strategy. A more appropriate treatment sequence, reflective of clinical practice, would be to add insulin to already established treatment with RSG, which may also be favourable from a safety perspective since these patients presumably are tolerating RSG. The MAH agreed that adding insulin to established oral therapy with careful up-titration of the insulin dose, as in study 009, appears to be a more favourable option from a safety perspective, and consequently, agreed to limit the order of dosing when Avandia is used in combination with insulin, such that insulin is added to established rosiglitazone therapy. This limitation of the indication could, according to study data, reduce the risk of cardiac adverse events. However, the experience of this posology is limited (study 009).

The CHMP noted that there are several indications that RSG may be associated with an increased risk of ischaemic heart disease (IHD). Even if these assumptions are not based on adequately designed outcome studies, but on meta-analyses with well-known limitations, they can not be ignored. There are also several indications that insulin-treated patients that get additional treatment with RSG may be a subgroup at an even higher risk of cardiac events and, as stated above, the experience of the addition of insulin to RSG is very limited. Considering these uncertainties concerning the safety profile for RSG, the proposed indication for the combination of RSG and insulin can not be considered as recommendable. However, since the MAH has presented a certain amount of safety and efficacy data concerning the insulin+RSG combination, the CHMP was of the view that the contraindication concerning the insulin+RSG combination could be deleted.

3. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Data from seven studies have been provided in support of the type II variation application to extend the Avandia indications to include combination use with insulin in patients who cannot take metformin due to contraindication or intolerance.

Concerning the efficacy associated with the combination of insulin and RSG, it can be concluded that the treatment results in a clinically significant reduction of HbA1c, despite concerns on the adequacy of design of some studies. At the same time insulin doses are reduced or unchanged which probably is a result of increased insulin sensitivity.

The main safety issue concerning the combination of insulin and RSG is the dose-dependent fluid retention effect that has been seen in previous studies and the complications associated with this side effect.

The incidences of oedema, anemia, weight increase, hypoglycaemia and CHF were increased when RSG was added to insulin. These side effects were increased to a smaller extent when the RSG dose was carefully titrated and patients with pre-existing risk factors for fluid related adverse events were excluded. The presented studies, except study 009, were all performed in patients who received RSG as add-on treatment to prior insulin therapy. According to treatment guidelines this does not represent a clinically adequate strategy. A more appropriate treatment would be to add insulin to already established treatment with RSG. The MAH agreed with the CHMP that adding insulin to established oral therapy is the more usual treatment paradigm, and therefore agreed to limit the order of dosing when RSG is used in combination with insulin, such that insulin is added to established RSG therapy. Addition of RSG to established insulin therapy is therefore not recommended.

There are several indications that RSG may be associated with an increased risk of ischaemic heart disease (IHD), and insulin-treated patients that get additional treatment with RSG may be a subgroup at an even higher risk. Furthermore, it has been shown in several studies that patients treated with the insulin+RSG combination have an increased risk of developing CHF and this could, at least from a theoretical point of view, also indicate an increased risk of IHD. Even if some of these assumptions are not based on adequately designed outcome studies, but on meta-analyses with well-known limitations, they can not be ignored.

Considering these uncertainties concerning the safety profile for RSG, an increased indication including patients that may be at an even higher risk of cardiac adverse events is not considered as recommendable. However, since the MAH has presented a certain amount of safety and efficacy data concerning the insulin+RSG combination, the CHMP concluded that this combination could be used in exceptional cases as long as the patients are kept under close supervision. Consequently, the CHMP agreed that the contraindication concerning the insulin+RSG combination could be replaced by a warning in section 4.4 of the SPC.