SCIENTIFIC DISCUSSION

1. Introduction

Type 2 diabetes (T2D) is a chronic progressive disease characterised by hyperglycaemia, that contributes to a massive social and economic burden globally. In industrialised countries the incidence of T2D is expected to rise as obesity and a sedentary lifestyle become more common.
In early stages T2D can be managed through diet and exercise alone, however most patients need oral glucose-lowering medicinal products after some time and some of them require insulin. The treatment guidelines recommend to start with diet and exercise, and to add antihyperglycaemic agents, first as monotherapy and in combination if no-control is achieved.

T2D is often associated with micro—and macrovascular complications. In order to reduce the risk of developing such complications, a multifactorial approach to the management of diabetes is recommended, with important risk factors such as progressive hyperglycaemia, hypertension, dyslipidaemia, obesity and physical inactivity highlighted as important targets for intervention.

Metformin (MET) is considered the first choice in type 2 diabetic patients with obesity although the choice of initial oral glucose-lowering agents is influenced by the medical history and characteristics of the patient as well as their expected susceptibility to the various side effects. Within 3 years of onset around 50% of patients require multiple therapy, and after nine years this number increases to 75%. Current guidelines recommend the addition of sulphonylurea (SU) as first line combination with metformin. In Europe, thiazolidines are licensed for combination with either metformin, particularly in overweight patients, or sulphonylureas (SUs) in patients who are intolerant of, or in whom metformin is contraindicated.

As the compliance with treatment is an important factor in order to achieve the target glycaemic control and the combination of two different classes of antihyperglycaemic agents in a single tablet can simplify the importance of combination use is increasingly recognised. Fixed dose combinations medicinal products with metformin have been developed. However in subjects for whom metformin is inappropriate because of contraindication or intolerance, these fixed dose combination treatments are not an option.

AVAGLIM is an oral fixed dose combination (FDC) of rosiglitazone (RSG) and glimepiride (GLIM) for the second line treatment of type 2 diabetes mellitus (T2D). Intensive management of T2D and associated co-morbidities, such as hypertension and dyslipidaemia, means that patients often receive long-term polypharmacy. The proposed RSG/GLIM FDC offers a convenient single daily tablet of a potential combination treatment for T2D and the possibility for increased compliance and hence potentially improved long term glycaemic control.

RSG is a thiazolidinedione which acts as a selective and potent agonist at the peroxisome proliferator activated receptor γ (PPARγ), and has been marketed in the EU since 2000. RSG is indicated for oral combination treatment in subjects with T2D with insufficient glycaemic control, despite maximal tolerated oral monotherapy with either metformin or a sulphonylurea (SU), and in subjects who show intolerance to metformin or for whom metformin is contraindicated. In addition, it is also indicated for monotherapy in T2D subjects, particularly the overweight, who are intolerant to metformin or for whom metformin is contraindicated. The worldwide-marketed exposure from launch to September 2004 is estimated to be over 6 million patients. The current total marketed exposure to RSG is in excess of 5 million unique patients. Therefore the widespread use of this product in humans, in conjunction with an acceptable toxicological profile at therapeutic doses, provides evidence of its safety and efficacy.

GLIM is a second generation SU marketed in the EU since first approval in 1995 in most European countries. GLIM has been shown to improve glycaemic control in patients with T2D when used as first-line monotherapy or as an add-on to metformin or insulin treatment. Since first launch, it is estimated that exposure exceeds 17 million patient years.

The dosage regimen proposed for the RSG/GLIM FDC is consistent with that currently approved for the two drugs when administered concomitantly. The maximum recommended daily dose of the RSG/GLIM FDC is 8 mg/4 mg (RSG/GLIM). The accepted strengths for this product are 4mg/4mg and 8mg/4mg RSG/GLIM.

The proposed indication for the RSG/GLIM FDC is treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient control on optimal dosage of sulphonylurea monotherapy, and for whom metformin is inappropriate because contraindications or intolerance.

2. Quality aspects

Introduction

Avaglim is a fixed dose combination containing rosiglitazone (as maleate) and glimepiride as active substances. Two strengths are proposed containing 4 mg or 8 mg of rosiglitazone (as free base) and 4 mg of glimepiride. They are presented as film coated tablets.

Apart from this difference in strength, the formulations are identical, excipients include in the tablet core: sodium starch glycollate, hypromellose, microcrystalline cellulose, lactose monohydrate, magnesium stearate, and in the film coat: hypromellose, titanium dioxide, macrogol and colorants.

Film coated tablets are supplied in PVC/PVdC/aluminium blisters.

Active substance

Rosiglitazone maleate

Rosiglitazone maleate was assessed in previous applications for both Avandia tablets (rosiglitazone monoproduct, MA number EU/1/00/137) and more recently Avandamet film coated tablets (rosiglitazone/metformin combination product, MA numbers EU/1/03/258. The currently submitted information on rosiglitazone maleate is identical to that for Avandamet.

The route of synthesis, site of manufacture, and control of rosiglitazone maleate active substance are the same as accepted earlier in the approved EC Dossiers.

Adequate In-Process Controls are applied during the manufacture. The specifications and control methods for intermediate products, starting materials and reagents, were presented.

Batch analysis data of the three batches of rosiglitazone maleate are provided. The three lots are within the specifications and consistent from batch to batch.

Rosiglitazone maleate specifications includes description, identity (IR, HPLC), assay (HPLC , 98-102%), maleic acid content (HPLC), related substances (HPLC), residual solvents (GC), water content, sulphated ash, heavy metals, particle size, and specific rotation.

The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance.

The stability studies concern the same studies and batches for which result already were provided for rosigliltazone/metformin fixed combination (Avandamet). Additional stability results have been provided: data on 4 commercial batches (36 months at 25°C/60% RH and 6 months at 40°C/75% RH) and data on 3 qualification batches (36 months at 25°C/60% RH and 12 months at 40°C/75% RH) . The proposed re-test period is the same as approved earlier for the other strengths of Avandamet, based on full stability data of three commercial batches. No significant changes in assay, impurity levels or solid state form from the initial time point were observed. Therefore, the re-test period proposed is acceptable according to the stability data submitted.

Glimepiride

Information on glimepiride has been supplied in the form of Active substance master file (ASMF).

Glimepiride is a white powder. No asymmetric carbon atom is present. The active substance is practically insoluble in water, it is soluble in dimethylformamide and dimethyl-sulfoxide, slightly soluble in diluted alkalines and acids as well as in common organic solvents such as methanol, acetonitrile, acetone and methylene chloride.
The solubility in water was found to be dependent on the pH value: at high pH values, the solubility of glimeperide is better in water than at lower pH values.
Two crystalline polymorphic forms of glimepiride are known, the applied manufacturing process yields to the thermodynamically more stable form. The presence of this form is controlled routinely in the scope of batch analysis.
The manufacturing and control information on glimepiride was provided in the form of an ASMF (Active Substance Master File) and was evaluated as satisfactory. Adequate In-Process Controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented.
Glimepiride specifications include tests for appearance, identification (IR, HPLC), appearance of solution, related substances, polymorphic form, sulphated ash, assay (HPLC, 98.0% - 101.0%), heavy metals, residual solvents, water content (Karl Fisher), microbial contamination, and specific surface area (BET). The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance.

Batch analysis data of the three production batches glimepiride are provided. The three batches are within the specifications and consistent from batch to batch.

The stability of glimepiride was evaluated for 3 full scale batches stored under normal and accelerate stability conditions at 5ºC (48 months), 25ºC / 60% RH (48 months), 30ºC / 60% RH (48 months), 40ºC/dry (6 months), and 40ºC / 75% RH (6 months).

The parameters tested were appearance, appearance of solution (clarity, colour), HPLC related substances, water (GC), HPLC assay, specific surface area (BET), and particle size distribution.

The re-test period proposed was considered acceptable according to the stability data submitted.

Finished product

As the product is a combination of two existing oral antidiabetics , the formulation was developed to provide fast release of both active substances, matching as closely as possible the release profiles of the commercial products containing the individual active substances and to be bioequivalent to this commercial individual substances.

To investigate the potential for interactions between the drug substances and other ingredients that might be used in tablet formulations, the binary compatibility of the active substances with each other and the excipients used for the finished product dosage forms was studied. Good compatibility was demonstrated between all of them.

The excipients used are sodium starch glycolate, hypromellose, microcrystalline cellulose, lactose monohydrate, magnesium stearate, macrogol and colorants. The excipients are conventional and meet the requirements in Ph. Eur. Lactose monohydrate is manufactured from bovine milk. The supplier confirms that the milk used in the manufacture of the lactose is sourced from healthy animals under the same conditions as for human consumption
The primary packaging chosen was PVC/ PVdC/ aluminium blisters.

- Manufacture of the Product

The manufacture of rosiglitazone / glimepiride film coated tablets tablets, comprises conventional tabletting and aqueous film-coating processes.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in three production-scale batches of each and is satisfactory. The in process controls are adequate for this film coated tablet preparation.

The batch analysis data show that the film coated tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for description, identification of the active substances (HPLC), identification of colorants, uniformity of dosage of the active substances (Ph Eur), dissolution of the active substances, uniformity of content of the active substances (HPLC), assay of the active substances (95-105%, HPLC), related substances (HPLC), and microbial limit (Ph Eur).
Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.
The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.
Batch analysis data confirm satisfactory uniformity of the product at release.

- Stability of the Product

24 months primary stability data are presented for three pilot scale batches of Avaglim 4 mg strength stored at 30°C/65% RH and at 25ºC/60% RH, and 6 month stability data at 40°C/75% RH. Six month stability data for three commercial scale batches of the 4 mg strength tablets stored at 30°C/65% RH and at 40ºC/75% RH were also provided. Additionally, 12 month stability data were presented for three pilot scale batches of rosiglitazone / glimepiride tablets 8 mg strength stored at 30°C/65% RH and at 25ºC/60% RH, and 6 months at 40°C/75% RH.
All stability batches were manufactured at the proposed commercial site in the proposed primary packaging.

In addition, data are presented following short-term storage of one batch of the 4 mg and 8 mg tablet strengths under stress conditions of exposure to light.

The batches were tested for description, rosiglitazone content and drug related impurities by HPLC, glimepiride content and drug-related impurities by HPLC, rosiglitazone/glimepiride dissolution using. Some additional non-specified parameters are tested at defined time points of the studies: hardness, disintegration, water content and rosiglitazone isomer ratio.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures

3. Non-clinical aspects

Introduction

With the exception of two new secondary pharmacology studies, all nonclinical data for RSG were submitted and reviewed as a part of the original Avandia (rosiglitazone) marketing authorisation application, with additional data submitted t and Avandamet (rosiglitazone/metformin) marketing application. The assessment of RSG was based upon the non-clinical overview and previous assessments for Avandia and Avandamet.
GLIM is marketed in all EU countries after approval via the Mutual Recognition procedure. Consequently, cross-reference to these submitted reports was not possible in this centralised application. Therefore, data to assess the nonclinical pharmacology, pharmacokinetics and toxicology of GLIM were described by reference to the literature and other published information. Additionally, the assessment of GLIM was based upon the written summaries of the studies provided by the applicant.

Pharmacology

The primary and secondary pharmacodynamics and the safety pharmacology of both RSG and GLIM have been investigated in a series of non-clinical studies, *in vitro* and *in vivo*. In these investigations, RSG and GLIM were administered individually. No non-clinical pharmacology studies have been performed with these drugs administered as the fixed combination.

- Primary pharmacodynamics

The individual efficacies of RSG and GLIM in the treatment of T2D patients have been clearly demonstrated.

RSG is claimed to be a potent and selective agonist at the nuclear peroxisomal-proliferator-activated receptor gamma (PPARγ) and has shown to be a potent and orally active insulin sensitizer with a marked antihyperglycaemic activity mediated by improvements in insulin resistance which is a common feature characterising the pathogenesis of T2D. The antidiabetic activity of RSG has been demonstrated in animal models of T2D in which hyperglycaemia and/or impaired glucose tolerance was associated with insulin resistance in target tissues. Its antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle and adipose tissues. RSG did not induce hypoglycaemia in animal models of T2D and/or impaired glucose tolerance. Long term studies in mice and rats clearly demonstrate that RSG has a durable β cell protective action, due to prevention of β-cell depletion of insulin and net β -cell loss. The slow onset of action of RSG is in line with the theory that the synthesis of the active products such as lipoprotein lipase and Glut4 induced by activation of PPARγ-responsive genes needs time. The antidiabetic action of RSG in nonclinical rodent models is seemingly closely aligned with its ability to reduce elevated plasma free fatty acids. At high concentrations, free fatty acids are known to impair insulin action in skeletal muscle, and they also stimulate hepatic gluconeogenesis. The mechanism whereby RSG treatment of insulin-resistant rodents results in a reduction of plasma free fatty acids is incompletely understood, but may involve changes in adipose tissue expression and activity of the cytokine, TNFα.

The effect of GLIM on glucose and insulin has been investigated in detail, both *in vitro* and *in vivo*. The pancreatic (insulin release) and extrapancreatic effects (non–insulin secretion dependent) involve hepatic glucose (uptake, metabolism, disposal and incorporation) and insulin homeostasis. The pancreatic effect of GLIM is dependent upon functioning of β-cells in the pancreatic islets. Single oral doses of GLIM lowered blood glucose concentrations in fed normal and diabetic rats, and in normal non-diabetic dogs. Tests in the dog showed this effect to be dose-dependent. Additional extrapancreatic actions, which have an influence on glucose utilisation, metabolism and transport, have been identified in nonclinical studies and are hypothesised to contribute to the blood glucose lowering effect of GLIM, although the clinical significance of these actions is contentious.

- Secondary pharmacodynamics

The effects of RSG on body weight as well as its protective actions against tissue damage associated with chronic diabetes therapy have been investigated in detail. Its antihyperglycaemic activity seems associated with an increase in body weight and hyperphagia. It has been shown that RSG has a pancreatic protective action (prevention of β-cell depletion), that early drug intervention protects against renal damage (blood pressure changes) and that long-term treatment protects against the impairment of vascular endothelial cell function. It has also been demonstrated that RSG prevents the formation of cataracts. The antidiabetic action of RSG is closely linked with its ability to reduce fatty acids (plasma triglycerides). Two new studies in diabetic rats clearly showed that RSG treatment resulted in cardiac injury protection to ischemia-reperfusion and improved cardiac contractile function. These actions were accompanied by a decreased infarct size and apoptosis, increased glucose metabolism, and insulin signalling. Also, RSG treatment inhibited ischemia-reperfusion leukocyte adhesion and reduced inflammatory biomarkers. The new studies have demonstrated its cardiac injury protection and improved cardiac contractile function as well as its protection against ischemia/reperfusion-induced leukocyte adhesion (atherosclerosis) in diabetic rats. The predictability of these findings for humans is yet unknown.

GLIM has a much lower propensity to cause effects in the cardiovascular system compared to other sulphonylureas. The beneficial effects of myocardial protective effects of ischemic reperfusion (reduced infarct size, prolonged action potential duration and preserved diastolic function) and reduction of cardiac functional loss are examples. GLIM produced little systemic haemodynamic changes (slight increase in blood pressure), has potent anti-atherogenic and anti-inflammatory effects. Even though GLIM markedly reduced the ischemia-induced cardiac functional loss, a quite marked and dose-dependent reduction in coronary blood flow (from 97 to 45.8%) was observed *in vitro*. *In vivo*, however, the effects of GLIM on coronary blood flow were less marked (only 21%).

- Safety pharmacology programme

RSG
There were no toxicologically significant findings in oral single dose safety pharmacology studies with RSG that examined its potential effects on the cardiovascular, renal, respiratory, nervous and gastrointestinal systems at the doses tested (up to 80 mg/kg). From a safety pharmacological point of view, although safety pharmacology studies after single dose administration revealed no unwanted effects, it has been generally recognised that RSG exerts its pharmacological effect only after multiple dosing. Clinical safety data and animal repeated dose toxicity studies indicate that RSG might cause liver toxicity and heart failure (due to fluid retention)

GLIM
Central Nervous System. The overt effects of GLIM were recorded during a single dose toxicity study in Wistar rats. Following the oral administration of GLIM at doses up to 10000 mg/kg to rats, no symptoms or deaths were recorded. Following a series of behavioural studies in mice it was reported that GLIM, at oral doses of up to 100 mg/kg, did not affect general behaviour, spontaneous activity or pentobarbital anaesthesia, and had neither an anticonvulsive nor an analgesic effect.

Cardiovascular and Respiratory Systems. *In vivo* In addition, it does not seem likely that GLIM will induce QT-interval prolongation in humans. Relatively high i.v. administration of GLIM in rats (40 mg/kg) caused minor ECG effects (ST-interval changes signifying ischemia), hypotension and two deaths. Nevertheless, these effects were clearly much lower than those observed after glibenclamide. Following intraduodenal administration of GLIM, at doses up to 1 mg/kg in cats, there were no reported effects on systemic blood pressure, arterial blood flow, left ventricular contractility and spirogram. Similarly, intraduodenal administration of GLIM at doses up to 10 mg/kg in dogs was reported not to affect systemic blood pressure, arterial blood flow, heart rate, ECG and respiratory frequency. During long-term general toxicity studies in male and female beagle dogs, in which GLIM was orally administered at doses up to 320 mg/kg/day for up to 12 months, ECGs were recorded, and heart rate and PR, QRS, QT intervals documented. No changes in the ECG and derived parameter values were reported. *In vitro.*The effects of GLIM on hERG potassium channels, present in the

plasma membrane of cultured neuroblastoma cells, were assessed *in vitro* using whole cell patch clamp methods. At the maximum concentration tested (500 μM), which was limited by the compound's solubility, GLIM inhibited hERG channel currents by approximately 45%. This concentration therefore approximates to the IC_{50} value for GLIM in this system. GLIM did not affect hERG channel currents at the lowest concentration tested of 10 μM. The estimated IC_{50} value (500 μM, equivalent to 245 μg/mL) and the no-effect-level (10 μM, equivalent to 4.9 μg/mL) for GLIM in this hERG assay is approximately 595 and 12 times higher than the highest C_{max} value recorded in patients (0.412 μg/mL) orally administered the maximum proposed dose of 4 mg GLIM in the FDC. However, more relevant is the fact that due to the high level of plasma protein binding of GLIM (99.5%) the IC_{50} value and no-effect-level are at least 110000 and 2300 times higher than the highest plasma concentration of free GLIM observed in humans, respectively.

Autonomic nervous system and smooth muscle. At concentrations up to 100 μM, GLIM was reported to have no effect on motility of the isolated guinea pig ileum.

Renal system. In rats, GLIM, at doses up to 100 mg/kg, was reported to have no effect on the volume or pH of the urine, or concentration of Na^+, K^+ and Cl^- in the urine.

Gastrointestinal system. Following oral administration at doses up to 100 mg/kg in mice, GLIM was reported to have no effect on intestinal charcoal transport. GLIM did not affect gastric emptying after oral doses of up to 1 mg/kg in rats. Additionally, following intraperitoneal administration in rats, doses of GLIM of up to 1 mg/kg had no effect on exocrine pancreatic secretion, bile secretion or histamine-induced gastric secretion.

In conclusion major general pharmacodynamics effects of GLIM or RSG in the central nervous, autonomic nervous, cardiovascular, respiratory and gastrointestinal system were not noted at relevant doses or oral doses up to 80 mg/kg.

- Pharmacodynamic drug interactions

GLIM shows partial agonistic activity at PPARγ receptors. However, because of the difference in the *in vitro* affinities of GLIM and RSG to PPARγ, pharmacodynamic interactions between RSG and GLIM are unlikely at therapeutic dose levels. Only at a concentration of 10 μM, which is approximately 30 times higher than the maximum clinical plasma concentration, did GLIM displace RSG in an *in vitro* competition-binding assay. The IC50 of GLIM that displaced RSG (0.04 μM) from PPARγ receptors (27 μM) was 90-times higher than the maximum plasma concentration of GLIM in clinical studies. From the original MAA for RSG, interaction with the antidiabetic drugs glibenclamide (SU), voglibose (α-glucosidase inhibitor) and human insulin was assayed in a 1-month toxicity study in the rats. There was no evidence of other unexpected or synergistic effects arising from the combination apart from the synergistic increase in brown fat weight observed upon co-adminstration with insulin or glibenclamide.

Pharmacokinetics

There were no new pharmacokinetic studies with the FDC or with RSG. For GLIM pharmacokinetic data were extracted from published literature. Details of the methods used in all pharmacokinetic studies performed with RSG and its major metabolites were submitted and reviewed in the former European MAA's for RSG.

The *in vitro* binding of ^{14}C-RSG to plasma proteins was high (> 98%) in mouse, beagle, rabbits, rats. In rats and beagles, the volume of distribution of unchanged RSG was considerably lower than the volume of total body water suggesting limited distribution into tissues. The tissue concentrations of drug-related material were generally lower than the corresponding plasma concentration. Virtually no radioactivity was found in the brain. In pregnant rats having received a single dose of ^{14}C-RSG, some radioactivity was found in fetal tissues. These tissue levels were considerably lower than maternal plasma concentrations of radioactivity. In lactating rats, some excretion into the breast milk was seen after a single administration of ^{14}C-RSG. The phase I metabolism of RSG in rats, mice, beagles and

humans proceeds via *N*-demethylation and pyridine ring hydroxylation. In addition, oxidative cleavage of RSG occurs to yield a phenoxyacetic acid derivative. Phase II metabolism results in the formation of sulphate and glucuronide conjugates. *In vitro* studies employing human liver preparations showed that cytochrome P450-2C8 is the main enzyme responsible for phase I metabolism of RSG in humans. In 14-day repeated dose studies, liver enzyme induction was demonstrated both in rats (CYP3A and CYP4A) and in beagles (CYP4A). In rats, mice and beagles, radioactivity is mainly excreted in the faeces (approximately 62-63%) upon administration of ^{14}C-RSG, the remainder being excreted in the urine. Most of the radioactivity excreted into the faeces of rats was shown to undergo biliary excretion. In contrast, the urine is the main route of excretion in humans.

Bioavailability of GLIM in the rat was 60 to 70%. In dogs and rabbits, similarity in the extent of renal elimination following oral or intravenous dosing provided evidence that most of the dose is absorbed in these species. Clearance was higher in male rats than in females and this resulted in a shorter terminal half-life in the males. Maximum observed blood/serum concentrations of total radioactivity in rats and dogs occurred at *ca.* 3 to 5 hours after oral dosing, suggesting a relatively slow rate of absorption. Blood/serum concentrations declined quite rapidly thereafter in the rat and were generally not measurable beyond 8 hours after dosing. In the dog, however, concentrations declined more slowly and were still measurable at 96 hours. There was also evidence that exposure to drug-related material was about 50% higher in male dogs than in females. At doses of up to *ca.* 30 mg/kg, close to dose-proportional increases in exposure with increasing dose were observed in the rat, whereas at higher doses increases in exposure were notably less than dose-proportional. In dogs, there were subproportional increases in GLIM serum concentrations with increasing dose (0.8 to 320 mg/kg). The highest concentrations in tissues were observed at 4 hours. Radioactivity levels were higher than blood only in the liver. Other organs and tissues investigated generally contained concentrations of radioactivity similar to, or lower than, that in blood. Studies in pregnant rats demonstrated that drug-related material crossed the placenta and reached the foetal tissues. The concentrations were notably lower in foetal tissues than in maternal tissues and blood. In lactating rats, drug-related material was secreted in the milk, the maximum concentrations being approximately one third of those in the blood. Serum protein binding of GLIM in the rabbit and dog, and in humans was in excess of 99%. CYP2C9 is considered the most important enzyme in the metabolism of GLIM. The main routes of metabolism were oxidation of the methyl group on the cyclohexyl ring to the alcohol (MI) and further to the acid (MII). MI and MII were the predominant radio-components in human urine and faeces (where they accounted for the majority of the dose) whereas, in animals, a more extensive range of metabolites was present. In mice, rats and dogs, faeces was the predominant route of excretion of drug-related material with at least 80% of an orally administered radioactive dose excreted by this route and urine accounting for most of the remainder. Conversely, in the rabbit and in humans, more than half of a radioactive dose was eliminated by the renal route, with faeces being the secondary route.

No information was provided regarding possible pharmacokinetic interactions between RSG and GLIM. However, different enzymes metabolize RSG and GLIM, the combination has been investigated clinically and there was no evidence for pharmacokinetic interactions.

Toxicology

No non-clinical toxicity studies have been performed using RSG/GLIM FDC. Therefore, the general toxicological profile of RSG and GLIM has been investigated for both drugs when administered individually. For GLIM data were extracted from published literature and the expert report from the original MAA. Combination studies of RSG and GLIM were considered to be not necessary because of extended clinical data with co-administration of both components of the combination.

- Single dose toxicity

Acute toxicity was low for both RSG and GLIM. RSG was slightly toxic after oral dosing in mice and rats. The calculated LD_{50} value in male and female animals was > 1500 mg/kg. LD_{50} of RSG after i.v. dosing in male and female mice and rats was > 120 mg/kg. In dogs, the LD_{50} after oral dosing was > 320 mg/kg. Observed effects in mice were reduced activity, abnormal breathing, slight ataxia, convulsions, and lens and/or corneal lesions (this was observed in a few mice at dosages ≥ 1000

mg/kg). Rats showed convulsions, abnormal breathing, and dilated pupils. In dogs, emesis, a slight decrease in blood cell parameters and increase in ALT were observed.

In the mice and rats, single oral doses of GLIM of up to 10000 mg/kg were well tolerated. The intraperitoneal median lethal values for single doses of the GLIM metabolites, MI and MII in the mice were reported to be greater than 2000 mg/kg. In dogs, the median lethal dose of GLIM and metabolites MI and MII was between 2000 and 10000 mg/kg.

- Repeat dose toxicity

Repeated dose toxicity studies with RSG revealed increased food and water consumption, body weight gain, increased fat deposition with displacement of haemopoetic tissue in bone marrow, an increased plasma volume which caused increased heart weight and left ventricular hypertrophy at exposure levels comparable to the human therapeutic exposure, and at higher dosages, hydrothorax in rats. These effects of RSG are well known and have already been discussed.

After repeated administration of GLIM, the only noticeable effects were of a pharmacological nature and consisted of degranulation in the β cells of the islets of Langerhans in the pancreas and changes in the serum glucose concentrations. Cataracts as were found in some high dose dogs, were shown to be not drug dependent in bovine lenses and in rats and were observed only at very high exposures.

- Genotoxicity

Both RSG and GLIM do not pose a genotoxic risk to humans. Table TX1 summarises the results of genotoxicity studies of RSG.

Table TX 1 Results of genotoxicity studies of RSG

Type of test/Study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria/ TF-1017/BRL-049653/1	Salmonella strains TA98, 100, 1535, 1537, 1538 E.coli strain WP2 uvrA	312.5 – 5000 µg/plate +/- S9	Negative
Gene mutations in mammalian cells/ TF-1006/BRL-049653/1	Mouse lymphoma L5178Y cells TK locus	12.5 – 400 µg/ml +/- S9	Inconclusive
Chromosomal aberrations in vitro/ TF-1034/BRL-049653/1	Human lymphocytes	20 – 540 µg/ml +/- S9	Negative
In vivo micronucleus/ TF-1015/BRL-049653/1	Mice, bone marrow	0, 350, 700 mg/kg	Negative
Unscheduled DNA synthesis	Hepatocytes from rats	0, 470.6, 1488 mg/kg	Negative

Although no data were obtained from the published literature, the Pharmacological-Toxicological Expert Report on GLIM discussed a number of genetic toxicology studies performed with GLIM. GLIM was also non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

- Carcinogenicity

An increased number of lipomas were observed in a 2-year carcinogenicity study of RSG in rats. In previous evaluations of RSG it was concluded that it is likely the result of persistent stimulation of adipose tissue. In an 8-week study in APC^{Min} mice, an increase in the incidence of large intestine adenomas was observed. In wild type mice, colon tumour incidence was not increased at an exposure approximately 10 times the human exposure. The results in the APC^{Min} mice indicate a possible higher risk for patients with familial adenomatous polyposis (FAP). However, additional evidence was provided that this model can be considered as extremely sensitive to colon tumours. Furthermore, patients with FAP are nowadays preventively treated by prophylactic colectomy and if not, the risk for colon cancer is high irrespective of drug treatment.

Regarding the possibility of interactions between RSG and GLIM, it is unlikely that GLIM will adversely influence the carcinogenic potential of the combination, because of the far lower affinity of GLIM for the PPARγ receptor. Results from studies with GLIM showed that indeed there were no PPARγ specific effects (either pharmacological or toxicological) caused by GLIM, indicating that it is unlikely that at clinically relevant doses, the combination of RGS and GLIM would result in synergistic or additive effects on carcinogenic activity mediated via PPARγ.

In GLIM carcinogenicity studies, islet cell adenomas were observed which were ascribed to chronic pancreatic stimulation. Bronchio-alveolar adenomas were observed in mice and uterine adenocarcinomas in rats. For these tumours, the safety margin was considered to be large enough.

- Reproduction Toxicity

In fertility studies, RSG caused decreased plasma progesterone and estradiol levels, resulting in altered oestrous cyclicity in rats and in monkeys, as well as a reduced female fertility in rats. In embryotoxicity studies, RSG caused placental abnormalities, increased embryo-foetal death, and intrauterine growth retardation and decreased skeletal ossification. After administration of RSG pre- and postnatally, an increased number of stillborn pups, a lower pup survival rate and a delayed physical development were observed.

No effect from GLIM on fertility was observed in male mice and in male and female rats. In embryotoxicity studies, GLIM caused several defects in small numbers of foetuses (eye and skeletal effects in rats and rabbits and abortions in rabbits), however not dose related. In pre- and postnatal studies, GLIM caused an increase in foetal death rate and skeletal defects, the latter also during the lactation period.

In a RSG juvenile toxicity study in rats, there were no target organs unique to juvenile rats. No juvenile toxicity studies were provided for GLIM, which is acceptable because the product is not indicated for children.

- Local tolerance

RSG was mildly irritant to rabbit skin and moderately irritant to rabbit eye. RSG was no sensitiser in guinea pigs. No local tolerance studies were provided for GLIM, which was considered appropriate because the product is in tablet form only.

- Other toxicity studies

The extent of irreversible binding of RSG to human serum albumin was assessed in an *in vitro* study, in which was found that there was some irreversible binding to serum (up to 6.7% of the added RSG). Subsequently, antigenicity studies were conducted. No antigenic potential was observed in the active systemic anaphylaxis test in guinea pigs and in the passive cutaneous anaphylaxis test in both guinea pigs and mice.

The Expert Report for GLIM describes that tThe results of an active systemic anaphylaxis test, and a homologous 4 hour passive cutaneous anaphylaxis test in guinea pigs and the a 4 hour passive cutaneous anaphylaxis test in rats were negative is assays with GLIM. . GLIM-sulphonamide presented no evidence of sensitizing properties when tested in the Magnusson and Kligman model.

Ecotoxicity/environmental risk assessment

An environmental risk assessment was provided. The company committed to provide further information as a follow-up measures.

Discussion on the non-clinical aspects

Pharmacology. RSG is a selective agonist at the PPARγ nuclear receptor and is a member of the thiazolidinedione class of antidiabetic agents. RSG is currently used in the clinical treatment of T2D. It reduces hyperglycaemia by reducing insulin resistance in adipose tissue, skeletal muscle and liver. The antihyperglycaemic activity of RSG has been demonstrated in several animal models with insulin resistance, and early treatment in genetically susceptible rodent strains has been shown to prevent the onset of overt diabetes. RSG did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rodents. The major metabolite (a para-hydroxy-sulphate), which has high affinity for the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mouse. The clinical relevance of this observation has not been elucidated. RSG administration influences body weight, although the specific effects are dependent upon the model used. Long-term studies in rodents have clearly demonstrated that RSG has a durable β-cell protective action. RSG has also been shown to protect against renal damage in rats, rises in systolic blood pressure seen in untreated fatty rats, impairment of vascular endothelial cell function ex-vivo, and the formation of cataracts, which occur at a high incidence in untreated diabetic rats. There were no significant findings in oral single dose safety pharmacology studies that examined potential effects of RSG on the cardiovascular, renal, respiratory, nervous and gastrointestinal systems. No findings of concern were reported in a limited number of pharmacodynamic drug interaction studies conducted with RSG.
GLIM is an oral hypoglycaemic agent and a SU currently used in the treatment of subjects with T2D. It lowers plasma glucose levels acutely by stimulating insulin release from the pancreas. This is dependent upon functioning β-cells in the pancreatic islets since Single oral doses of GLIM lowered blood glucose concentrations in fed normal and diabetic rats, and in normal non-diabetic dogs. Tests in the dog showed this effect to be dose-dependent. Repeat administration of GLIM in diabetic KK-Ay mice ameliorated hyperglycaemia and hyperinsulinaemia associated with this strain. The primary mechanism of action of GLIM is considered to be via the inhibition of opening of ATP-sensitive K-channels (K_{ATP}-channels) found in the cell membrane of pancreatic β-cells, which ultimately results in the release of insulin. Additional extrapancreatic actions, which have an influence on glucose utilisation, metabolism and transport, have been identified in nonclinical studies and are hypothesised to contribute to the blood glucose lowering effect of GLIM, although the clinical significance of these actions is contentious. Overall, nonclinical studies have demonstrated that GLIM possesses a lower propensity to cause effects in the cardiovascular system compared to other SUs. A number of studies have shown that GLIM does not affect the myocardial protective effects of ischemic pre-conditioning in rat and rabbit isolated heart preparations and in vivo in rabbits. There were no findings of concern reported in safety pharmacology studies that examined the potential effects of GLIM on the nervous, cardiovascular, respiratory, renal and gastrointestinal systems. GLIM has been demonstrated to have partial PPARγ agonist activity with a potency 16-25% of that of pioglitazone.

Pharmacokinetics. The bioavailability of RSG was approximately 100% and 60% in the rat and dog, respectively. Absorption was rapid with T_{max} values generally being 0.5 to 2 hours. The elimination of RSG was rapid; the elimination half-life was 2 hours and 1 hour in the rat and dog, respectively. Exposure to RSG (C_{max} and AUC) in animals increased with increasing dose. There was no accumulation or decrease in AUC values on repeat dosing, and differences in exposure between the sexes were seen only in the rat where AUC values in females were about 50 to 100% higher than in males. Tissue distribution studies with ^{14}C-RSG in the rat indicated that the highest observed tissue concentrations of drug-related material occurred at about 1 hour post-dose, and were generally lower

than the corresponding plasma concentration. Tissue concentrations declined rapidly in most tissues; some degree of melanin binding was noted. Blood cell association was limited in rat, dog and human samples, and plasma protein binding was high in mouse, rat, rabbit, dog and humans samples. The routes of metabolism were similar in the mouse, rat and dog, and in humans. The sulphate conjugates of N-demethylation and pyridine ring hydroxylation products were the major circulating components in all species, after the parent compound. In the mouse, rat and dog, the major route of elimination of drug-related material was via the faeces (at least 60%) with the remainder being excreted in the urine. In humans, the majority of drug-related material was excreted in the urine.
The oral bioavailability of GLIM in rats was 60 to 70%; T_{max} was approximately 2 hours. Females exhibited higher exposure (C_{max} and AUC values) compared to males (generally about two fold). Following oral administration of ^{14}C-GLIM, absorption of radioactive drug-related material was virtually complete in rats, rabbits and dogs. At doses ≤ 30 mg/kg/day in rats, systemic exposure increased approximately proportionately with increasing dose. At doses of GLIM above 30 mg/kg/day in rats, and at all doses tested in the dog (0.8 to 320 mg/kg/day), systemic exposure increased subproportionately to increasing dose. Female rats exhibited significantly higher serum levels than males. This difference was not seen in immature rats or in dogs. No accumulation of drug-related material was noted. Following the oral administration of ^{14}C-GLIM in rats, the highest concentrations of radioactivity were recorded in the liver and gastrointestinal tract. Twenty-four hours after dosing, only these organs contained detectable levels of radioactivity; no radioactivity was detectable at 7 days post-dose. The distribution pattern following 10 day repeat oral dosing was similar to that noted after single administration. In vitro, ^{14}C-GLIM was > 99% bound to plasma proteins. Following the oral administration of ^{14}C-GLIM in pregnant rats, drug-related radioactivity was found to distribute to the foetus. At all time points, concentrations of radioactivity in the foetal tissues were lower than those recorded in the corresponding tissues of the dam. Two major metabolites, termed MI and MII, and a variety of other minor metabolites were identified in the plasma, urine and faeces of the mouse, rat, rabbit, dog (not MII) and monkey. MI and MII were the major metabolites detected in human urine and faeces; no other notable metabolites were detected in human samples. Following oral or intravenous doses of ^{14}C-GLIM in the rat and dog, the majority of drug-related material was excreted in the faeces. In the rabbit, the majority of drug-related material was excreted in the urine. Enterohepatic recirculation of drug-related material was demonstrated in the rat.
Clinical data regarding the administration of RSG and GLIM in patients with T2D, either concomitantly or as the FDC, or RSG in combination with other SUs, are submitted in support of this application. In this perspective the lack of studies concerning the nonclinical pharmacokinetics of the drugs in combination was considered acceptable.

Toxicology. Not all GLIM data were covered by published literature. Data on toxicokinetics, genotoxicity, carcinogenicity, fertility, and pre-and postnatal development were completely based on the GLIM Expert Report, and the underlying studies were provided. Combination studies of RSG and GLIM were considered to be not necessary because of extended clinical data on this combination available. Acute toxicity was low for both RSG and GLIM. Repeated dose toxicity studies with RSG revealed increased food and water consumption, body weight gain, increased fat deposition with displacement of haemopoetic tissue in bone marrow, an increased plasma volume which caused increased heart weight and left ventricular hypertrophy at exposure levels comparable to the human therapeutic exposure, and at higher dosages, hydrothorax. After repeated administration of GLIM, the only noticeable effects were of a pharmacological nature and consisted of degranulation in the β cells of the islets of Langerhans in the pancreas and changes in the serum glucose concentrations. Cataracts as were found in some high dose dogs, were shown to be not drug dependent in bovine lenses and in rats and were observed only at very high exposures. Both RSG and GLIM have hepatotoxic potential. Because no repeat-dose toxicity studies have been done with the combination, it is not known whether a potentiation in hepatotoxicity is to be expected and the potential effect is supposed to be followed. Both RSG and GLIM were not genotoxic. An increased number of lipomas were observed in a 2-year carcinogenicity study of RSG in rats. In the evaluations of former RSG dossiers it was concluded that these were likely the result of persistent stimulation of adipose tissue. In an 8-week study in APC^{Min} mice, an increase in the incidence of large intestine adenomas was observed. Since the APC^{Min} mice were specifically sensitive to intestinal adenomas, the clinical relevance of the findings in this model is not clear. RSG tumours are possibly due to a class effect. Regarding the possibility of interactions between RSG and GLIM, it is unlikely that GLIM will adversely influence the carcinogenic potential

of the combination, because of the far lower affinity of GLIM for the PPARγ receptor. Results from studies with GLIM showed that indeed there were no PPARγ specific effects (either pharmacological or toxicological) caused by GLIM, indicating that it is unlikely that at clinically relevant doses, the combination of RGS and GLIM would result in synergistic or additive effects on carcinogenic activity mediated via PPARγ. In GLIM carcinogenicity studies, islet cell adenomas were observed which were ascribed to chronic pancreatic stimulation. Bronchio-alveolar adenomas were observed in mice and uterine adenocarcinomas in rats. For these tumours, the safety margin was considered to be large enough. In fertility studies, RSG caused decreased plasma progesterone and estradiol levels, resulting in altered oestrous cyclicity in rats and in monkeys, as well as a reduced female fertility in rats. In embryotoxicity studies, RSG caused placental abnormalities, increased embryo-foetal death, and intrauterine growth retardation and decreased skeletal ossification. After administration of RSG pre- and postnatally, an increased number of stillborn pups, a lower pup survival rate and a delayed physical development were observed. No effect from GLIM on fertility was observed in male mice and in male and female rats. In embryotoxicity studies, GLIM caused several defects in small numbers of foetuses (eye and skeletal effects in rats and rabbits and abortions in rabbits), however not dose related. In pre- and postnatal studies, GLIM caused an increase in foetal death rate and skeletal defects, the latter also during the lactation period. In a RSG juvenile toxicity study in rats, there were no target organs unique to juvenile rats. No juvenile toxicity studies were provided for GLIM, which is acceptable because the product is not indicated for children. RSG was mildly irritant to rabbit skin and moderately irritant to rabbit eye. RSG was no sensitiser in guinea pigs. No local tolerance studies were provided for GLIM, which is acceptable because the product is in tablet form. No evidence for antigenicity potential was observed for RSG and GLIM. No immunotoxicity studies were provided for RSG and GLIM, but the clinical practice did not indicate that RSG and GLIM are immunotoxic.
The impurity profile of RSG was similar to that of presented in previous dossier of RSG assessed via Centralised Procedure and thus adequately qualified. GLIM impurities GLIM-sulphonamide and the cis-isomer were sufficiently qualified, since it is not expected that in the combination product, the quantities of these impurities will be increased.

Environmental Risk Assessment.

An environmental risk assessment was provided. The company committed to provide results of the additional tests as a follow-up measures.

4. Clinical aspects

Introduction

Four clinical pharmacology studies were submitted with this application. These studies serve to bridge the clinical safety and efficacy data for RSG and GLIM used concomitantly as presented in this MAA to the FDC tablet. In addition, six clinical studies were submitted: four specific RSG+GLIM studies (one with the FDC tablets, three with concomitant RSG and GLIM) and two sub-studies from the ongoing RECORD study, in which SU+RSG is compared to SU+MET.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The clinical data to support the FDC includes 4 clinical pharmacology studies in healthy volunteers: (a bioequivalence study (study 797620/002), a food effect/bioequivalence study (study 797620/003), a dose-proportionality study (study 797620/001) and an interaction study between RSG and GLIM, that was already assessed as part of type II variation for AVANDIA (EMEA/H/C/268/23, approved February 2005)). These studies demonstrated notably bioequivalence between RSG/GLIM FDC tablets and concomitant administration of GLIM and RSG. Overall, the information provided was in

accordance with that included in the SPC in the UK for GLIM and in the SPC for RSG. The demonstrated bioequivalence was used to bridge to further safety and efficacy studies where RSG and GLIM were administered concomitantly. The formulations of RSG/GLIM tablets used in the clinical studies were identical in formulation and method of manufacture to those proposed for commercial use.

- Bioequivalence

Study SB-797620/002 was a bioequivalence study with a FDC of RSG and GLIM (4 mg/4 mg) compared to concomitant dosing of RSG 4 mg and GLIM 4 mg (4 mg+4 mg) commercial tablets in healthy subjects. The objective of the study was to demonstrate the bioequivalence of a combination formulation of RSG 4 mg/GLIM 4 mg relative to concomitant dosing of RSG 4 mg and GLIM 4 mg commercial tablets in the fasting state. Bioequivalence of the combination tablet formulation of RSG and GLIM (4mg / 4mg) relative to concomitant dosing of RSG and GLIM commercial tablets (4mg + 4mg) was demonstrated for the RSG component (AUC and C_{max}) and for AUC of the GLIM component, while 90% CI for the ratio A:B was not completely contained within the range 0.80 to 1.25 for GLIM C_{max}. The GLIM C_{max} was estimated to be, on average, 12% lower following administration of the combination tablet, compared with values obtained after concomitant administration of the commercially available tablets. The lack of strict bioequivalence for GLIM C_{max} was considered not clinically significant, as no safety issues would be associated with a reduction in C_{max}. Efficacy should be unaffected as there was bioequivalence between GLIM AUCs.

Study SB-797620/003. Because the SU and SU combination treatments are not dosed in the fasted state, but rather dosed at mealtime, a study SB-797620/003 was designed to assess the relative bioavailability of the FDC compared to the separate components, in the more clinically relevant fed state. It was designed to assess the effect of food on the pharmacokinetics of a RSG 4 mg and GLIM 4 mg FDC tablet and to compare the pharmacokinetics of RSG 4 mg and GLIM 4 mg FDC tablet to concomitant dosing of RSG 4 mg and GLIM 4 mg commercial tablets in the fed state in healthy subjects. When the combination tablet was administered with a meal, RSG $AUC_{(0-\infty)}$ was unchanged compared to administration in the fasted state. The RSG C_{max} was moderately decreased approximately 32% with food, on average. Administration of the combination tablet (4mg/4mg) with food led to an increase in GLIM exposure relative to administration in the fasted state. GLIM $AUC_{(0-t)}$ and C_{max} were increased by 30% and 55%, respectively, on average. This information was added to SPC of the FDC. For both RSG and GLIM, AUC and C_{max} were similar following administration of the combination tablet compared to concomitant administration of RSG and GLIM, both in the fed state. T_{max} and $t_{½}$ were also similar between the two formulations when each was given with a meal. Following administration of the RSG/GLIM (4mg/4mg) combination tablet, the extent of absorption of RSG was statistically significant different but considered not a clinically relevant different in the fed state compared to the fasted state, but the rate of absorption was reduced. The rate and extent of absorption of GLIM were modestly increased following administration of the combination tablet in the fed state compared to results obtained in the fasted state. Incomplete or a decreased rate of GLIM dissolution at 4mg in the fasted state might explain the higher (relative to fasting) C_{max} and AUC values observed in the fed state. The modest increases in GLIM exposure in the fed state (relative to the fasting state) are clinically inconsequential, given that dosing with meals is recommended for thiazolidinedione/sulphonylurea combination therapy, and diabetic patients are titrated to an appropriate glycaemic response. The rate and extent of absorption of RSG and GLIM, in the fed state, were equivalent following administration of the combination tablet compared to concomitant administration of RSG and GLIM as the currently approved commercial formulations. Under fed conditions RSG/GLIM FDC tablet or the concomitantly administered RSG and GLIM tablets are considered bioequivalent, since the 90% confidence intervals for $AUC_{(0-t)}$ and C_{max} for both RSG and GLIM were within the bioequivalence acceptance range of 0.80-1.25.

- Dose proportionality and time dependencies

Study SB-797620/001. There was one dose proportionality study performed with a combination tablet formulation of RSG and GLIM (4mg/1mg; or 4mg/2mg; or 4mg/4mg) in healthy subjects. The objective of this study was to assess the dose proportionality of GLIM across three RSG/GLIM

combination formulations 4mg/1mg, 4mg/2mg, and 4mg/4mg after a light breakfast. Four consecutive subjects exhibited pharmacokinetic data that clearly showed inconsistency between observed PK parameters and assigned dosing sequence. Their data were not consistent with the other 20 subjects in whom GLIM exhibited dose proportionality for AUC and C_{max} over the dose range 1 to 4mg. Most probably these subjects received a different treatment sequence as was indicated by the clinical site. The clinical study site and bioanalytical site were inspected but there were no issues identified during the audits, which could have resulted in the problem identified. For these reasons, discussion of the pharmacokinetic results and conclusions are based primarily on results from the statistical analysis that excluded data from these four subjects (n=20); analyses of the full data set (including outliers, n=24) are provided in the study report for completeness. The analysis that includes the outliers (n=24) indicates that there is a less than dose-proportional increase in exposures, and thus there is no safety concern.
Based on dose-normalised $AUC_{(0-t)}$ and C_{max} values in 20 subjects, the pharmacokinetics of GLIM appears to be dose linear in the 1 mg to 4 mg dose range. This is in line with information on GLIM tablets, for which dose-linearity has been demonstrated in the range 1-8 mg for AUC values. The composition of the 4 mg RSG FDC and 8 mg RSG FDC tablets are dose proportional (i.e. the ratio between RSG and excipients is the same except for the filler lactose to compensate for the increased amount RSG granulate), dissolution profiles across all tablet strengths are similar, and as, the pharmacokinetics of RSG have been shown previously to be dose linear in the range 0.2 to 20 mg, also the RSG, the 8mg FDC tablets, for which no studies were submitted, can be considered bioequivalent with respect to extent and rate of absorption of RSG.

- Pharmacokinetic interaction studies

Results of the *in vivo* studies to date do not show any clinically relevant interactions between RSG and SUs, and they are frequently used concomitantly. The potential for a clinically relevant drug-interaction between RSG and GLIM is low since RSG and GLIM are predominantly metabolised via different enzyme systems (CYP2C8 and CYP2C9, respectively).

Study BRL-049653/340 in healthy male and female volunteers was undertaken to investigate the pharmacokinetic interaction between 8 mg RSG and 4 mg GLIM. This study has been assessed previously in the type II variation of Avandia® (EMEA/H/C/268-270/II/23). Pharmacokinetic data from this study showed that the concomitant administration of RSG in steady-state and single dose GLIM caused modest 22% and 24% decrease in GLIM AUC and C_{max} respectively, accompanied by a decrease of $t_{1/2}$ by 1 to 3 hours. This decrease is considered as clinically insignificant since GLIM requires individualised dosing to desired glucose-lowering response. RSG AUC decreased on average 17% upon repeated administration, which is consistent with previous observations. C_{max} and T_{max} values were similar following single or repeated administration of RSG. It was concluded the pharmacokinetics of RSG (8 mg) in combination with GLIM (4 mg) have been sufficiently investigated.

- Pharmacokinetics using human biomaterials

No studies have been identified from the GLIM published literature discussing use with other human biomaterials. No such studies have been carried out with RSG either. Absence of these studies did not hinder the evaluation of the safety or efficacy of the FDC.

Discussion on pharmacokinetics

Under fasted conditions, bioequivalence of the RSG/GLIM combination tablet (4mg / 4mg) relative to concomitant dosing of RSG and GLIM commercial tablets was demonstrated for the RSG component (AUC and C_{max}) and for AUC of the GLIM component. The GLIM C_{max} was estimated to be, on average, 12% lower following administration of the 4mg/4mg FDC tablet, compared with values obtained after concomitant administration of the commercially available tablets. However, when administered with a high fed breakfast, RSG/GLIM 4mg/4mg FDC tablet or the concomitantly administered RSG and GLIM tablets are considered bioequivalent, since the 90% confidence intervals for $AUC_{(0-t)}$ and C_{max} for both RSG and GLIM were within the bioequivalence acceptance range of

0.80-1.25. The bioequivalence under fed conditions is clinically relevant, as RSG/GLIM combination should be taken with a meal (SPC section 4.2). When the combination tablet was administered with a meal, RSG AUC was unchanged compared to administration in the fasted state. The RSG C_{max} was moderately decreased approximately 32% with food, on average. These RSG food-effect results with the fixed dose combination are consistent to those from previous pharmacokinetic studies examining the effect of food on RSG alone submitted with the original marketing application for RSG. Administration of the combination tablet (4mg/4mg) with food led to an increase in GLIM exposure relative to administration in the fasted state. GLIM $AUC_{(0-t)}$ and C_{max} were increased by 30% and 55%, respectively, on average. GLIM has previously been reported to be 100% bioavailable relative to i.v. administration, however, this observation is based on a 1mg dose. In a previous food effect study, with an earlier formulation of GLIM 1mg, GLIM C_{max} and AUC decreased 8-9%, and t_{max} increased 12% on average upon coadministration with food. Incomplete or a decreased rate of solubilisation of GLIM at the higher dose of 4 mg in the fasted state might cause the higher (relative to fasting) C_{max} and AUC values observed in the fed state. Based on dose-normalised $AUC_{(0-t)}$ and C_{max} values in 20 subjects, the pharmacokinetics of GLIM appears to be dose linear in the 1 mg to 4 mg dose range. This is in line with information on GLIM tablets, for which dose-linearity has been demonstrated in the range 1-8 mg for AUC values. The 4mg/4mg and the 8mg/4mg FDC tablets are dose proportional. As the pharmacokinetics of RSG have been shown previously to be dose linear in the range 0.2 to 20 mg, also the RSG 8mg FDC tablets, for which no studies were submitted, can be considered bioequivalent with respect to extent and rate of absorption of RSG.

Pharmacodynamics

No new pharmacodynamic studies with FDC were submitted.

Clinical efficacy

The efficacy of RSG and GLIM were documented in their respective marketing applications, and both drugs are approved for use in the treatment of T2D, although RSG has still a limited indication. The clinical data package of this submission consisted of (1) a review of the scientific literature on GLIM, (2) data from previously submitted for RSG studies and (3) main studies (specific data on RSG+GLIM, both in combination and concomitant administration).

(1) A review of the scientific literature on GLIM

The review of the scientific literature included: 5 placebo-controlled studies, 6 active-controlled and 9 combination studies. The placebo and active-controlled studies contributed 4238 subjects to the efficacy database with 2412 subjects receiving GLIM monotherapy. More than 500 further subjects were treated with GLIM in combination with other anti-diabetic medications such as TZDs, insulin and MET. In addition, 3 observational/open-label studies are discussed which include more than 22,000 subjects. Data from the placebo-controlled studies indicate that the dose response characteristics of GLIM appear to mirror those of other SUs, such as glipizide (GLIP), with a steep rectangular hyperbolic response to increasing drug dose. This dose response curve indicates that lower SU doses give the majority of the anti-hyperglycaemic effects such that half maximal doses of SUs appear to offer essentially all of the long-term glycaemic benefit in most subjects. In the Goldberg study there was little additional benefit of 8mg GLIM compared to 4 mg GLIM (change in HbA1c at week 14 was 1.8% with 4 mg GLIM compared to 1.9% with 8 mg). In Rosenstock's study, statistically significant reductions in HbA1c were achieved with all GLIM dosage regimens (4 mg and 8 mg twice daily; 8 mg and 16 mg once daily) compared with placebo, but there were no clinically relevant differences among the four GLIM dose regimens. HbA1c increased from 7.7% at baseline to 9.7% at week 14 ($p<0.001$) in the placebo group whereas HbA1c values for the GLIM groups were 7.9-8.1% at baseline and 7.4-7.6% at week 14 across the 4 dose regimens. Active comparator studies with other SUs have demonstrated no significant differences in glycaemic efficacy between GLIM and glibenclamide (GLIB). These studies had similar designs; dosages were titrated to target FPG values of 90–150 mg/dL over 8-12 weeks and treatment continued for between 27 and 52 weeks. In the two studies comparing GLIM to GLIB, the doses used for both study medications were at the higher end of their respective dose-response curves. In Dill's study, GLIM was up-titrated from 1mg to a maximum of 12 mg daily and GLIB from 1.25mg to a maximum of 15mg daily. The mean daily dosages were

GLIM 12.4 ± 3.5 mg and GLIB 15.0 ± 4.1 mg. After a two-month dose titration phase in Draeger's study, the majority of subjects were taking GLIM 8mg od or GLIB 10mg bd. Although the dose of GLIM used in these studies was high, the dose of the comparator, GLIB, was also high, doses being above the half maximal dose (4mg GLIM and 7.5 mg glibenclamide) of each agent. Thus in the studies by Dills and Draeger both agents were being used at maximally clinically effective doses and hence similar glycaemic efficacy would have been seen at half-maximal doses of GLIM and GLIB to that seen at the higher doses used in these studies.

(2) Data from previously submitted RSG studies

The key data from previously submitted RSG studies are those from the integrated dataset of studies, investigating 4mg and 8mg RSG given concomitantly with SUs, which were submitted as part of the recent Type II Variation to AVANDIA Tablets (EMEA/H/C/286/II/23). This dataset was made up of 9 double-blind studies and 3 open-label studies and included 3633 subjects.

In a meta-analysis across the double-blind studies, 8mg RSG in combination with SU produced clinically relevant reductions in HbA1c and fasting plasma glucose (FPG) from baseline to 6 months. A dose-response was clearly demonstrated as greater decreases in HbA1c and FPG were observed at the 8mg RSG dose compared to the 4mg dose. Furthermore, for those subjects that did not achieve adequate glycaemic control with 4mg RSG+SU, an increase in dose to 8mg was associated with an incremental improvement in glycaemia with a larger proportion of subjects achieving glycaemic goals. Additional significant data from the RSG+SU dataset are discussed as part of the discussion of the efficacy data from the clinical studies presented with this application

(3) Main studies

Efficacy and safety data relevant to the RSG/GLIM FDC come from existing RSG+SU data (previously submitted) and some specific data on RSG+GLIM (both combination and concomitant administration). The specific RSG+GLIM data come from four double-blind studies in T2D subjects; one study with RSG/GLIM FDC tablets and three studies with concomitant RSG and GLIM administration. In addition, 18-month efficacy data and 12-month ABPM data are presented from two-sub-studies from the ongoing, randomised, open-label study (study 231) comparing SU+RSG to the gold standard therapy SU+MET.

Table 1. Overview of the clinical studies submitted.

Study No.	Study type	Duration	Treatment Group[1]	RSG/GLIM Dose	N
Clinical Studies					
RSG + any SU Studies					
49653/231 [2]	Open-label	18 months	RSG+SU, SU+MET	4 to 8mg + SU[3]	573 (301) [4]
49653/231	Open-label	12 months	RSG+SU, SU+MET	4 to 8mg + SU[3]	327 (160) [5]
RSG + GLIM Studies					
797620/004	Double-blind	28 weeks	RSG/GLIM FDC, GLIM, RSG	4mg/4mg[7], 8mg/4mg[7]	883 (435) [6]
49653/325	Double-blind	24 weeks	RSG+GLIM, GLIM	4mg+2mg, 4mg+4mg	362 (181) [6]
49653/234 [2]	Double-blind	26 weeks	RSG+GLIM, GLIM	4mg+3mg, 8mg+3mg	172 (115) [6]
HOE490/4034	Double-blind	26 weeks	RSG, RSG+GLIM	4 to 8mg + 2 to 8mg	40 (25) [6]

1. RSG = rosiglitazone, GLIM = glimepiride, SU = sulphonylurea (glimepiride [GLIM], glibenclamide [GLIB], gliclazide [GLIC])
2. Previously submitted to the CHMP as part of Type II Variation for AVANDIA
3. SU dose (GLIM, 4mg/day; GLIB, 15mg/day; GLIC, 240mg/day)
4. 18 months RECORD glycaemic sub-study (SU stratum only) and those taking RSG + any SU in parentheses.
5. 12 months RECORD ABPM (ambulatory blood pressure monitoring) sub-study (SU stratum only) Efficacy Population and those taking RSG + any SU in parentheses
6. Indicates intent-to-treat (ITT) population and those taking RSG+GLIM in parentheses.
7. Indicates the maximum dose the subjects might receive. Starting doses were 4mg/1mg in both FDC groups and up-titration occurred to maintain the glycaemic target set for the study.

METHODS

Study Participants

The number of subjects participating in each of the main studies is described in the Table EF 1. The mean age across studies 325, 234, 4034 and 231 was approximately 58 years (although it was 54 years in study 325) and the proportion of male subjects ranged from 42–59%. The majority of subjects were white (range 67–100%), particularly in the studies conducted in Europe. The mean baseline BMI was approximately 30 kg/m^2 in the European studies and 34 kg/m^2 in the predominantly US studies. The mean duration of diabetes ranged from 5-8 years across the studies, 92-100% of subjects had failed previous oral anti-diabetic monotherapy and the mean baseline HbA1c and FPG ranged from 7.9–8.4% and 155-191mg/dL, respectively (which were slightly lower than the ranges in the integrated RSG+SU datasets; HbA1c ranged from 8.9-9.4% and FPG from 184-201 mg/dL).
The drug-naïve subject population of study 004 were slightly younger (mean age 54 years) compared to the other studies (except study 325, where the mean age was also 54 years) with a mean duration of diabetes of 2.9 years. Other baseline characteristics were similar to the other studies: 77% of subjects were white, 59% were male, the mean baseline BMI was 32 kg/m^2 and mean baseline HbA1c and FPG were 9.1% and 11.7mmol/L (211mg/dL), respectively.

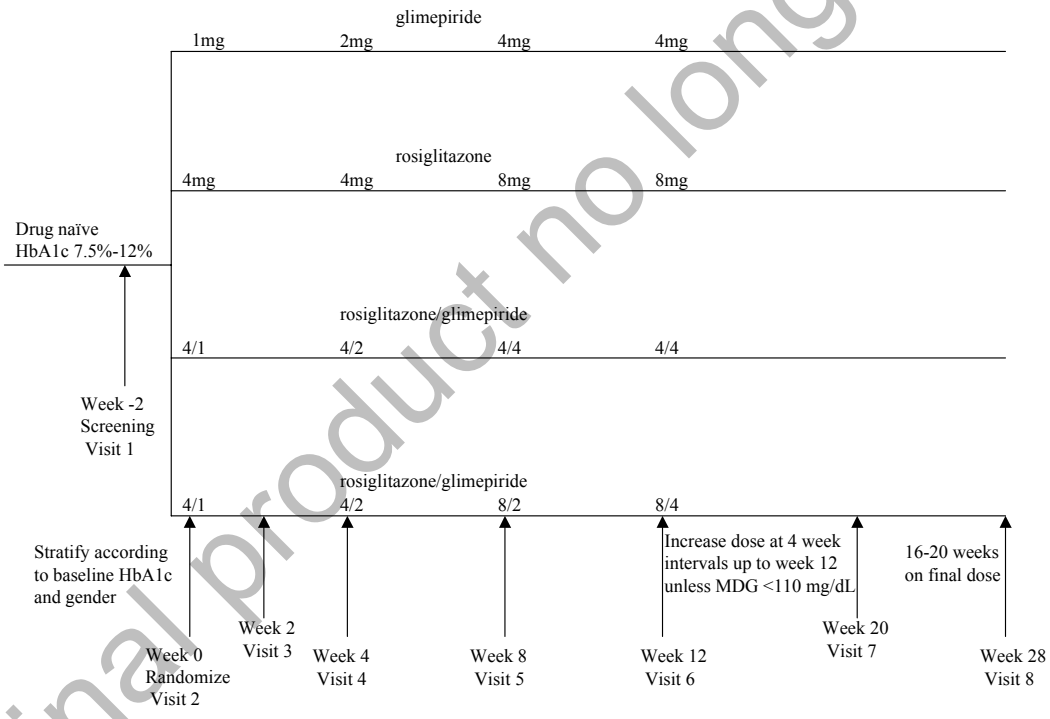
Objectives and treatment

The study 49653/231 (RECORD) comprised two sub-studies: 18 months glycaemia sub-study and 12-month Ambulatory Blood Pressure Monitoring (ABPM) sub-study. In 18 months glycaemia sub-study subjects were randomised following a 4-week run-in period to receive either RSG in combination with background MET or SU or the standard combination of MET+SU. Subjects received open-label treatment, were treated to a target HbA1c ≤7.0 %, and were up-titrated accordingly to a total daily dose of 8mg RSG or maximum permitted doses of MET/SU in the control arms. Results from this sub-study (6-months data) were included in type II variation for AVANDIA (EMEA/H/C/268/II/23). A 12-month Ambulatory Blood Pressure Monitoring (ABPM) sub-study was conducted to compare the effect of RSG in combination with either MET or SU versus MET+SU on 24-hour ambulatory blood pressure at months 6 and 12. This application includes the 12-months data, however, this efficacy document summarises the data for the SU-stratum only (380 subjects enrolled).

The following studies were all randomised, parallel-group studies in T2D subjects.

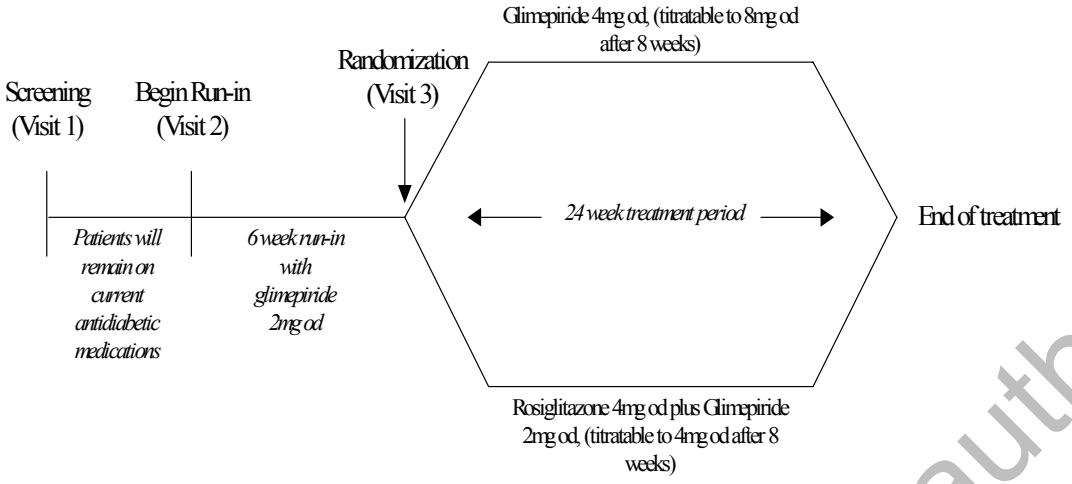
Study 004
Study 004 was a 28 week randomised, double blind, parallel group study that compared RSG/GLIM FDC [4mg/1mg od titrated to a maximum of 4mg/4mg od (FDC A) or 8mg/4mg od (FDC B), as required to meet glycaemic targets] to GLIM (1mg od up to 4mg od, to meet glycaemic targets) or RSG (4mg od up to 8mg od, to meet glycaemic targets) in drug naïve subjects. This study was carried out as part of the global development to support a first-line indication.

- Study design



Study 325
Study 325 was a 24 week randomised, double blind, parallel group, placebo controlled study that compared RSG (4mg) added to GLIM (2mg, up-titrated to 4mg from week 8 if required to meet glycaemic targets) with up-titrated GLIM alone (4mg up to 8mg from week 8 if required) in subjects failing monotherapy (who had not achieved glycaemic goals on half-maximal GLIM monotherapy prior to study entry).

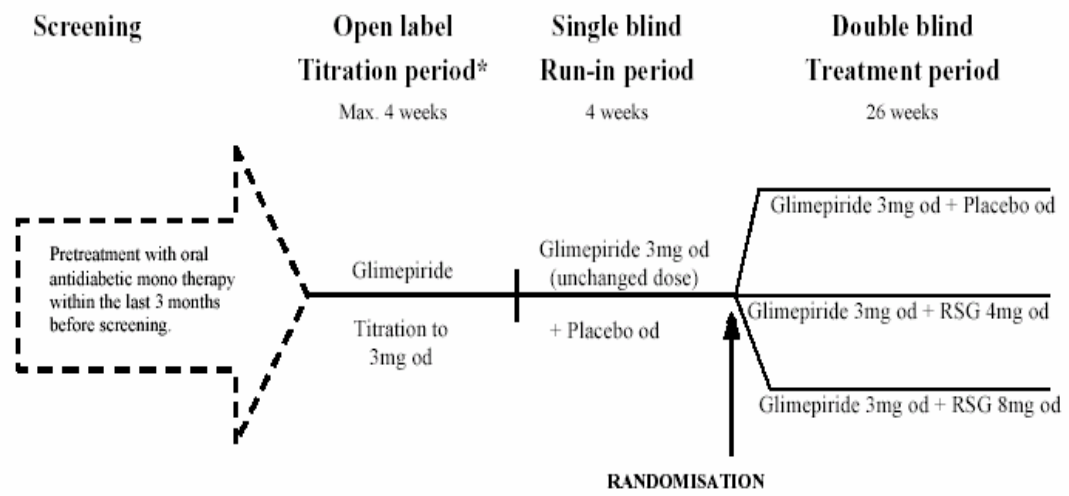
- Study design



Study 234

Study 234 was a 26 week randomised, double blind, parallel group, placebo-controlled study that compared RSG (4mg or 8mg) plus GLIM (3mg) to GLIM alone (3mg) in subjects inadequately controlled on GLIM monotherapy. Data from this study were included in the recent Type II variation for Avandia tablets (EMEA/H/C/268/II/23).

- Study design



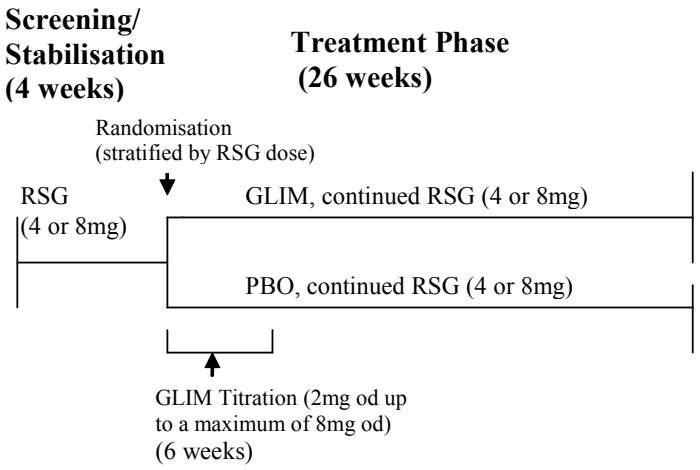
* In patients already treated with 3mg Glimepiride the open label titration period was not required.

The run-in period of 4 weeks was short to identify 'real' non-responders. Stable treatment of 8 to 12 weeks preceding the study should be recommended to ensure that the maximal effect of the previous treatment has been observed.

Study 4034

Study 4034 was a 26 week randomised, double-blind, parallel group, placebo-controlled study that compared the addition of GLIM (2mg/day, titrated to a maximum of 8mg/day to achieve target fasting blood glucose levels) to RSG (4mg or 8mg/day) versus RSG alone (4mg or 8mg/day) in subjects inadequately controlled on RSG monotherapy. This study was terminated early by the sponsor due to difficulty in recruiting eligible subjects and provides limited subject data (n=40).

- Study Design



Outcomes/endpoints

The primary efficacy endpoint in the four double-blind studies, 004, 325, 234 and 4034 was mean change from baseline in HbA1c at the end of double-blind treatment. In addition, mean change from baseline in HbA1c at Month 18 was the primary efficacy endpoint for the open-label 18-month glycaemia sub-study 231. For the ABPM sub-study, the primary efficacy analysis was mean change from baseline in 24-hour ambulatory diastolic blood pressure at 6 months (submitted to the CHMP as part of the 8mg RSG + SU Type II variation. ABPM data after 12 months dual combination treatment were considered supportive and are included in this application.

Mean change from baseline in fasting plasma glucose (FPG) to study endpoint was a main secondary efficacy variable collected for all studies.

The proportion of subjects who achieved a target HbA1c (≤7% in studies 231, 325, 234 and 4034, <7% in study 004) and the proportion of subjects who achieved a target FPG (<126mg/dL [<7.0mmol/L] in study 004, ≤126mg/dL in study 325 and 231, ≤140mg/dL [7.8mmol/L] in study 325 and 234) were evaluated. These responder rate analyses were defined in accordance with CHMP and treatment guidelines. Additionally, the percentage of subjects who responded to treatment with a defined fall in HbA1c and FPG at the study endpoint was assessed. HbA1c responders were defined as subjects who had ≥0.7% decrease in HbA1c from baseline. FPG responders were defined as subjects who had ≥30mg/dL (1.7mmol/L) decrease in FPG from baseline. Both these criteria were based on regulatory precedents (0.7% acarbose; 30mg/dL troglitazone).

Other variables included: change in lipid parameters, measures of HOMA insulin sensitivity and β-cell function, inflammatory and thrombotic markers, and albumin: creatinine ratio (ACR).

Sample size

In study 231, 77% and 91% of subjects in the 18-month sub-study and 12-month ABPM sub-study, respectively, were still receiving dual combination therapy; the proportion of withdrawals was similar for both treatment groups in each sub-study.

In study 004, a similar proportion (approximately 87%) of drug-naïve subjects in each treatment group completed the study. In the concomitant RSG+GLIM studies (325, 234, 4034), 80-97% of subjects treated with RSG+GLIM completed the studies compared to 72-91% of subjects in the control arm of each study. This is similar to that seen in the RSG+SU integrated dataset where 85% of subjects treated with RSG+SU and 73% treated with SU+PBO completed the studies, respectively.

In the double-blind studies, the proportion of subjects withdrawing due to an AE was low and comparable across the different treatments (range 0-4%). As expected, a higher proportion of subjects

withdrew due to lack of efficacy from the monotherapy control groups (2-13%) compared to the RSG+GLIM or RSG/GLIM FDC groups (0-4%).
Despite the different inclusion and exclusion criteria for studies 325, 234, 4034 and 231, the demographic and baseline characteristics of the subjects were broadly similar and were considered representative of a T2D population failing monotherapy. In addition, the subjects were similar to the population included in the RSG+SU integrated dataset.

Statistical methods
The primary population for statistical analyses within each study (with the exception of the 12 month ABPM sub-study 231) was the intent-to-treat (ITT) population. This population consisted of all randomised subjects who had received at least one dose of study medication and had at least one valid on-therapy data value for an efficacy parameter.
The primary analysis population for studies 004, 325, 234 and 4034 was ITT with the last observation carried forward (LOCF) for withdrawn subjects or those with missing values. A secondary statistical analysis for studies 004 and 325 included the ITT population without LOCF. For study 234, a secondary statistical analysis was carried out on the 'Per-Protocol' population defined as those subjects who adhered to the protocol without any major deviation.
For the 18 month glycaemia sub-study 231, the primary analysis population was ITT with a repeated measure analysis using all available data at each visit that compared RSG+SU with SU+MET at 18 months. A secondary supportive statistical analysis was carried out for a 'Per Protocol' population (all subjects in the ITT population who had no major protocol deviations at study entry or at any time during the first 18 months of add-on treatment). A further supportive analysis assessed the differences between treatment arms with regard to changes from baseline in HbA1c at 18 months, using analysis of covariance on the ITT population with LOCF for missing visit outcomes.
The primary analysis population for the 12 month ABPM sub-study 231, was the 'Efficacy Population'. This was defined as all randomised subjects who received add-on treatment, who had a successful 24 h ABPM assessment at baseline and post-baseline (at either Month 6 or 12, or at early withdrawal, if this occurred sooner). The primary analysis employed LOCF for withdrawn subjects or those with missing values. A secondary analysis was performed on subjects in the Efficacy population who had ABPM data available at baseline and 12 months (i.e., without LOCF)

Results

HbA1c Endpoint

A summary of mean change from baseline in HbA1c at treatment end for all studies is shown in Table 2. In 18-month glycaemia sub-study (321) SU+RSG was non-inferior to SU+MET after 18 months of dual combination treatment.

In study 004, conducted in drug naive patients, there were significant ($p<0.0001$) decreases in HbA1c in both the RSG/GLIM FDC groups compared to GLIM monotherapy (-0.63%, for FDC A and 0.66%, for FDC B) and compared to RSG monotherapy (-0.73%, for FDC A and -0.77%, for FDC B) after 28 weeks of treatment. There was no difference between the two RSG/GLIM FDC groups. This lack of dose response can be attributed to the design of the study with two different titration strategies. A demonstration of dose response relationship was not intended.

Study 325 (patients inadequately controlled by non-TZD oral diabetic therapy) and study 234 (patients inadequately controlled by glimepiride 3mg od) also showed RSG+GLIM to be superior to glimepiride monotherapy in reducing HbA1c with mean differences between groups of –0.55 for RSG 4mg to –1.10 for RSG 8mg. Although not formally statistically tested, there is evidence of a dose-related reduction in HbA1c with RSG+GLIM.

Study 4034 is the only study which recruited patients inadequately controlled by RSG monotherapy, but it has limited subject data. RSG+GLIM caused a statistically significant decrease in mean HbA1c at week 26 compared to RSG+PBO. Subjects in the RSG+PBO group had a non-statistically significant higher mean baseline HbA1c than subjects in the RSG+GLIM group, however taking this

into account, the reduction in HbA1c in the RSG+GLIM group was statistically significantly greater than the RSG+PBO group at all post-randomisation visits.

Table 2. Summary of mean change in HbA1c at treatment end: Study 004, 325, 234, 4034, 231.

Study & Treatment	Baseline	Change from baseline		Comparison with Control group(s)	
	mean±SD	mean±SD	p-value	Adjusted mean	p-value
Rosiglitazone + Glimepiride					
004					
GLIM[1]	8.96 ± 1.32	-1.72 ± 1.36	-	-	-
RSG[2]	9.13 ± 1.27	-1.75 ± 1.49	-	-	-
RSG/GLIM[3]	9.02 ± 1.30	-2.41 ± 1.39	-	Diff from GLIM, -0.63 Diff from RSG, -0.73	<0.0001 <0.0001
RSG/GLIM[4]	9.16 ± 1.36	-2.52 ± 1.40	-	Diff from GLIM, -0.66 Diff from RSG, -0.77	<0.0001 <0.0001
325					
GLIM[5] + PBO	8.01±1.01	-0.08±0.84	0.2143	-	-
RSG(4mg) + GLIM[6]	8.15±1.08	-0.68±0.95	<0.0001	-0.56	<0.0001
234					
GLIM[7] + PBO	7.9±1.3	-0.08±0.16	0.625	-	-
4mg RSG+ GLIM[7]	8.2±1.4	-0.63±0.16	0.00015	-0.55	0.0305
8mg RSG+ GLIM[7]	8.1±1.5	-1.17±0.16	<0.0001	-1.10	0.0001
4034[12]					
RSG[8] + PBO	8.4±0.17	-0.3±0.18	-	-	-
RSG[8] + GLIM[9]	7.9±0.13	-1.2±0.13	-	-0.9	0.0007
Rosiglitazone + Sulphonylurea					
231					
SU[10] + MET[11]	7.97±0.05	-0.61±0.05	-	-	-
SU[10] + RSG[8]	7.98±0.04	-0.55±0.06	-	0.06	0.459

1. GLIM 4mg od to up to max possible dose of 4mg od
2. RSG 4mg od up to a maximum of 8mg od
3. 4mg/1mg od up to maximum possible dose 4mg/4mg od
4. 4mg/1mg od up to maximum possible dose 8mg/4mg od
5. GLIM dose 4mg od up to a maximum possible dose of 8mg od
6. GLIM dose 2mg od up to a maximum 4mg od
7. GLIM dose 3mg od
8. RSG dose 4 or 8mg/day
9. GLIM dose 2mg od up to maximum of 8mg od
10. Glibenclamide 15mg/day or gliclazide 240mg/day or glimepiride 4mg/day
11. MET up to 2.55g/day
12. Data for study 4034 is presented as adjusted mean ±SE

Baseline data
Despite the different inclusion and exclusion criteria for studies 325, 234, 4034 and 231, the demographic and baseline characteristics of the subjects were broadly similar and were considered representative of a T2D population failing monotherapy. In addition, the subjects were similar to the population included in the RSG+SU integrated dataset.
The mean age across studies 325, 234, 4034 and 231 was approximately 58 years (although it was 54 years in study 325) and the proportion of male subjects ranged from 42–59%. The majority of subjects were white (range 67–100%), particularly in the studies conducted in Europe. The mean baseline BMI was approximately 30 kg/m^2 in the European studies and 34 kg/m^2 in the predominantly US studies. The mean duration of diabetes ranged from 5-8 years across the studies, 92-100% of subjects had failed previous oral anti-diabetic monotherapy and the mean baseline HbA1c and FPG ranged from 7.9–8.4% and 155-191mg/dL, respectively (which were slightly lower than the ranges in the integrated RSG+SU datasets; HbA1c ranged from 8.9-9.4% and FPG from 184-201 mg/dL).
The drug-naïve subject population of study 004 were slightly younger (mean age 54 years) compared to the other studies (except study 325, where the mean age was also 54 years) with a mean duration of diabetes of 2.9 years. Other baseline characteristics were similar to the other studies: 77% of subjects were white, 59% were male, the mean baseline BMI was 32 kg/m^2 and mean baseline HbA1c and FPG were 9.1% and 11.7mmol/L (211mg/dL), respectively.

Analysis performed across trials (pooled analyses and meta-analysis)
Due to the differences in study populations and study treatments, it was not appropriate to integrate the efficacy data from any of these studies.

Clinical safety

- Introduction

The safety profile of the individual components of the FDC: RSG and GLIM has been well documented in their respective marketing applications. To support the use of GLIM, a thorough review of scientific literature has provided a comprehensive assessment of GLIM safety and the key points from these data are discussed below. A discussion of the key data from the previously submitted RSG data is provided to support this. The new clinical data supporting the RSG/GLIM FDC is presented. Safety data relevant to the RSG/GLIM FDC come from existing the RSG+SU data and RSG+GLIM data (both combination and concomitant dosing). For the study 231 sub-studies, safety evaluations were collected as *per protocol* but safety data have not been reported in order to maintain the integrity of the primary study outcome (cardiovascular death and/or hospitalisation). Body weight and selected laboratory tests have been analysed for exploratory purposes only, i.e., to aid interpretation of ABPM data.

- Patient exposure

The review of the GLIM scientific literature done by Schneider in 1996 includes a review of clinical trials conducted in the US, Europe and Japan with a minimum duration of 2 weeks. This review concentrated mainly on the 21 US and European trials of which there were 4 placebo controlled, 12 active controlled, and 5 non-comparative trials. Over 5500 subjects were included, with more than 3500 treated with GLIM; 1472 of these were treated for at least 1 year. This safety overview is the largest identified in the literature and it concluded that the incidence and profile of AEs during GLIM treatment were similar to that of other SUs. A further key review of safety was that of Rosskamp who described the safety of GLIM from PBO controlled studies, and showed a similar safety profile to that of Schneider. Evidence from the literature suggests that the incidence of hypoglycaemia with GLIM is at least not worse, and possibly slightly less, than with other SUs. The incidence of deaths, non-fatal SAE and AEs leading to withdrawal were similar to GLIB and GLIP. In addition, in common with other SUs, the frequency of clinically noteworthy laboratory abnormalities was very low for all treatment groups.

The key data from previously submitted RSG studies are those from the integrated dataset of studies, investigating 4mg and 8mg RSG given concomitantly with SUs, which was submitted as part of the

recent Type II Variation to AVANDIA Tablets (EMEA/H/C/268/II/23, approved January 2005). This dataset was made up of 9 double-blind studies and 3 open-label studies and included 3633 subjects. The double-blind dataset included 885 subjects treated with 8mg RSG+SU, 622 subjects with 4mg RSG+SU and 1213 subjects were treated with PBO+SU. In the double-blind and open-label dataset, 1384 subjects were treated with 8mg RSG+SU and 1036 subjects were treated with 4mg RSG+SU.

The overall safety profile of 8mg RSG+SU was consistent with the product label and that described with 4mg RSG+SU. In addition, the overall incidence of AEs was similar between the 4mg and 8mg RSG+SU groups (approximately 71% of subjects) and higher than the SU group (61%). The two most commonly reported AEs were dose-related hypoglycaemia and weight increase, which were both more frequently reported in the RSG+SU groups than in the SU group. The overall incidence of serious adverse events (SAEs) was low and was broadly comparable to the SU group. Deaths with RSG+SU were rare and comparable across treatment groups. The specific RSG+GLIM safety data presented in this application, come from the clinical pharmacology and biopharmaceutical studies and four double-blind, 6 month studies. In total 779 T2D subjects were treated in the double-blind clinical studies with the combination of RSG+GLIM; 442 received RSG/GLIM FDC tablets and 337 received concomitant RSG+GLIM. Due to the differences in subject populations and study treatments, it was not appropriate to integrate the safety data from these studies. Bearing in mind that the double-blind treatment period ranged from 24–28 weeks across the four studies, the mean duration of exposure for the RSG+GLIM (combination and concomitant) treated subjects ranged from 148–185 days and 141–182 days for the monotherapy control groups.

- Adverse events

The clinical pharmacology and biopharmaceutical studies showed no differences in safety profile between RSG/GLIM FDC and concomitant RSG+GLIM administration. Table S 1 shows the on-treatment AEs reported in >4% of subjects in the double-blind studies, excluding hypoglycaemia which wasn't reported as an AE in all studies. Hypoglycaemia and other AEs of interest are discussed in section 0. The type of AEs reported in subjects treated with RSG+GLIM (both RSG/GLIM FDC and concomitant administration) in the double-blind clinical studies in this submission is consistent with that described previously with 4mg and 8mg RSG+SU. Within studies (except 4034), the proportion of subjects with on-treatment AEs was similar across the treatment groups. Study 4034 did not report an overall frequency of AEs for each group, however more AEs were reported in the RSG+GLIM group than in the RSG+PBO group. The overall reported AE frequency was higher in both treatment groups for study 325 compared to the other studies which may reflect the fact that hypoglycaemia was included in the analysis of AEs in this study. However, the overall incidence of AEs in all four double-blind studies with RSG+GLIM, both RSG/GLIM FDC and concomitant RSG+ GLIM administration, was lower than that reported for the integrated double-blind RSG+SU dataset (4mg RSG+SU: 70.9%, 8mg RSG+SU: 71.5%, SU: 61.3%).

The incidence of treatment-related AEs in study 325 was again higher than in the other studies, 36% and 21% of AEs in the RSG+GLIM and GLIM+PBO groups respectively. Hypoglycaemia was the most frequent treatment-related AE in both groups (16% and 9% for RSG+GLIM and GLIM+PBO, respectively). Only two events were considered treatment-related in study 234, flatulence in the GLIM+PBO group and hypoglycaemia in the 4mg RSG+GLIM group and in study 4034, two reports of weight gain were considered treatment-related in the RSG+GLIM group; other treatment-related AEs occurred with a frequency of one. In study 004, the overall incidence of treatment related AEs was similar between all the treatment groups and ranged from 8-11%. Weight increase was the most commonly reported treatment related AE and occurred with a frequency of 0-3% across the treatment groups. In the studies that reported severity of AEs, the majority were mild or moderate in severity and there were no differences in the frequency of severe AEs across the treatment groups. SUs are reported to cause some gastrointestinal side effects, however the incidence of GI effects in the current development programme was low and ranged from 7–13% across the treatment groups. There was a very low incidence of hepatobiliary-associated AEs, 1 SAE (cholelithiasis, study 234) and no AE withdrawals recorded which was similar for the RSG+GLIM (both RSG/GLIM FDC and concomitant RSG+GLIM administration) and monotherapy control groups.

Table 3. Incidence of on-treatment AEs reported by more than 4% of subjects in any treatment group (safety population)

Study 004	**GLIM N=222 n(%)**	**RSG N=230 n(%)**	**FDC A[1] N=224 n(%)**	**FDC B[1] N=218 n(%)**
Any AE	103 (46.4)	116 (50.4)	110 (49.1)	114 (52.3)
Headache	5 (2.3)	14 (6.1)	7 (3.1)	13 (6.0)
Nasopharyngitis	8 (3.6)	12 (5.2)	9 (4.0)	10 (4.6)
Hypertension	8 (3.6)	12 (5.2)	7 (3.1)	5 (2.3)
Upper respiratory tract infection	4 (1.8)	9 (3.9)	9 (4.0)	7 (3.2)
Arthralgia	1 (0.5)	6 (2.6)	7 (3.1)	10 (4.6)
Weight increased	0	1 (0.4)	9 (4.0)	9 (4.1)

Study 325	**GLIM+PBO N=195 n(%)**	**RSG+GLIM N=196 n(%)**
Any AE	117 (60.0)	132 (67.3)
Nasopharyngitis	19 (9.7)	10 (5.1)
Upper respiratory tract infection	7 (3.6)	15 (7.7)
Peripheral oedema	11 (5.6)	8 (4.1)
Tremor	6 (3.1)	10 (5.1)
Back pain	5 (2.6)	8 (4.1)
Influenza	10 (5.1)	3 (1.5)

Study 234	**3mg GLIM+PBO N=58 n(%)**	**4mg RSG+3mg GLIM N=57 n(%)**	**8mg RSG+3mg GLIM N=59 n(%)**
Any AE	27 (46.6)	24 (42.1)	27 (45.8)
Bronchitis	9 (15.5)	7 (12.3)	5 (8.5)
Arthritis	3 (5.2)	3 (5.3)	3 (5.1)
Back pain	1 (1.7)	5 (8.8)	3 (5.1)
Pharyngitis	4 (6.9)	3 (5.3)	1 (1.7)
Gastritis	0	3 (5.3)	4 (6.8)
Other events	0	1 (1.8)	6 (10.2)
Fever	1 (1.7)	4 (7.0)	0
Urinary tract infection	3 (5.2)	0	2 (3.4)
Carpal tunnel syndrome	0	0	3 (5.1)
Pain	3 (5.2)	0	0

Study 4034	**RSG+PBO N=15 n(%)**	**RSG+GLIM N=25 n(%)**
Upper respiratory tract infection	3 (20.0)	2 (8.0)
Weight gain	0	4 (16.0)
Headache	0	4 (16.0)
Common Cold	0	3 (12.0)
Ankle oedema	0	2 (8.0)
Foot pain	0	2 (8.0)
Productive cough	0	2 (8.0)

1. Fixed Dose Combination of RSG/GLIM. FDC A starting dose 4mg/1mg up to a possible maximum of 4mg/4mg. FDC B starting dose 4mg/1mg up to a possible maximum of 8mg/4mg.

Special attention was paid to the well-known side effects of RSG of plasma volume expansion and fluid retention. Fluid effects can result in oedema, congestive heart failure, anaemia and weight increase.

Oedema
In the RSG+SU dataset the incidence of oedema was greater in the 8mg RSG+SU group (12.4%) and the 4mg RSG+SU group (7.4%) than in the SU alone group (1.6%). In study 004 the incidence of oedema AEs was low and similar between treatment groups (range 2.3-3.2%). All the oedema AEs were either mild or moderate in intensity. One subject each in the RSG, FDC A and FDC B treatment groups withdrew due to an oedema related AE. There were no oedema-related SAEs during the study. In study 325 incidence of oedema AEs was 4.1% for the RSG+GLIM group and 5.6% for the GLIM+PBO group. All of the AEs associated with oedema in both treatment groups were either mild or moderate. One subject (in the RSG+GLIM group) withdrew due to a peripheral oedema. There were no oedema related SAEs. In study 234, two subjects (3.4%) in the GLIM+PBO group, one subject (1.8%) in the GLIM+RSG (4 mg) and no subjects in the GLIM+RSG (8 mg) group had an oedema AE. For all three subjects the AEs were either mild or moderate and were considered by the investigator to be either unlikely or not related to study medication. In study 4034, 2 subjects in each group reported treatment-related oedema. Intensity was not reported.

Congestive Heart Failure
In the current studies there were 3 reports of CHF. One (0.5%) was in a GLIM monotherapy subject (study 325), it was moderate in intensity, considered serious and led to early withdrawal of the subject. After corrective treatment the event resolved. One (0.4%), in a RSG monotherapy subject (study 004), was severe in intensity, considered serious and led to early withdrawal of the subject. The third report (0.5%) of CHF was in a subject in FDC B group of study 004 but was not serious and did not lead to early withdrawal from the study. These results are consistent with the incidence of CHF seen in the integrated RSG+SU dataset - 6 subjects (0.7%) in the 8mg RSG+SU group, 2 subjects (0.3%) in the 4mg RSG+SU group and 2 subjects (0.2%) in the SU alone group.

Anaemia
The incidence of anaemia AEs was low and similar for RSG+GLIM (both RSG/GLIM FDC and concomitant RSG+GLIM administration) and the monotherapy groups (range 0-2%). None were considered serious, all were mild/moderate in intensity (intensity was not reported in study 234 or study 4034) and only 1 subject withdrew due to anaemia (from the GLIM alone group in study 325). The incidence of anaemia in the current studies was comparable to that seen with the integrated RSG+SU dataset in the previous submission (8mg RSG+SU (n=27, 3.1%), 4mg RSG+SU (n=8, 1.3%), and SU (n=8, 0.7%) groups).

Body weight
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 also to fat deposition. In all four double-blind clinical studies and in the open label ABPM sub-study the subjects mean body weight increased between baseline and the study endpoint. Weight gain seen in the RSG+GLIM treated subjects (both RSG/GLIM FDC and RSG+GLIM concomitant administration) in this development programme was larger than in the monotherapy groups but was comparable to that seen previously with RSG plus any SU.

Hypoglycaemia
Although the incidence of hypoglycaemia in the RSG+GLIM studies was higher than previously reported for RSG in combination with any SU, the increased reporting is suspected to be primarily as a result of the design of the studies and the way hypoglycaemia episodes were monitored in the studies i.e. daily self-monitoring of blood glucose and recording in diary cards rather than a real increase in incidence of hypoglycaemia with RSG+GLIM vs RSG plus any SU. This observation is supported by the lower incidence in study 234 which did not use self-monitoring of blood glucose/diary cards. The risk of developing hypoglycaemia with RSG in combination with GLIM is reflected in the Special Warnings and Special Precautions for Use section of the SPC and dosing advice is given accordingly.

- Serious adverse event/deaths/other significant events

Few SAEs were reported during the double-blind treatment period, with even fewer considered to be treatment-related, and there was little difference in the incidence across the treatment groups. The overall incidences of SAEs in these studies are comparable to those reported in the RSG+SU

integrated double-blind dataset (4.6% for 8mg RSG+SU, 3.4% for 4mg RSG+SU and 3.9% for SU alone). In the previous RSG+SU submission, myocardial infarction was the most frequently reported SAE; the actual numbers were low (5 (0.6%) in the 8mg RSG+SU group, 1 (0.2%) in the 4mg RSG+SU group, and 2 (0.2%) in the placebo + SU group).

Table 4 Summary of Overall Incidence of Nonfatal On therapy SAEs Considered to be Treatment-related by the Investigator

Study 004	**GLIM N=222 n(%)**	**RSG N=230 n(%)**	**FDC A N=224 n(%)**	**FDC B N=218 n(%)**
Any SAE	**4 (1.8)**	**12 (5.2)**	**8 (3.6)**	**8 (3.7)**
Facial palsy	1 (0.5) [1]	0	0	1 (0.5)
Study 325	**GLIM+PBO N=195 n(%)**		**RSG+GLIM N=196 n(%)**	
Any SAE	**8 (4.1)**		**7 (3.6)**	
Bacterial infection	1 (0.5)		0	
Hypoglycaemia	1 (0.5)		0	
Study 234	**3mg GLIM+PBO N=58 n(%)**	**4mg RSG+3mg GLIM N=57 n(%)**	**8mg RSG+3mg GLIM N=59 n(%)**	
Any SAE	**2 (3.4)**	**3 (5.3)**	**0**	
Cholelithiasis	0	1 (1.8)	0	
Study 4034	**RSG+PBO N=15**		**RSG+GLIM N=25**	
Any SAE	**0**		**0**	

1. Not considered to be treatment-related

In the individual studies included in this submission, the only SAEs reported by more than one subject were unstable angina (2 subjects in the RSG+GLIM group of study 325), facial palsy (1 subject in the GLIM group and 1 subject in FDC B group of study 004) and non-cardiac chest pain (1 subject in the GLIM group and 1 subject in FDC B group of study 004). Further, in the individual studies, there were small numbers of reports of cardiac ischaemia, but no reports of myocardial infarction. All other SAEs occurred in only 1 subject. It is important to note that there were no SAEs reported for 8mg RSG + 3mg GLIM in study 234 (the only study that directly compared 4mg and 8mg RSG) suggesting that the higher dose of RSG does not lead to a worse safety profile, a fact supported by the overall frequency of AEs across the 3 treatment groups in study 234. Similarly in study 004, the overall incidence of AE and SAEs for the two RSG/GLIM FDC groups were similar. There were two deaths reported, both from study 234. One non-randomised subject died from rectal carcinoma during the run-in phase of the study. The other subject died from oesophageal carcinoma. He received approximately 4 months of double-blind treatment in the 4mg RSG+GLIM group. The investigator considered the SAE to be unlikely to be related to the study medication.

Laboratory findings

Slight decreases in haemoglobin and haematocrit were seen. These are known side effects of RSG, due to plasma volume extension. The percentage of subjects with ALT values of potential clinical concern while on RSG+GLIM treatment was very low in any of the studies and comparable to those on monotherapy treatment. There were no other notable effects on laboratory parameters.

- Safety in special populations

Renal impairment is a clinically important consideration in the treatment of T2D with SU's since reduced drug (and insulin) elimination may lead to an increased risk of hypoglycaemia. There is no data specifically evaluating the use of the FDC in renally impaired patients. However, a recent post-hoc analysis of studies using RSG and SU combination provides some useful safety data in renally impaired patients. The analysis of data from 3 double blind studies compared the tolerability and efficacy of RSG+SU in 301 mild to moderate renally impaired patients (Cl_{Cr} of 30 to 80 mL/min) with T2D and 423 patients without renal impairments (Cl_{Cr} >80mL/min) [Agrawal, 2003]. Despite the patients with renal impairment being older and having longer disease duration than patients with normal renal function, examination of the AE profile in the population studied did not reveal obvious differences between the subgroups in terms of pattern or magnitude of AEs. Reassuringly, symptoms suggestive of hypoglycaemia were reported in 4.8% (7 patients) with renal impairment and 5.4% (14 patients) with normal renal function. With respect to GLIM, data is limited to two small studies. The first, a single-dose study in 15 patients with renal impairment, demonstrated minor changes in pharmacokinetic profile. The second, a 3-month dose range study, demonstrated similar pharmacokinetic results. In the 3-month study, patients with a Cl_{Cr} >30 mL/min maintained glycaemic control with a range of doses between 1-8 mg daily (increased gradually). A 1 mg dose was sufficient for all patients whose Cl_{Cr} ≤22 mL/min [Rosenkrantz, 1996b; Profozic, 1999a], which is consistent with disease related impairment of insulin elimination. These findings must be interpreted with caution because of the small number of patient involved. However, it is reassuring that analysis of combined data from three placebo controlled clinical trials suggests no difference in efficacy or adverse effects with GLIM between patients younger or older then 65 [Campbell, 1998]. It is also noted that the mutually recognised European label for GLIM makes no specific recommendations within the dosage section for renally impaired patients (other than contra-indication of those who are severely impaired) [Amaryl UK SPC, 2005]. To maintain consistency with the currently approved GLIM SPC [Amaryl UK SPC, 2005], GSK propose that the FDC should be contraindicated in patients with severe renal impairment (Cl_{Cr} <30mL/min). The GLIM SPC provides no dosing advice for the mild to moderate patients (Cl_{Cr} 30 – 80mL/min), however GSK consider that some advice is useful to aid the clinical management of the patient as they transition to the FDC. The advice highlights the need to initiate and dose-escalate-glimepiride component of the FDC with care in RSG monotherapy failures. In patients moving from an SU other than GLIM, prescribers are advised to consider risk factors for hypoglycaemia prior to initiating use of the FDC, and to monitor for hypoglycaemia once FDC therapy is initiated.

There are no data available for the use of RSG/GLIM FDC or concomitant use of RSG+GLIM in children. Therefore, the use of RSG/GLIM FDC is not recommended in children. In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of RSG or GLIM to any significant extent. However, it is recommended in the SPC that the initiation and maintenance of therapy with RSG/GLIM FDC in elderly subjects should be under close medical supervision due to an increased susceptibility to hypoglycaemia.

A number of other precautions and contraindications are listed in Sections 4.3 and 4.4 of the accepted SPC. These reflect what is known about the individual components, whether used alone or in combination.

- Safety related to drug-drug interactions and other interactions

There have been no formal interaction studies with RSG/GLIM FDC, however the concomitant use of RSG+GLIM in studies and in widespread clinical use has not resulted in any unexpected interactions. Drugs that should be used with caution with the RSG/GLIM FDC are listed in SPC based on either

pharmacokinetic interaction studies with the individual components (RSG and GLIM) or on theoretical class effects (GLIM), and reflect the currently approved SPCs for RSG and GLIM.

- Discontinuation due to adverse events

The overall proportion of subjects withdrawn due to an AE during the clinical programme was low. Less than 4% of subjects were withdrawn from any treatment group with the exception of the RSG monotherapy group in study 004 where 6% of subjects were withdrawn. The only AE resulting in discontinuation of more than one subject was hyperglycaemia, which resulted in the withdrawal of 4 and 2 subjects in the RSG monotherapy and FDC B group of study 004, respectively. The frequency of withdrawal from the current studies is slightly lower than that reported for the RSG+SU integrated dataset of the RSG 8mg+SU submission where 7.8%, 3.7% and 6.7% of subjects withdrew due to an AE from the 8mg RSG+SU, 4mg RSG+SU and SU alone groups, respectively. No new or unexpected AEs were reported. There was no difference in the safety profile between concomitant and FDC use of RSG and GLIM. The profile reported is consistent with that described previously with RSG plus any SU. Few SAEs were reported with a similar incidence across treatment groups. The overall proportion of patients withdrawn due to an AE during the clinical studies was low as were the number of deaths.

- Post marketing experience

No access to GLIM post-marketing safety database was available for this MAA however, limited data has been provided for the reporting period 1995 to Q2 2003. The estimated subject exposure to GLIM during this time period is 17,109,573 subject years, and the data provided supports a predictable well characterised safety profile with no additional concerns not signalled from the clinical trial database. With more than 6 million subject years of exposure from launch to September 2004, the post-marketing safety experience with RSG supports the predictable well-characterised safety profile established from an extensive clinical trial programme. Further, this review of the post-marketing events associated with RSG+SU demonstrates that the safety profile of RSG+SU is consistent with the previously described safety profile of RSG monotherapy. Finally, although the data are limited, the safety profile of concomitant use of RSG+GLIM appears to be similar to that of RSG and RSG+SU.

- Discussion on clinical safety

The safety profile of the individual components of the FDC, RSG and GLIM has been documented in their respective marketing applications. To support the use of GLIM, a thorough review of scientific literature has provided a comprehensive assessment of GLIM safety. A discussion of the key safety data from the previously submitted RSG data is provided to support this application. Safety data relevant to the RSG/GLIM FDC come from existing the RSG+SU data and RSG+GLIM data (both combination and concomitant dosing). For the study 231 sub-studies, safety evaluations were collected as per protocol but safety data have not been reported in order to maintain the integrity of the primary study outcome (cardiovascular death and/or hospitalisation). Body weight and selected laboratory tests have been analysed for exploratory purposes only, i.e., to aid interpretation of ABPM data. No new or unexpected AEs were reported. There was no difference in the safety profile between concomitant and FDC use of RSG and GLIM. The profile reported is consistent with that described previously with RSG plus any SU. Few SAEs were reported with a similar incidence across treatment groups. The overall proportion of patients withdrawn due to an AE during the clinical studies was low as were the number of deaths. In the RSG+SU dataset the incidence of oedema was greater in the 8mg RSG+SU group (12.4%) and the 4mg RSG+GLIM group (7.4%)than in the SU alone group. In the four RSG+GLIM trials, incidence of oedema was similar between treatment groups. Incidences of congestive heart failure, anaemia and body weight gain were also comparable to that seen previously with RSG plus any SU. The incidence of hypoglycaemia was higher than previously reported for RSG in combination with any SU. This might be due to the design of the studies and the way hypoglycaemia episodes were monitored. The risk of developing hypoglycaemia with RSG in combination with GLIM is reflected in the SPC. No new or unexpected laboratory findings were noted.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks that Require Further Action		
PPAR γ fluid retention (oedema/CHF)	Routine pharmacovigilance <u>Ongoing Studies:</u> A long term, open label, randomised study in patients with T2DM, comparing the combination of rosiglitazone and either metformin or sulphonylurea with metformin plus sulphonylurea on cardiovascular endpoints and glycaemia (RECORD - Study 231) A randomized, double-blind study to compare the durability of glucose lowering and preservation of pancreatic beta-cell function of rosiglitazone monotherapy compared to metformin or glyburide/glibenclamide in patients with drug-naive, recently diagnosed Type 2 Diabete Mellitus (≤2 years) (ADOPT – Study 048). A 16-week, randomised, double-blind, placebo-controlled, single-centre study to investigate fluid retention in insulin-treated subjects with T2DM and varying degrees of autonomic neuropathy when administered rosiglitazone 4 mg bd (Study 376)	Section 4.3 of SPC. Contraindication for history of cardiac failure (NYHA class I to IV) Warning in Section 4.4 of SPC for fluid retention and cardiac failure Oedema and heart failure listed as ADR in Section 4.8 of the SPC
Macular Oedema	Routine pharmacovigilance Examine incidence of macular oedema over longer RSG exposure in ADOPT and RECORD Implementation of targeted follow up questionnaires Continue to closely monitor spontaneous reports of macular oedema	Type II variation to add macular oedema to SPC (information for prescribers and patients) It will be added to SPC as soon as Type II for Avandia finalised.
Hypoglycaemia, especially in the elderly	Routine pharmacovigilance	Advice in section 4.2 of SPC to consider and monitor for

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		hypoglycaemia when switching to Avaglim, particularly in the elderly Warning section in SPC section 4.4 regarding hypoglycaemia Hypoglycaemia listed as a ADR in Section 4.8 of the SPC
Potential Risks that Require Further Evaluation		
Hepatic Events	Routine pharmacovigilance Close monitoring hepatic adverse in clinical trials and postmarketing experience Ongoing activities of the Avandia Hepatology Safety Board Annual Reports of hepatic adverse events received in association with RSG –provided as part of annual Avandia PSUR	Advice in section 4.2 of SPC regarding patients with history of hepatic impairment Contraindication for patients with hepatic impairment (Section 4.3 SPC) Warning in Section 4.4 of SPC regarding monitoring of liver function. Hepatic function abnormal listed as ADR in Section 4.8 of SPC.
Cardiovascular Outcomes	Routine pharmacovigilance Statistical modeling of clinical trial data to investigate cardiovscular events – ongoing updates have been provided to the CHMP (most recent March 2006) <u>Ongoing Studies:</u> A long term, open label, randomised study in patients with Type 2 Diabetes Mellitus, comparing the combination of rosiglitazone and either metformin or sulphonylurea with metformin plus sulphonylurea on cardiovascular endpoints and glycaemia (RECORD - Study 231) A randomized, duble-blind study to compare the durability of glucose lowering and preservation of pancreatic beta-cell function of rosiglitazone monotherapy compared to metformin or	Contraindication for history of cardiac failure (NYHA class I to IV) Warning in Section 4.4 of SPC for fluid retention and cardiac failure

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	glyburide/glibenclamide in patients with drug-naive, recently dagnosed Type 2 Diabetes Mellitus (≤2 years) (ADOPT – Study 048) <u>Worldwide Epidemiology:</u> "Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents". This study has a retrospective cohort design with propensity score matching using administrative claims data to examine endpoints of myocardial infarction and coronary revascularization.	
Carcinogenicity	Routine pharmacovigilance Follow-up of patients enrolled onto RECORD study extended to 10 years to monitor for neoplasma	
Missing Information		
Lack of data regarding Avaglim use in children < 18 years of age and in pregnant women	Routine pharmacovigilance	Section 4.3 of SPC. Avaglim is not recommended in children < 18 years and in pregnant women, which is reflected in the SPC.

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

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

Non-clinical pharmacology and toxicology

The primary and secondary pharmacodynamics and the safety pharmacology of both RSG and GLIM have been investigated in a series of non-clinical studies, *in vitro* and *in vivo*. In these investigations, RSG and GLIM were administered individually. No non-clinical pharmacology studies have been performed with these drugs administered as the fixed combination. The individual efficacies of RSG and GLIM in the treatment of T2D patients have been clearly demonstrated. There were no new pharmacokinetic studies with the FDC or with RSG. For GLIM pharmacokinetic data were extracted from published literature. Details of the methods used in all pharmacokinetic studies performed with RSG and its major metabolites were submitted and reviewed in the previous European MAA's for RSG. No information was provided regarding possible pharmacokinetic interactions between RSG and GLIM. However, different enzymes metabolize RSG and GLIM, the combination has been investigated clinically and there was no evidence for pharmacokinetic interactions. No non-clinical toxicity studies have been performed using RSG/GLIM FDC. Therefore, the general toxicological profile of RSG and GLIM has been investigated for both drugs when administered individually. For GLIM data were extracted from published literature and the expert report from the original MAA. Combination studies of RSG and GLIM were considered to be not necessary because of extended clinical data with co-administration of both components of the combination. Acute toxicity was low for both RSG and GLIM. Repeated dose toxicity studies with RSG revealed increased food and water consumption, body weight gain, increased fat deposition with displacement of haemopoetic tissue in bone marrow, an increased plasma volume which caused increased heart weight and left ventricular hypertrophy at exposure levels comparable to the human therapeutic exposure, and at higher dosages, hydrothorax. These effects of RSG are well known and have already been discussed. After repeated administration of GLIM, the only noticeable effects were of a pharmacological nature and consisted of degranulation in the β cells of the islets of Langerhans in the pancreas and changes in the serum glucose concentrations. Cataracts as were found in some high dose dogs, were shown to be not drug dependent in bovine lenses and in rats and were observed only at very high exposures. Both RSG and GLIM do not pose a genotoxic risk to humans. An increased number of lipomas were observed in carcinogenicity study of RSG and islet cell adenomas, bronchio-alveolar adenomas and adenocarcinomas were observed in carcinogenicity studies of GLIM but with a large safety margin. It is unlikely that GLIM will adversely influence the carcinogenic potential of the combination, because of the far lower affinity of GLIM for the PPARγ receptor. In fertility studies, RSG caused decreased plasma progesterone and estradiol levels, resulting in altered oestrous cyclicity. In embryotoxicity studies, RSG caused placental abnormalities, increased embryo-foetal death, and intrauterine growth retardation and decreased skeletal ossification. After administration of RSG pre- and postnatally, an increased number of stillborn pups, a lower pup survival rate and a delayed physical development were observed. No effect from GLIM on fertility was observed in preclinical studies. In embryotoxicity studies, GLIM caused several defects in small numbers of foetuses. In pre- and postnatal studies, GLIM caused an increase in foetal death rate and skeletal defects, the latter also during the lactation period. An environmental risk assessment was provided. The company committed to provide additional information as a follow-up measures.

Efficacy

The efficacy of RSG and GLIM were documented in their respective marketing applications, and both drugs are approved for use in the treatment of T2D, although RSG has still a limited indication. The clinical data package of this submission consisted of (1) a review of the scientific literature on GLIM, (2) data from previously submitted for RSG studies and (3) main studies (specific data on RSG+GLIM, both in combination and concomitant administration). The results of the studies provided indicate that GLIM, RSG and RSG+GLIM are effective in patients with T2D. RSG is only indicated as add on therapy for patients inadequately controlled on monotherapy and as monotherapy to obese patients for whom MET is inappropriate. The reason to limit RSG monotherapy to obese patients for whom MET is inappropriate were based on safety concerns. The reason for this still holds. The proposed indication for the RSG/GLIM FDC is treatment of T2D patients who are unable to achieve sufficient control on optimal dosage of sulphonylurea monotherapy, and for whom metformin is inappropriate because contraindications or intolerance. The dosage regimen proposed for the RSG/GLIM FDC is consistent with that currently approved for the two drugs when administered

concomitantly. The maximum recommended daily dose of the RSG/GLIM FDC is 8 mg/4 mg (RSG/GLIM). The accepted strengths for this product are 4mg/4mg and 8mg/4mg RSG/GLIM. As a follow up measure the Applicant committed to include in section 4.8 of the SPC "macular oedema" to conform the ongoing variation for AVANDIA and to submit the up-dated risk management plan.

Safety

The safety profile of the individual components of the FDC, RSG and GLIM has been documented in their respective marketing applications. To support the use of GLIM, a thorough review of scientific literature has provided a comprehensive assessment of GLIM safety. A discussion of the key safety data from the previously submitted RSG data is provided to support this application. Safety data relevant to the RSG/GLIM FDC come from existing the RSG+SU data and RSG+GLIM data (both combination and concomitant dosing). For the study 231 sub-studies, safety evaluations were collected as per protocol but safety data have not been reported in order to maintain the integrity of the primary study outcome (cardiovascular death and/or hospitalisation). Body weight and selected laboratory tests have been analysed for exploratory purposes only, i.e., to aid interpretation of ABPM data. No new or unexpected AEs were reported. There was no difference in the safety profile between concomitant and FDC use of RSG and GLIM. The profile reported is consistent with that described previously with RSG plus any SU. Few SAEs were reported with a similar incidence across treatment groups. The overall proportion of patients withdrawn due to an AE during the clinical studies was low as were the number of deaths. In the RSG+SU dataset the incidence of oedema was greater in the 8mg RSG+SU group (12.4%) and the 4mg RSG+GLIM group (7.4%)than in the SU alone group. In the four RSG+GLIM trials, incidence of oedema was similar between treatment groups. Incidences of congestive heart failure, anaemia and body weight gain were also comparable to that seen previously with RSG plus any SU. The incidence of hypoglycaemia was higher than previously reported for RSG in combination with any SU. This might be due to the design of the studies and the way hypoglycaemia episodes were monitored. The risk of developing hypoglycaemia with RSG in combination with GLIM is reflected in the SPC. No new or unexpected laboratory findings were noted.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

During the approval process for Avandia (rosiglitazone), user consultation was undertaken for the patient information leaflet. The Avaglim patient information leaflet has been developed using the Avandia leaflet as key document. Therefore, the CHMP considered that the submission of a user consultation was not necessary.

Risk-benefit assessment

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

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- no additional risk minimisation activities were required beyond those included in the product information.

The efficacy of adding RSG to SU, and GLIM in particular, is sufficiently demonstrated. The optimal dosage of GLIM is 4mg daily, and this dose is considered equally effective as the optimal dose of

other SU's. The CHMP accepts that patients treated with other SU's (except chlorpropamide) could be switched to Avaglim.
Avaglim 4mg/4mg and 8mg/4mg can be used in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control on optimal dose of sulphonylurea monotherapy, and for whom metformin is inappropriate because of contraindication or intolerance.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Avaglim in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient control on optimal dosage of sulphonylurea monotherapy, and for whom metformin is inappropriate because contraindications or intolerance was favourable and therefore recommended the granting of the marketing authorisation.