European Medicines Agency

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WITHDRAWAL ASSESSMENT REPORT FOR

ARXXANT
(Ruboxistaurin (as mesilate monohydrate)

EMEA/H/C/753

Day 120 Assessment Report as adopted by the CHMP
with all information of a commercially confidential nature deleted.

To be read in conjunction with the Question and Answer document on the withdrawal of the application, as the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

COM	Center of macula
CPK	Creatine phosphokinase
CSME	Clinically significant macular edema
DME	Diabetic macular edema
DR	Diabetic retinopathy
ED	Erectile dysfunction
ESRD	End-stage renal disease
ETDRS	Early Treatment of Diabetic Retinopathy Study
Focal PC	Focal photocoagulation
HbA_{1c}	Glycated fraction of hemoglobin
MVL	Moderate visual loss; 3 line loss, doubling of the visual angle
mSMVL	Modified sustained moderate visual loss
NPDR	Nonproliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
PC	Photocoagulation
PRP	Panretinal photocoagulation
PKC	Protein kinase C
RBX	Ruboxistaurin mesylate (ruboxistaurin)
SMVL	Sustained moderate visual loss
VA	Visual acuity
VEGF	Vascular endothelial growth factor

I. CHMP RECOMMENDATION PRIOR TO WITHDRAWAL

Based on the review of the data on quality, safety and efficacy, the CHMP considered that the application for Arxxant 32mg film-coated tablet in the treatment of diabetic retinopathy in adult patients with moderate to severe non-proliferative diabetic retinopathy, was not approvable since "major objections" had been identified, which precluded a recommendation for marketing authorisation at the time.

This Withdrawal Public Assessment Report is based on the Day 120 CHMP assessment report, which is the latest adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. It reflects the CHMP assessment of the initial submission.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Major objections

Quality
Drug substance
3.2.S.2.

1. Since acetone is used in the last crystallization step the impurity mesityl oxide (4-methyl-3-penten-2-one) can be formed. It should be demonstrated that mesityl oxide is absent in the final drug substance (or present within a toxicologically acceptable level).

Efficacy

2 (a). There is insufficient evidence of efficacy.

- The pivotal evidence of efficacy comes from study MBCM alone. There were concerns related to a) robustness, b) methodology and c) clinical relevance as outlined below:

  The single pivotal study provided only marginal evidence of efficacy in the ITT population. This was not confirmed in the population of completers or per protocol. Thus, the study does not provide robust evidence of efficacy and does not comply with the CHMP "Points to consider document" on application with 1. Meta-analysis; 2. One Pivotal study (CPMP/EWP/2330/99). Further confirmatory evidence of efficacy is required.
  The mean visual acuity score showed a difference of 1.83 letters in RBX 32mg group after three years of treatment. The clinical relevance of this is questioned and needs to be justified by the applicant.

2(b) Insufficient evidence for drug efficacy

- The primary efficacy analysis reached a marginal statistical significance in the ITT population. No significant difference compared to placebo in the "completers" and "per protocol" cohorts was determined. The statistical significance in the ITT population is based on one single events, that if it had been in the RBX group, the test would no longer have been significant.
- Non homogenous drug response across important patients sub-groups with overall study results driven only by the effect in one specific patient stratum of no clinical relevance, in women and non-caucasian population.
- Insufficient number of type I diabetic patients in the pivotal trial and lack of clear drug effect in this population.
- Dose selection for the pivotal trial not adequately justified

As a consequence, this application does not follow the recommendation of CHMP Scientific Advice (EMEA/CPMP/SAWG/5651/03) does not comply with the CHMP/EWP/2330/99 "Points to consider on Application with One Pivotal Study"

Safety

3. There was a concern regarding QT prolongation with ruboxistaurin. The applicant should provide further analysis of outliers in the scatter plot in study B7-LC-MBDT as many outliers show QTc prolongation beyond 10ms. These are of particular concern since these subjects are at high risk for ventricular arrhythmias. A specific analysis of all the outliers in all studies with their QT measurements, blood concentrations, weight, gender, adverse event,if any, etc should be provided. In addition all QT evaluations should be carried out with 95% calculations
The development of diabetic retinopathy is a slow process and takes many years while adverse implications of drug prolonging QT is immediate (VT and sudden death). The applicant should analyse all occurrences of dizziness (serious and non-serious) and other adverse events suggestive of transient arrhythmias including their relation to QT interval duration and possible prolongation. Detail analysis of ECG data from phase 3 trials should also be provided.

4. There is a concern regarding CPK increase with RBX and in particular possible interactions with statins given the high usage of these drugs and their possible effects on muscle related adverse events. The applicant should analyse patients with increased CPK levels any time during treatment and their relation to myalgia, rhabdomyolysis, and statin treatment (the name and the dosage of the administered statin should be specified). In addition, the time to event should be displayed by treatment group (pooled RBX and 32mg RBX) separately. This applies to Primary safety database and the DR safety database.
Further, the interaction with tricyclic anti-depressants, neuroleptics and other non anti-arrhythmic QT prolonging drugs, in view of possible additive/synergistic effects on Q-T interval prolongation is a matter of concern. The applicant should provide further data as regards pharmacokinetic and pharmacodynamic interactions with statins as well as with other QT prolonging drugs.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Diabetes mellitus is a common disease affecting about 58.6 million people in Europe (International Diabetic Federation), with type 2 accounting for the majority of diagnosed cases. The majority of patients suffering from both types of diabetes develop microvascular complications such as DR, a progressive disorder involving microvascular changes in the capillaries of the retina that can lead to vision loss over time. The factors leading to vision loss associated with DR include diabetic macular oedema (DME) involving the centre of the macula, and haemorrhage from new blood vessels associated with neovascularisation.

Retinopathy in diabetic patients is caused by microvascular damage and leakage which contributes to progressive visual loss with retinopathy and macular oedema. Overactivation of protein kinase (PKC) β is responsible for endothelial dysfunction and impaired retinal blood flow leading to vascular damage in eyes. Ruboxistaurine is an orally bioavailable, selective, potent inhibitor of protein kinase C (PKC β).

Protein kinase C is a family of isoenzymes comprising at least 12 members of which β isoform has been most closely linked to the development of diabetic microvascular complication. Hyperglycaemia in patients with diabetes mellitus activates PKC β. Protein kinase C is an intracellular signalling mechanism responsible for regulation of vascular functions, including permeability, vasodilator release, endothelial activation, and growth factor signalling. This activation of PKC β can affect retina, kidney and nerves. In addition to increased vascular permeability it can also affect nitric oxide dysregulation, increased leucocyte adhesion and altered blood flow.

Diabetic retinopathy differs in type 1 and type 2 disease. In initial stages it usually is non-proliferative, mild and asymptomatic but in later stages it becomes proliferative and may be associated with loss of

vision or visual impairment. While type I diabetics commonly develop vision loss due to proliferative diabetic retinopathy (PDR), type 2 patients commonly develop diabetic macular oedema. The development and progression of DR is affected by poor control of diabetes, blood pressure and metabolic abnormalities like lipid levels. Thus effective control of these is important part of the management and prevention of development of DR and consequential vision impairment or loss.

II.2 About the product

Ruboxistaurin mesylate is an orally bioavailable, selective, potent inhibitor of protein kinase C β. In vitro and in vivo non-clinical models have demonstrated that ruboxistaurin decreases PKC β activity and ameliorates many of the effects of PKC β on pathologic processes in the retina. Ruboxistaurin prevents the slowing of retinal blood flow that is observed by fluorescein videoangiography in the eyes of diabetic rats. It is also reported to cause regression of retinal neovascularisation produced by laser-induced major branch vein occlusions in a porcine model.

Ruboxistaurin positively affected the diabetes-induced retinal blood flow abnormalities in a Phase Ib study in diabetic patients (MBBC).

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The applicant obtained scientific advice from the CHMP in November 2003 (EMEA/H/SA/333/2/2003/II). The main points were:

- Choice of dose
- Drug interactions particularly the product's influence on diabetic control
- Potential safety concerns related to involvement of Protein kinase Cβ in other systems, such as the immune system.
- Consistency with CHMP document related to single pivotal trial. "The applicant should consider advice given in the CPMP points to consider on one pivotal trial (CPMP/EWP/2330/99), in particular noting that in cases where the confirmatory evidence is provided by one pivotal trial only, this study will have to be exceptionally compelling, and statistical evidence considerably stronger than $p<0.05$ is usually required. Study MBBM is considered a hypothesis generating trial, and hence the data from that trial cannot be considered as strong supportive evidence. Ideally, one trial will show a homogeneous response across subgroups in terms of risk benefit. If benefit is confined to one particular subgroup, for example based on type of diabetes, age, severity of eye disease, or diabetic control, then further studies may be necessary to adequately define the target population and confirm the subgroup benefit".
- "Photocoagulation is a confounding factor; the protocol should standardise the indications for laser therapy intervention. Any large difference in incidence or reasons for photocoagulation between the treatment groups will be a cause of concern.

- Classification of patients as success: It is not agreed that those who do not experience the primary study outcome should be classified as `success'. Instead, sensitivity analyses should be performed to investigate the influence of missing data and the drop out issue. A single pivotal trial can be adequate only if it is particularly well designed, well carried out and analysed appropriately. Any ambiguities in the interpretation of the results that may be acceptable in a trial supported by other trials may be problematic in a single pivotal trial".

II.4 General comments on compliance with GMP, GLP, GCP

A declaration from the Qualified person of the finished product manufacturer that attests to the compliance of the drug substance manufacturer to GMP. Evidence of the suitability of the two sites of finished product manufacturer (and the UK packaging site) in relation to GMP have also been provided.

The pivotal toxicity studies were conducted in compliance with the principles of GLP.

In pivotal study B7A-MC-MBCM, 31 sites were not compliant with GCP principles Because of these GCP deficiencies in the pivotal study an inspection was requested.

II.5 Type of application and other comments on the submitted dossier

This is a complete application for a new active substance submitted through centralised route.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Ruboxistaurin is a novel drug substance isolated as the mesylate monohydrate. It is poorly soluble in aqueous solutions. Manufacture of the drug substance has been described in detail. Controls of the starting materials and critical intermediates are generally sufficient to ensure the quality of the final compound although points have been raised in relation to the bis-mesylate linker starting material. Toluene can be used during one of the proposed re-work steps in the synthesis. It should therefore be demonstrated that toluene is adequately removed by subsequent steps. Ruboxistaurin mesylate monohydrate also been well characterised by appropriate analytical techniques. The stability of the polymorph has also been demonstrated. Potential impurities have been discussed in relation to their origin and potential carry-over in to the final compound. Since acetone is used in the last crystallization step the impurity mesityl oxide (4-methyl-3-penten-2-one) can be formed. It should be demonstrated that mesityl oxide is absent in the final drug substance (or present within an toxicologically acceptable level). Further information should also be provided on the potential for formation of alkyl mesilates.

The drug substance specification is suitable for this compound. Limits for specified impurities are acceptable and follow toxicological qualification. Stability data demonstrate no observable deterioration of the drug substance after storage under long-term (30°C/60% RH) and accelerated conditions (48 & 6 months respectively) and support a re-test period of 36 months.

Drug Product

The drug product is presented as red, rounded square film-coated tablets containing 32 mg of ruboxistaurin packaged in PVC/PE/PCTFE/Al blisters. Formulation development has been well documented and follows a logical sequence. A number of formulations were used during development and a series of bioavailability studies have been presented to summarise the clinical/formulation development and to compare the bioequivalence (BE) of those formulations used in Phase I/II/III studies with the proposed commercial formulation. The commercial formulation was used during Phase III clinical studies. No IVIVC has been demonstrated hence the dissolution method is used as a quality control. Further evidence of the ability of the method to indicate batch differences has been requested. Physicochemical characteristics of the drug substance and the dosage form have been investigated to ensure reproducible manufacture of a product at the desired quality.

The manufacturing process is a standard wet granulation. Process validation has been performed on commercial scale batches manufactured at both the proposed sites of manufacture. The product specifications generally cover appropriate parameters for this dosage form. However, the shelf-life limits for assay should be tightened to 95.0-105.0%. The release and shelf-life limits for total degradation products should also be tightened in line with batch and stability data. Validations of the analytical methods have been presented. Batch analysis has been performed on commercial scale batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guidelines. A matrix design was performed in primary stability studies and this is supported by stability data for batches manufactured at the second site of manufacture. The data demonstrate good product stability and the proposed 3 year shelf-life is considered acceptable.

In conclusion, Module 3 of the dossier is of a high quality and this is reflected in the small number of points for clarification that should be resolvable through provision of further information or tightening of controls. One major objection has been raised in relation to the potential formation of the toxic impurity mesityl oxide.

III.2 Non clinical aspects

Pharmacology

Protein kinase C (PKC) is a serine-threonine kinase, the isoforms of which are involved in the regulation of several vascular functions, including contractility, haemodynamics and endothelial cell proliferation.

Hyperglycaemia-induced activation of PKC has been implicated in the development and/or progression of diabetic retinopathy. PCK activation has been reported to impair endothelial and nitric oxide (NO)-dependent vasodilation, which may contribute to the vascular dysfunction seen in diabetes. A direct effect of PKC activation on the microvasculure as well as an indirect effect via vascular endothelial growth factor (VEGF) signalling may play a role.

In vitro studies showed that ruboxistaurin exhibits ATP-dependent competitive inhibition of PKCβ, and inhibits cloned human PKCβ1 and PKCβ2 with IC_{50}'s of 4.7nM and 5.9nM, respectively.

A number of non-clinical pharmacology studies have looked at the effects of ruboxistaurin administration on vascular and endothelial dysfunctions resulting from PKC activation in animal models of diabetes.

In diabetic rats, PKC activity in the retina and kidneys is increased compared with normal rats. Ruboxistaurin administered for 2 months at 10mg/kg/day to diabetic rats totally inhibited the diabetes-induced PKC elevation in the retina.

Increased leukocyte entrapment in the retinal microcirculation may be involved in blood flow disturbances in the diabetic retina. Oral administration of ruboxistaurin at 0.1, 1 and 10mg/kg/day for 4 weeks significantly decreased the number of trapped leukocytes in the retinal microcirculation of streptozotocin (STZ)-induced diabetic rats.

VEGF is increased in the eyes of patients with proliferative diabetic retinopathy. Intravitreal injection of VEGF in nondiabetic rats at similar concentrations to those seen in these patients increased retinal permeability. Intravitreal or oral administration (25mg/kg/day in feed for 1 week) of ruboxistaurin inhibited the VEGF-induced permeability by >95%.

Inhibition of neovascularisation was investigated in a porcine branched retinal vein occlusion model. After occlusion of the veins, pigs administered ruboxistaurin (0.5mg/kg twice daily for 12 weeks) showed significant inhibition of neovascularisation, whereas all untreated eyes showed clinically evident neovascularisation.

Activation of PKCβ during acute hyperglycaemia in rat intestinal vasculature has been shown to depress endothelial formation of nitric oxide (NO) both at rest and during stimulation by NaCl hyperosmolarity. This effect could be minimised by inhibition of PKCβ by ruboxistaurin before hyperglycaemia and could be reversed to some extent by PKCβ inhibition after hyperglycaemia-induced abnormalities had occurred.

In summary, the primary pharmacodynamic studies have shown that inhibition of PKCβ by ruboxistaurin can have beneficial effects on the biochemical and physiological effects that result from hyperglycaemia-induced PKC activation in animal models of diabetes.

A number of pharmacology studies were reported that investigated effects of ruboxistaurin on nerve and renal function in animal models of diabetes. Ruboxistaurin, typically administered orally for 2 to 4

weeks at doses of 10mg/kg/day, ameliorated the deficits in nerve function and endoneurial blood flow in STZ-induced diabetic rats. The same dose administered for 12 weeks to STZ-induced diabetic rats or for 16 weeks to db/db mice showed improvements in diabetes-induced changes in transforming growth factor (TGF) β expression and its sequelae associated with nephropathy.

Safety pharmacology studies investigated receptor binding of ruboxistaurin and its major metabolite N-desmethyl ruboxistaurin, their effects on hERG channels and canine Purkinje fibres and the effects of ruboxistaurin on cardiovascular, behavioural and renal functions.

There was no indication that either ruboxistaurin or N-desmethyl ruboxistaurin had any specific muscarinic or adrenergic binding properties.

In a hERG assay, ruboxistaurin and N-desmethyl ruboxistaurin blocked the hERG channel with IC_{50} values of 35.6nM and 62.6nM, respectively. The lower potency of the metabolite in this respect, and its circulating unbound levels suggest it may have lower potential than ruboxistaurin to affect cardiac repolarisation, but the hERG data indicate that administration of ruboxistaurin to man may have the potential to prolong QTc (by about 5msec) at the highest exposures.

The potential effects of ruboxistaurin on cardiac repolarisation were further investigated in isolated canine Purkinje fibre preparations. At the highest concentration tested (nominally 1000nM, but in fact 580nM for ruboxistaurin and 430nM for N-desmethyl ruboxistaurin), both compounds significantly prolonged APD_{90}. These effects were less than expected based on the results of the hERG channel assay. The possibility of the hERG assay being over-sensitive is discussed in the 'Integrated Risk Assessment of the Potential for Ruboxistaurin to prolong Cardiac Repolarisation in Man', which was appended to the applicant's non-clinical overview. In contrast to the similar effects that the positive control, dl-sotalol had on APD_{50} and APD_{90} (32% prolongation of both), ruboxistaurin prolonged APD_{50} by 11% and APD_{90} by 21%, suggesting that ruboxistaurin is not a selective I_{Kr} blocker and that other cardiac ion channels may also be involved.

ECG was monitored in conscious dogs in a 1-month toxicity study at oral doses of up to 25mg/kg/day. There were no statistically significant effects on QTc in this study. Plasma concentrations of ruboxistaurin in the dog ranged from 50 to 1700nM, and for N-desmethyl ruboxistaurin, from 95 to 9070nM. Using a value of 66 to 95 nM for maximum concentrations of ruboxistaurin in man, and of 37 to 57 nM for N-desmethyl ruboxistaurin, the concentrations seen in the dog range from similar concentrations to those in man, to 18-fold (ruboxistaurin) or 150-fold (N-desmethyl ruboxistaurin) higher. These values for concentrations and safety margins are taken from the 'Integrated Risk Assessment' mentioned above. However it is unclear how these values were derived from the toxicokinetic data available in the study report, which stated concentrations in ng/ml. The applicant is requested to clarify the derivation of these figures. Furthermore, the non-clinical overview states the safety margins as 22- to 189-fold and this apparent discrepancy between the integrated risk assessment and overview also needs clarification.

Therefore although the hERG assay suggests that ruboxistaurin has the potential to prolong QTc to a modest degree at clinically relevant concentrations, the dog Purkinje fibre assay suggests a lesser risk, and in vivo there was no effect on QTc seen in dogs at concentrations similar to or exceeding those anticipated in man. However, a 'thorough QT' clinical study was conducted and produced a small (6msec) increase in QT interval, similar to that predicted from the hERG assay. The applicant should provide additional information that will ensure the safety of ruboxistaurin in the treatment of diabetes, particularly with respect to its channel blocking properties and QT-interval prolongation (Torsade de Pointes) and consideration that co-administration of drugs that affect plasma protein binding could elevate plasma levels of ruboxistaurin.

At single oral doses up to 200mg/kg, there were no significant effects on blood pressure or heart rate in conscious rats, nor on CNS function in behavioural studies in mice.

There were alterations in urinary electrolyte composition and urine volume in rats following single oral doses of 20 and 200mg/kg, although the effects differed depending on the dose and the

mechanism is unclear. In the absence of renal effects in chronic toxicity studies in rats, these renal effects were not considered of concern.

An initial battery of safety pharmacology studies should include assessment of effects on respiratory, cardiovascular and CNS functions, in accordance with ICH guideline S7A, therefore investigation of respiratory effects is absent from this package. The applicant has adequately justified this omission. The safety pharmacology studies were completed before the guidance was brought into operation, and the absence of any findings associated with an effect on respiratory tissues in the chronic toxicity studies suggests that the absence of respiratory safety pharmacology will not comprise the evaluation of non-clinical safety.

Pharmacokinetics
Pharmacokinetic parameters were investigated in mice, rats, pregnant rabbits and dogs.

In vivo conversion of the S-enantiomer of ruboxistaurin to the R-enantiomer does not appear to occur when ruboxistaurin mesylate monohydrate is administered as an oral solution to rats. It is also stated that conversion does not occur in vitro in aqueous solution or in rat plasma.

Absorption following oral administration did not appear to be particularly rapid, with mean Tmax of ruboxistaurin ranging from 2 to 4 hours in mouse, rat and dog in the single dose studies. However, individual values varied, and ranged from about 1 to 8 hours.

Plasma levels of both ruboxistaurin and N-desmethyl ruboxistaurin were evaluated in the pharmacokinetic and toxicokinetic studies as N-desmethyl ruboxistaurin is the major metabolite in all species investigated and is equipotent with ruboxistaurin.

Early non-clinical studies used the hydrochloride salt of ruboxistaurin. The bioavailability of ruboxistaurin and N-desmethyl ruboxistaurin combined was 12.6% in rats and 47.4% in dogs when the hydrochloride was administered.
Comparison of the hydrochloride and mesylate salts in a dog study showed higher AUC and Cmax values for both ruboxistaurin and N-desmethyl ruboxistaurin when the mesylate salt was administered. The mesylate salt was selected for further development.
In a pharmacokinetic study in mice using the mesylate, combined oral bioavailability of ruboxistaurin and N-desmethyl ruboxistaurin was 33.0%.

There is a high first pass effect in each of these species.

Elimination half-lives were generally longer for N-desmethyl ruboxistaurin than for ruboxistaurin in mice, rats and dogs following oral administration. In rats, there appear to be other metabolites with longer half-lives than either ruboxistaurin or N-desmethyl ruboxisaturin. In the dog, the half-life of both ruboxistaurin and N-desmethyl ruboxisaturin appeared to increase as the oral dose increased.

In rodents, but particularly in the rat, there was a sex difference in exposure, with females having higher exposure than males. It has also been reported that there is a gender difference in humans (Clinical Overview, section 2.5.3.2). Oral bioavailability was reported to be 30% lower in male patients than in female patients, although the wide inter-individual variability, overlap between distribution of individual pharmacokinetic values and absence of exposure-limiting side effects suggest that the exposure difference in males and females is not clinically relevant.

Distribution studies were carried out in rats using quantitative whole body autoradiography (QWBA). In male rats following a single oral dose of [^{14}C]-ruboxistaurin, radioactivity peaked in most tissues at 3h post-dose and declined thereafter with low levels present only in liver and intestinal contents at 48h post-dose. It did not accumulate in tissues in this study.

In a study in female rats using single and repeated oral doses for up to 14 days, there was some evidence of accumulation after repeated dosing. After 7 daily doses, low levels of radioactivity were associated with the ears, feet, kidney, liver, spleen and thyroid gland, with high levels in the GI

contents. After 14 daily doses, distribution was similar to that after 7 days and accumulation of radioactivity was not evident in most tissues, although radioactivity in kidney, liver, spleen and thyroid persisted for longer periods.

The concentrations in the ears and feet were only slightly greater than the limits of quantitation, and there was no indication of accumulation of radioactivity in the eye after 14 days of dosing. Red pigmentation, attributable to the accumulation of ruboxistaurin, was seen in the lens of eyes in the 6-month rat toxicity study at the high dose. Pigmentation of the skin, ears, feet, nose and/or tail was seen in the carcinogenicity studies in mice and rats, which is again assumed to reflect distribution of ruboxistaurin/N-desmethyl ruboxistaurin to these tissues following prolonged dosing. The distribution and carcinogenicity studies were conducted in albino animals. The applicant is asked to comment on whether the use of pigmented animals in the distribution studies may have produced a different pattern of tissue distribution to that seen in the albino rats, and discuss the clinical implications of accumulation for long term treatment.

Distribution in pregnant rats showed a similar pattern to that in non-pregnant rats. Although radioactivity was detectable in the placenta, it was not detectable in the fetuses after a single oral dose to the dam on GD18.

Ruboxistaurin and its metabolites are excreted in rat milk but this is only a relatively low proportion of the total dose.

Plasma protein binding was not measured in the animal species, although it has been investigated in humans. Binding studies were performed with human plasma at only two concentrations, and there was a wide variability in binding at each concentration. This variability has not been explained. Furthermore, it is not clear whether unbound or total concentrations in human plasma were used to calculate safety margins for cardiovascular effects in comparison with concentrations in dog plasma in the 1-month study in which ECGs were measured ('Integrated Risk Assessment of the Potential for Ruboxistaurin to prolong Cardiac Repolarisation in Man' and also the non-clinical overview). The applicant should comment on whether the interpretation of safety margins for cardiovascular effects may be compromised by the absence of plasma protein binding data in the dog. In addition, plasma protein binding should be (re)assessed for all species including man, both for the parent compound and its active metabolite in order to allow a proper interpretation of exposure in the various species investigated, and to assess the safety of the drug based on free concentrations.

Ruboxistaurin is extensively metabolised in all species investigated. The major metabolite in most matrices in all species was N-desmethyl ruboxistaurin (M1), which has similar pharmacological activity to the parent compound. Both ruboxistaurin and N-desmethyl ruboxistaurin are further metabolised, mainly by single hydroxylations at various sites. Di-desmethylation (to M2), N-oxidation and glucuoronidation also occurred. There were differences in some of the minor metabolites between the species, but disposition was largely similar across species and supports the use of rat and dog in the toxicology studies.

In humans, CYP3A4 appears to be responsible for the production of M1.

The main route of elimination following an oral dose is in the faeces, much of this being via the bile although some unabsorbed material is also eliminated in the faeces. Renal elimination is a minor route in all species investigated, with <3% of the dose being eliminated by this route. In mice and rats, most of the dose was eliminated within 24 hours, and within 96 hours in dogs.

The absence of non-clinical pharmacokinetic drug interaction studies is acceptable given that these were conducted during the clinical development programme.

Toxicology

The maximum dose in acute oral toxicity studies in rats and mice (800mg/kg) was limited by the poor solubility of ruboxistaurin and showed no effects in rats and only a mild reduction in body weight gain in mice. The dog was more sensitive, with a single oral dose of 300mg/kg producing dose-limiting

emesis and/or abnormal faeces. In contrast to the low acute oral toxicity in rodents, acute intravenous administration to rats (30mg/kg) resulted in injection site irritation that was severe enough to warrant euthanasia in the males.

Repeated dose studies were conducted in rats and dogs, which were appropriate species as metabolic and excretion pathways are similar to those in man. A repeated dose study was also conducted in mice as a dose range-finding study for the carcinogenicity study.

Red coloured urine and/or faeces were seen in mice, rats and dogs and were attributed to the presence of ruboxistaurin and its metabolites in excreta.

Target organ toxicity differed between species, with mice showing effects on the immune system that were not seen in rats or dogs.

In mice, there was a dose-related increase in incidence and severity of lymphocytic necrosis of the thymus and decreases in lymphocyte and monocyte counts. Specific immunotoxicity studies were carried out in mice to investigate this further and are discussed below.

In rats and dogs, there was pigmentation of biliary epithelial cells and intestinal villi, which was presumably due to localisation of the drug and/or its metabolites in lysosomes. This pigmentation was sometimes associated with inflammatory changes and increased serum markers suggestive of hepatic injury and cholestasis and was (partially) reversible. These findings were seen in rats and dogs at exposures that were approximately 60 or 40 times, respectively, those in man following a therapeutic dose. Similar changes were not seen in the 12-month dog study, where systemic exposure at the high dose (NOAEL) was 26-fold that in man following a therapeutic dose. Although histopathologic liver effects occurred at relatively high dosages, hepatic enzyme increases were observed at dosages corresponding to exposures from approximately 4 times the human exposure and there seemed to be a dose-related increase in the number of dogs with multifocal chronic inflammation in the 6-month study, starting at exposures comparable to or just above the human exposure.

The main finding in the dog was of cataracts in the lens. These lenticular changes were seen at the high doses of 25mg/kg in the 1-month study and 10mg/kg in the 6-month study (approximately 40 times human exposure). No such effects were seen in the 12-month dog study, in which the systemic exposure at the NOAEL (high dose) was 26-fold that in man. In the 6-month rat study, a red discolouration was seen in the eyes at the high dose, although only one animal had a histopathological finding (minimal peripheralisation of the epithelium of the lens) associated with this. There were no similar histopathological findings in the eye in the carcinogenicity study in rats. Therefore the cataractous changes appear to occur only in dogs and there is a reasonable safety margin.

Increased creatine phosphokinase (CPK) was seen at the high doses in the 6-month rat and 1-month dog studies (100/150mg/kg/day and 25mg/kg/day, respectively), although this was minimal in the dog. Increases in CPK have been reported in clinical studies. No signs of muscle wastage were seen in the rat or dog and no increases in CPK were seen in the 6-month or 12-month dog studies, where the high dose was lower than in the one-month study. Plasma exposures in the 12-month study were 26-fold the systemic exposure in human patients.

In the toxicokinetic studies, exposure to both ruboxistaurin and its equipotent metabolite N-desmethyl ruboxistaurin was measured.

In the mouse, absorption of ruboxistaurin was rapid (Tmax 1 hour), although this was delayed at the high dose (3 to 6h). AUC and C_{max} increased linearly and in proportion with dose for both ruboxistaurin and N-desmethyl ruboxistaurin. Females had greater exposure than males to ruboxistaurin. Exposure of females to N-desmethyl ruboxistaurin was also higher than males after 3 months of dosing and plasma accumulation of both compounds was seen in high dose females. The terminal half-life for both compounds was similar for both sexes, all doses and time points and ranged from 0.9 to 7.2h. Exposure at the NOAEL of 30mg/kg was twice that in humans.

In the rat, AUC for both ruboxistaurin and N-desmethyl ruboxistaurin increased with dose, although not always in proportion to it. As in the mouse, exposure (AUC and Cmax) to ruboxistaurin was higher in females than males. However, there was no gender difference in exposure to N-desmethyl ruboxistaurin in this species.
Both compounds accumulated in plasma after multiple doses. Half-life ranged from 2 to 8h for both compounds and was biphasic, the slower terminal phase possibly contributing to the accumulation seen with increasing treatment duration.
The NOAEL was considered to be 30mg/kg/day in the one month rat study, at which systemic exposure was 4- to 6-fold that in man. In the 6-month rat study, the exposure at the NOAEL of 5mg/kg/day was similar to that in man.

In contrast to rodents, there were no sex differences in toxicokinetics in the dog, although there was a trend to higher exposure in females in the 12-month study. AUC for both ruboxistaurin and N-desmethyl ruboxistaurin increased with dose although the increases were not always proportional to dose and were generally greater than proportional to dose for N-desmethyl ruboxistaurin in the one month study. The biphasic elimination of N-desmethyl ruboxistaurin, with a slow terminal phase of about 132 hours as characterised in the 6-month study, would explain the accumulation of metabolite seen in the 1-month and 6-month study. There was no marked accumulation of either ruboxistaurin or N-desmethylruboxistaurin in the 12-month study, in which exposure was lower than in the shorter studies.

A battery of in vitro and in vivo genotoxicity studies was conducted with both ruboxistaurin and N-desmethyl ruboxistaurin. Both compounds produced negative results in a bacterial reverse mutation assay in Salmonella strains and E.coli WP2uvrA, in L5178Y mouse lymphoma cells at the thymidine kinase locus, and in vivo in mice following oral dosing on two consecutive days. Toxicokinetic analysis in a separate study in mice demonstrated systemic exposure to ruboxistaurin. Exposure to the active metabolite was extrapolated from exposure in rats administered N-desmethyl ruboxistaurin. This lack of direct toxicokinetic analysis is not considered to affect the conclusion that compounds produced negative results. In vitro studies in Chinese hamster ovary cells showed an increased percentage of treated cells with diplochromosomes, suggestive of endoreduplication. The significance of this is not clear and although the literature reports a number of possible mechanisms, there is no evidence of a direct correlation between endoreduplication and clastogenesis. Therefore the battery of studies suggests that neither ruboxistaurin nor N-desmethyl ruboxistaurin are genotoxic.

In 2-year carcinogenicity studies in rats and mice, there were no treatment-related increases in neoplasms in either species. Toxicokinetic analysis was limited in these studies, so only Cmax and Tmax were reported. As Tmax was prolonged at higher doses in a 90-day study in mice, Cmax could have been underestimated at high doses in the carcinogenicity study. In both studies, exposure to ruboxistaurin and its metabolites was evident from the orange discolouration that was seen in the skin, eyes, nose and/or tail with prolonged treatment. In the rat, inflammation and fibroplasias were seen at a number of sites and were apparently associated with the orange colouration.
According to the applicant, the higher incidence of interstitial cell tumours seen in rats in the two high dose groups is within the historical range while the incidence in the control and low dose groups is historically low. According to the guideline on carcinogenic potential (CPMP/SWP/2877/00) if historical control data are used, they must be primarily derived from the same strain and testing facility, from several studies during the last 5 years prior to the study, taking into account genetic drift. According to the applicant the historical data range at Covance test facility is 74 to 98 %. However the data of the studies underlying these numbers have not been submitted. The applicant should provide these data. In addition, the applicant should provide an assessment of the carcinogenic data in respect of the time to occurrence of the tumours and their further development.

In a fertility and general reproductive performance study in rats, there were no treatment-related effects in males. At the high dose in females (150mg/kg), oestrus was extended although this in itself did not appear to affect reproductive performance. There was a slight reduction in fertility indices and in number of corpora lutea and implantations compared with controls. As adult female reproductive tissues exhibit angiogenesis as a normal physiological process, effects of ruboxistaurin on VEGF-

induced endothelial cell proliferation and permeability, as shown in the pharmacological studies, may help explain these effects seen in the females.
In embryo-fetal developmental studies, ruboxistaurin decreased fetal viability and increased developmental variations (effects on ossification) in rats at doses that decreased body weight in the dams. There were no developmental effects in the rabbit study although the doses were relatively low as a pilot study using higher doses resulted in mortality of the dams.
In a peri- and post-natal study in rats that investigated parameters including immunotoxicity in the F1 generation as well as their reproductive performance and the subsequent development of the F2 generation, ruboxistaurin was well tolerated. The only effect was a slight developmental delay (reduced pup body weight and delayed eye opening) for the F1 generation at the high dose.

Immunotoxicity was investigated in mice because of findings in the 90-day mouse toxicity study of decreased lymphocyte counts, decreased spleen and thymus weights and lymphocytic necrosis of the thymus. Furthermore, PKCβ knock-out mice have been reported to have suppressed immune responses. The effects seen in the specific immuntoxicity studies were relatively mild and reversible (a decrease in IgM response to T-independent antigen and reduction in spleen cell density at high dose). The effect on specific IgM responses to T-independent antigens is consistent with the expected mechanism of action of this compound on PKCβactivity in lymphocytes. No immune effects were noted in rats and dog toxicity studies, but the occurrence of infections in the long-term mouse study as well as the inflammatory effects described in the 2-year rat study suggests that ruboxistaurin might be immunosuppressive to a certain extent. This should be reflected into the Risk Management Plan, as data from the studies present in the dossier are unlikely to be sensitive enough.

Dermal and ocular irritation studies in rabbits showed ruboxisataurin to be a slight dermal irritant and severe ocular irritant. Irritant effects were also seen in the acute intravenous toxicity study in rats. However the acute oral toxicity was low and no specific gastrointestinal effects were reported in the subchronic and chronic toxicity studies using the oral route of administration.

The limits set for related substances in the drug substance specification are considered to be adequately justified.

Phototoxicity studies were not conducted. The applicant has suggested that these studies are not warranted, although ruboxistaurin absorbs light in the relevant wavelength range, because there was no significant distribution to skin or eyes in the QWBA distribution studies and there is a lack of clinical adverse effects suggestive of photosensitivity. However, evidence of distribution to skin and eyes has been seen in the 6-month rat study and carcinogenicity studies in mice and rats, as evidenced by pigmentation in these tissues. The applicant should investigate the potential for phototoxicity more extensively, as further reassurance is required that chronic treatment of diabetic patients with ruboxistaurin will not result in phototoxicity, given the current absence of non-clinical data to investigate this possibility. Long-term effects should be considered in the discussion, since substantial incorporation of ruboxistaurin in the skin only occurred in the 2-year studies.

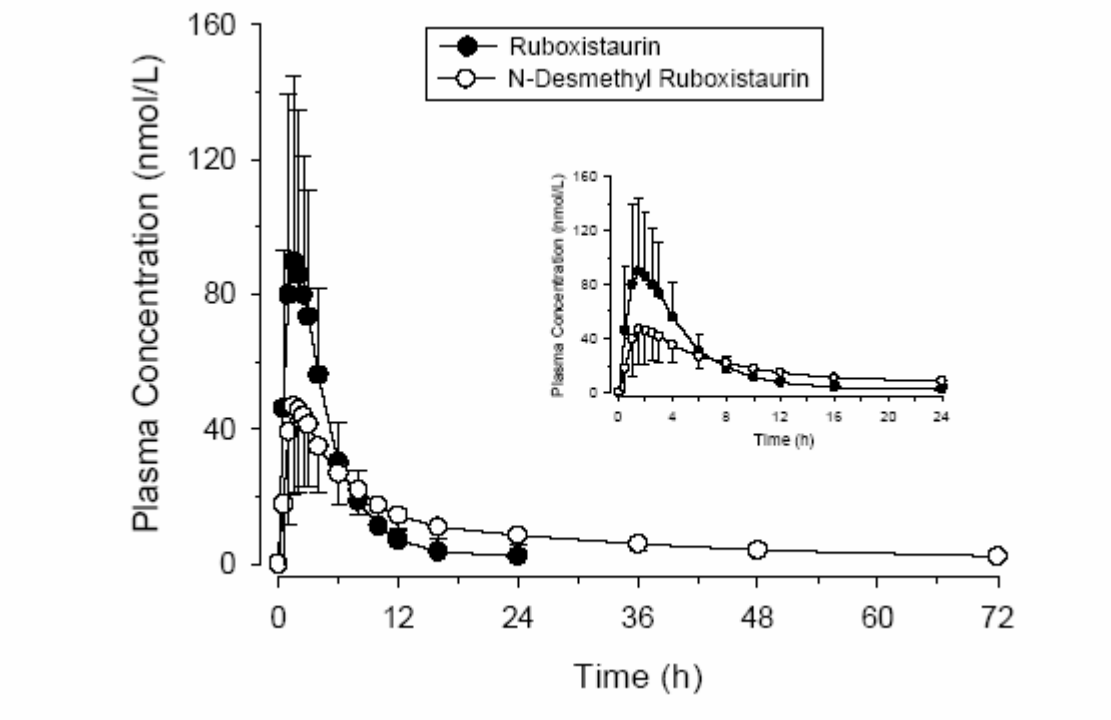
An environmental risk assessment was carried out, including Phase I and Phase II, Tier A studies. The studies and calculations suggest that the therapeutic use of ruboxistaurin mesylate is unlikely to pose a risk to the environment. However an additional sediment toxicity study is required to complete the environmental risk assessment for sediment.

III.3 Clinical aspects

Pharmacokinetics
The clinical pharmacology of ruboxistaurin and its major active metabolite N-desmethyl ruboxistaurin were investigated in healthy subjects, in subjects with diabetes, hepatic impairment (Child-Pugh B) and with end-stage renal disease (ESRD). A total of 250 subjects were recruited in 20 clinical pharmacology studies.
In general the pharmacokinetics of ruboxistaurin was well investigated. The kinetics was linear and there was considerable intra- and inter-subject variability. The maximum absorption was achieved in

approximately 2 hours for ruboxistaurin and 2.33 hours the main metabolite. The t-half was 5.25 hours and 23.9 hours respectively.

PK Fig. 1 – Mean plasma concentration versus time profile following single-dose administration of 32 mg ruboxistaurin in healthy subjects (study MBCO)



PK table 4 - Ruboxistaurin and N-desmethyl Ruboxistaurin Pharmacokinetic Parameters in Healthy Subjects Following Single-Dose Administration of 32 mg under Fed Conditions[a] (Ref: Table 2.7.2.3)

	Geometric Mean (CV%)	**Median (5^{th} – 95^{th} percentiles)**
Ruboxistaurin (N=269)		
Cmax (nM)	90.7 (57.0)	91.1 (37.4 – 206)
tmax [(h)]	1.99 (58.1)	2.00 (1.00 – 5.00)
AUC0-∞ (nmol.h/L)	489 (57.9)[a]	483 (186 – 1210)[a]
CL/F (L/h)	127 (58.1)[a]	132 (52.5 – 311)[a]
V_z/F (L)	966 (105)[a]	850 (265 – 5570)[a]
t½	5.25 (94.7)[a]	4.10 (2.23 – 26.8)[a]
N-desmethyl Ruboxistaurin (N=269)		
Cmax (nM)	43.5 (49.7)	45.1 (19.9 – 90.9)
tmax [(h)]	2.33 (58.7)	2.50 (1.00 – 6.00)
AUC0-∞ (nmol.h/L)	654 (50.2)	675 (283 – 1286)
t½ (h)	23.9 (31.1)	23.8 (16.0 – 38.7)

Abbreviations: AUC (0-∞) – area under the concentration-time curve from 0 to infinity, Cmax = maximum observed drug concentration; CL/F = apparent total body clearance of drug; tmax = time of maximum observed drug concentration; t½ = terminal half-life; Vz/F = apparent volume of distribution.
a N=268 observations

PK table 5 **Ruboxistaurin and N-desmethyl Ruboxistaurin Pharmacokinetic Parameters in Healthy Subjects Following Administration of Ruboxistaurin under Fed Conditions (Ref table 2.7.2.15)**

	Geometric Mean (CV%) Median (5th – 95th percentiles)			
	Single-Dose (N=233)	Multiple-Dose (N=58)	Single-Dose (N=233)	Multiple-Dose (n=58)
Ruboxistaurin				
C_{max}(nM)	87.3 (58.0)	87.1 (42.1)	86.2 (36.4 – 199)	90.5 (48.2 – 169)
t_{max}(h)	1.97 (60.3)	1.74 (47.3)	2.00 (1.00 – 5.40)	2.00 (1.00 – 3.18)
AUC (nmol·h/L)	464 (56.5)	429 (38.4)	455 (185 – 1162)	443 (221 – 822)
CL/F (L/h)	132 (57.8)	159 (38.4)	136 (52.7 – 320)	155 (83.3 – 310)
V_Z/F (L)	949 (101)	939 (65.7) a	842 (261 – 5562)	824 (503 – 3044) a
$t_{1/2}$ (h)	4.97 (89.3)	3.46 (47.1)	4.00 (2.21 – 21.8)	3.36 (1.69 – 7.29)
N-desmethyl Ruboxistaurin				
C_{max}(nM)	43.1 (51.0)	67.9 (48.7) b	45.1 (18.3 – 91.3)	71.4 (24.7 – 135) b
t_{max}(h)	2.27 (59.6)	2.22 (39.8)	2.00 (1.00 – 6.00)	2.00 (1.00 – 4.00)
AUC (nmol·h/L)	628 (50.2)	609 (48.0) b	634 (255 – 1252)	645 (240 – 1280) b
$t_{1/2}$ (h)	23.4 (30.9)	12.4 (110)	23.1 (15.9 – 37.8)	10.5 (3.00 – 39.9)

Abbreviations: AUC = area under the concentration-time curve from 0 to infinity [AUC(0-∞)] for single doses, area under the concentration-time curve from 0 to tau (AUCss) for multiple-doses;
Cmax = maximum observed drug concentration for single doses, maximum observed drug concentration at steady-state (Cmax,ss) for multiple doses; CL/F = apparent total body clearance of drug; tmax = time maximum observed drug concentration; t1/2 = terminal half-life; Vz/F= apparent volume of distribution.
a N = 42 observations.
b N = 40 observations.

The bioavailability, compared to oral solution was 96% (90% CI 88 – 105%). The apparent volume of distribution was 966 L. The absorption increased following administration with food. Females had greater exposure. Patients with severe hepatic impairment were not investigated in PK studies. Race, body mass index and age did not affect the kinetics significantly. No accumulation was observed in repeat dose studies. Ruboxistaurin and its main metabolite are predominantly excreted through faeces and bile. A tiny percentage (4%) appears in urine. Ruboxistaurin is primarily metabolised to N-desmethyl ruboxistaurin by cytochrome P450 3A (CYP3A). Additional metabolites are also noted but in much lower concentration. Dose-proportionality was demonstrated in a number of studies. There was doubling of exposure from 32mg to64mg but the change was less than dose-proportional for 16mg and 128mg.

Elimination

A mass balance study showed that 82.6% and 4.1% of ^{14}C labelled ruboxistaurin oral dose was recovered in feces and urine respectively (total 87%). The renal clearance was low for ruboxistaurin (0.05-0.09 l/h) and N-desmethylruboxistaurin (0.37-0.87 l/h). The plasma concentration profile declined in a biphasic manner with two elimination phases, one with a half life up to 3.6 h and 7.5 h for ruboxistaurin and N-desmethylruboxistaurin respectively and a slower one with a half life up to 40 h and 42 h for ruboxistaurin and N-desmethyl ruboxistaurin respectively. CYP3A4 is mainly involved in the biotransformation of ruboxistaurin into N-desmethylruboxistaurin i.e the major metabolite which is equipotent to the parent compound at inhibiting β1 and β2 isoforms of PKC. At steady-state, the AUCss N-desmethylruboxistaurin/AUCss ruboxistaurin ranged from 1.5 to 2 across doses.

The exposure to ruboxistaurin and N-desmethylruboxistaurin was altered by concomitant administration of potent inhibitors or inducers of CYP3A. It is also an inhibitor of PgP transporter. Although a number of in-vivo interaction studies were conducted, no conventional interaction study was done with commonly used oral anti-diabetic agents.

Ketokonazole caused a 4-fold increase in AUC for ruboxistaurin but no change in exposure to metabolite (<1-fold increase). Rifampicin reduced the exposure of both ruboxistaurin and its main metabolite by 24- fold and 5-fold respectively. No interaction was noted with warfarin.

PK in target population

The pharmacokinetics of RBX and its main metabolite, in patients with diabetes type 1 and 2 were investigated in study MBBC by conventional methods. The study evaluated the kinetics on day 1 and in steady state following 8mg BD, 16mg QD and 16mg BD ruboxistaurin under fed conditions. The average estimate for ruboxistaurin CL/F and Vz/F following single dose on Day 1 ranged from 116 to 234 L/hour and 623 to 1100 L respectively, across doses. These are similar to values reported in healthy subjects.

No conventional pharmacokinetic study was done with patients with diabetes receiving 32mg QD ruboxistaurin. Population pharmacokinetic study suggests that the oral clearance of diabetic patients was lower than that of healthy subjects. Gender and concomitant troglitazone were covariates which had the strongest influences on the population pharmacokinetics in patients with diabetes.

A population approach was also used to evaluate the pharmacokinetics of RBX and N-desmethyl ruboxistaurin for daily doses of 4 to 32 mg for periods of 1 month to 3 years. The predicted exposure from the PK model in patients receiving 32mg RBX are shown in the table below

PK table 8 - Predicted Exposure (Median [5th – 95th Percentiles]) from the Final Population Pharmacokinetic Model (B7A-MC-MBBK/MBBM/MBBO) (Ref table 2.5.3.2)

	AUC (nmol•hr/L)	C_{max} (nmol/L)	Half-Life (hours)
Ruboxistaurin			
Males	668 (231 - 2000)	58.7 (44.8 - 110)	8.03 (2.78 – 24.1)
Females	994 (378 - 2850)	85.2 (65.5 – 157)	8.42 (3.20 – 24.1)
N-desmethyl Ruboxistaurin			
Males	710 (258 - 1850)	31.2 (12.1 – 78.6)	32.7 (11.8 – 85.5)
Females	1040 (375 - 2780)	45.2 (17.5 – 117)	33.7 (12.1 – 90.3)

Ruboxistaurin and N-desmethyl ruboxistaurin exposures were calculated from 1000 simulation iterations. Simulated steady-state concentrations are for a patient in Study MBBK or MBBM, receiving 32 mg of ruboxistaurin once daily. The patient had a serum albumin of 38 g/L and was not receiving troglitazone.

Abbreviations: AUC = area under concentration-time curve; C_{max} = peak concentration.

Special populations

Renal impairment appears to have little influence on the pharmacokinetics of ruboxistaurin and N-desmethylruboxistaurin.

Due to increase in ruboxistaurin exposure (34%) and to decrease in N-desmethyl ruboxistaurin exposure (33%), the overall exposure resulting from both compounds appear to be unchanged in hepatically impaired subjects compared to healthy subjects. No dose adjustment is necessary in Child Pugh Class A and B mild hepatic impairment. However because there are no data in Child Pugh Class C patients, ruboxistaurin should be contraindicated in severe hepatic impairment.

In females the ruboxistaurin exposure is 43% higher than in males. The reason for the reported difference in mean exposures across gender is unknown. The overlap does not indicate a need for specific dose adjustments based upon gender alone.

The population pharmacokinetic analysis (study MBBK) showed that the pharmacokinetics of ruboxistaurin and N-desmethylruboxistaurin were not significantly affected by body mass index.

Moderate increases in ruboxistaurin (22%) and N-desmethylruboxistaurin (up to 37%) were noted in elderly subjects aged between 65 and 75 as compared to young healthy volunteers (Study MBBI). There are no pharmacokinetic data in elderly subjects aged over 75 years old.

Drug - drug interactions

In vitro

Ruboxistaurin (RBX) and N-desmethyl ruboxistaurin do not appear to be inhibitors of CYP1A2, CYP2C9, CYP3A, CYP2C19, or CYP2C8. Therefore, excepted for CYP2C9, no in vivo drug interaction studies were performed on drugs that are metabolized by these enzymes. A study with lovastin, a CYP3A4 substrate, was conducted as stated below. RBX and N-desmethyl ruboxistaurin are moderately weak inhibitors of CYP2D6. Therefore, in vivo drug interaction studies with substrates of CYP2D6 (i.e. desipramine) were performed. While RBX and N-desmethyl ruboxistaurin were not significant competitive inhibitors of CYP3A in vitro, results from the study assessing the induction effect of RBX demonstrated the potential for time-dependent inhibition of CYP3A activity. Therefore, a ruboxistaurin multiple dose in vivo drug interaction study with a substrate of CYP3A (lovastatin) was performed. RBX has no significant induction effect on CYP1A2 or CYP3A. Hence none in vivo drug interaction studies were performed to assess the potential for ruboxistaurin to induce the metabolism of these isoenzymes. Ruboxistaurin appears to be an inhibitor of P-glycoprotein (Pgp)-mediated transport but does not appear to be a substrate of this transporter. Therefore, a clinical study in healthy volunteers had been performed to assess the potential effect of ruboxistaurin on digoxin (a P-gp substrate) exposure.

In vivo

Effect of other active substances on ruboxistaurin

The metabolism of ruboxistaurin is catalyzed principally by CYP3A, then, in vivo drug interactions studies were performed to assess the impact of CYP3A inhibition and CYP3A induction on ruboxistaurin disposition.

Interaction with ketoconazole, a potent CYP3A4 inhibitor

For both the 32- and 64-mg doses of ruboxistaurin, coadministration of ketoconazole resulted in a substantial increase in ruboxistaurin exposure (>4-fold increase in AUC for ruboxistaurin) but an insignificant raise in the N-desmethyl ruboxistaurin exposure (<1-fold increase in AUC) is observed. These results indicate that potent CYP3A inhibitors will substantially increase the exposure to ruboxistaurin, and mildly, its active metabolite. Therefore, coadministration of ruboxistaurin with known potent CYP3A inhibitors (such as ketoconazole, itraconazole, protease inhibitors) is not recommended.

Interaction with rifampicin, a potent CYP3A4 inducer

Rifampicin 600 mg once daily reduced the mean AUC of ruboxistaurin and N-desmethyl ruboxistaurin by 24-fold and 5-fold, respectively. Therefore, coadministration of known potent inducers of CYP3A activity (such as phenytoin, rifampicin, carbamazepine, barbiturates and St John´s wort - *Hypericum perforatum*) with ruboxistaurin is not recommended.

Effect of ruboxistaurin on other active substances

Interaction with desipramine, a CYP2D6 substrate

In healthy subjects, a dose of 32 or 64 mg/day of ruboxistaurin increased the systemic exposure of desipramine by 20% or 56%, respectively. These results suggest that ruboxistaurin weakly inhibits CYP2D6. Therefore, based on the small magnitude of the interaction, only drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, such as certain antidepressants (such as nortriptyline, amitryptyline, imipramine), Type 1C antiarrythmics (such as propafenone, flecainide) and thioridazine should be used with caution when administered with ruboxistaurin.

Interaction with lovastatin, a CYP3A4 substrate

Ruboxistaurin 64 mg given once daily for 12 days increased the geometric mean AUC and Cmax of lovastatin by 43% and 30%, respectively. These results indicate that ruboxistaurin at 64 mg/day is a weak inhibitor of CYP3A activity. Therefore, at the recommended ruboxistaurin dose of 32 mg/day, there is unlikely to be any clinically relevant inhibition of CYP3A activity.

Interaction with warfarin, a CYP2C9 substrate
In healthy subjects, after multiple doses of RBX for 7 days, RBX did not alter the acute pharmacokinetics of (R)- and (S)–warfarin or the anticoagulant effects of racemic warfarin. Thus, warfarin and RBX can be coadministered without the need to adjust the warfarin dose or additional monitoring of the INR.

Interaction with digoxin, a P-glycoprotein substrate
Although in vitro studies suggested that ruboxistaurin is a potential inhibitor of P-gp transporter, once-daily oral administration of 32 mg ruboxistaurin did not alter the plasma AUC of digoxin, a substrate of P-gp, in healthy subjects. No adjustment of digoxin dose is needed when giving digoxin with ruboxistaurin.

Other interactions
Interaction with antidiabetic agents
The Applicant has not assessed the potential for ruboxistaurin to interact with oral antidiabetic agents and justifies their safety use by lesser potent effect of these drugs, on the inhibition or induction of CYP3A, than compounds involved in the clinical interaction studies supplied (i.e. rifampicin and ketoconazole). It should be noticed that through the PK population studies, the concomitant use of ruboxistaurin with troglitazone (a CYP3A4 inducer that has been withdrawn in 2000) was assessed and results showed a decreased of ruboxistaurin oral bioavailability by 55% and an increase of its active metabolite.
Nevertheless, most of antidiabetic agents are metabolised through CYP2C (sulfonylureas, second generation thiazolidinediones, repaglinide). From results of in vitro studies, ruboxistaurin does not appear to inhibit significantly these CYP but, regarding the possibility for ruboxistaurin to induce CYP2C, no data are provided in the submitted fill.

Pharmacodynamic Interaction
As RBX normalizes nitric oxide signalling in diabetic animals and restores vascular function, a study was conducted to assess a possible interaction between RBX and an exogenous nitric oxide donor, nitroglycerin, on blood pressure. In 20 patients with stable angina pectoris, 96 mg QD ruboxistaurin dosed for 8 days did not alter the hypotensive response to intravenous nitroglycerin, as measured by orthostatic standing systolic blood pressure. Therefore, there is no pharmacological interaction between RBX and nitrate drugs.

Pharmacodynamics
RBX is stated to exert inhibitory effects on protein kinase C (PKC) β. This latter is an intra-cellular signalling molecule which can regulate several vascular functions including permeability and nitric oxide release.

Pharmacodynamic studies were limited to thorough QT study, dose-selection study and vascular reactivity study. Proof of concept was sought in a study on retinal circulation and in a model of forearm vascular reactivity. In addition, the limited pharmacodynamic clinical programme has mainly tried to bring clues to support the selected dose of the phase III pivotal trial.

Vascular reactivity study (MBBN) investigated affect of RBX on hyperglycaemia-induced impairment in endothelium-dependent vasodilatation. Results of this study showed that the hyperglycaemia-induced endothelial dysfunction was prevented, albeit modestly, by RBX 32 mg/day. There were no relationships between plasma concentrations of RBX and metabolite and the pharmacodynamic measurements.
The vascular reactivity study demonstrated the biological plausibility of therapeutic use of ruboxistaurin, however there were divergent views from rapporteurs' on this.

Study MBBC was essentially a safety and dose-finding study but in different group of patients (mild NPDR) than chosen for the main therapeutic trial. This was a DB, randomised, placebo-controlled study in a very limited number of diabetic patients (29) with none to mild NPDR (level 20 or less on ETDRS DR scale). Patients received either RBX 8 mg twice daily (n=7) or RBX 16 mg once daily

(n=7) or RBX 16 mg twice daily (n=8) or placebo (n=7) for 28 days. The primary aim of this trial was safety, retinal blood flow (RCT) being a secondary objective. The mean retinal circulation time (RCT) was determined at baseline and study conclusion.

The results showed 1 second prolongation in diabetics with no NPDR compared to non-diabetics. Patients on RBX 16 mg twice daily (8 patients in all) experienced a baseline-to-endpoint change in RCT of -0.68 ±0.73 seconds compared to 0.16 ±0.80 second change in placebo-treated patients.). Baseline mean RCT was significantly associated with mean RCT change from baseline with increasing baseline RCT resulting in larger decreases in mean RCT. Baseline mean RCT was higher in the 16mg BID RBX group compared to the placebo group. Therefore, the mean RCT change unadjusted to baseline with 16mg BID RBX was marginally significant (p=0.046) compared to placebo but no longer significant (p=0.066) when adjusted to baseline RCT. Strictly speaking, the study has not demonstrated clear evidence on RCT with the 16mg BID dose. No dose response was shown, the 8mg BID and 16mg QD RBX doses having not demonstrated any relevant effect. This study might be of interest for a proof of concept, but there are divergent views from rapporteurs regarding relevance of this in the dose determination of a phase III pivotal study.

The pharmacodynamic clinical programme has not brought convincing data in support of the drug mechanism of action. Two remote surrogates of PKC-β inhibitory effects have been evaluated: retinal circulation time and forearm vascular reactivity. The drug effects on more pertinent patho-physiologic characteristics of DR in particular vascular leakage or ischemic maculopathy using fluorescein angiographies or ocular coherence tomography (OCT) have not been evaluated.

QT study (Study B7a-LC-MBDT)
In a single blind, placebo-controlled, multi-centre, three period cross-over study, the effect of a single supra-therapeutic dose of RBX (256 mg) on the QT interval in 77 healthy subjects was investigated. The reference product used was moxifloxacin as a positive control.. The dose of moxfloxacin used was 400 mg as a single dose.The ECG was recorded at 2, 6 and 12 hours post dose. Population pharmacokinetic modelling approach was used to estimate exposure and maximum observed drug concentration.
The results showed a positive plasma concentration effect of RBX and its's active metabolite with QT interval. The largest mean QT interval, noted 6 hours post dosing was 6.10 msec (90% CI; 4.45, 7.75) and comparable to moxifloxacin. Using the Fredericia correction QT prolongation was 6.46 msec (90% CI; 4.73, 8.19. Females (an exploratory endpoint) showed larger effect than males 6.96 msec (90% CI; 4.68, 9.24).

PK table 1 - Comparison of Least-Squares Mean Changes in QT interval Adjusted for the RR Interval (ms) Between 256 mg RBX and Placebo at 2, 6, and 12 Hours Post-dose by Gender (Ref table 2.7.4.143)

Gender	Time Post dose (h.)	Treatment	N	Least-Squares Mean Change in QT Interval	Least-Squares Mean Difference of Change in QT Interval (90% Confidence Interval)
Female	2	Ruboxistaurin 256 mg	36	4.63	4.87 (2.59, 7.16)
		Placebo	35	-0.24	
	6	Ruboxistaurin 256 mg	36	6.33	6.96 (4.68, 9.24)
		Placebo	35	-0.63	
	12	Ruboxistaurin 256 mg	36	6.07	6.05 (3.77, 8.33)
		Placebo	35	0.02	
Male	2	Ruboxistaurin 256 mg	37	1.22	2.16 (-0.23, 4.55)
		Placebo	40	-0.95	
	6	Ruboxistaurin 256 mg	37	4.94	5.28 (2.90, 7.67)

		Placebo	40	-0.35	
	12	Ruboxistaurin 256 mg	37	2.26	3.87 (1.48, 6.26)
		Placebo	40	-1.61	

(Clinical safety summary, Page 353)

This study on QT interval has evidenced a significant prolongation of QT in normal subjects exposed to a single supra-therapeutic dose of RBX. The average QT prolongation is beyond the 5ms threshold level of regulatory concern. With the 90% CI, the upper bound of the CI in women is close to 10ms and is prolonged for at least 12 hours. Therefore this "thorough" QT/QTC study should be considered as positive and calls for a further expanded ECG safety evaluation. As expected with drugs prolonging the QT interval, there is a clear gender effect with a larger QTc in women. RBX is metabolised through the CYP3A system and is subject to many potential interactions. Modelling of the data from study MBCB predicted that inhibition of CYP3A would yield RBX exposures at steady state 5 to 12 times those found with the 32mg dose. With a single dose administration of 256 mg in this study, patient exposure is within that range. Therefore, this drug profile is of particular concern.
There were many outliers with QTcF > 10 msec in the scatter plot (page35, clinical safety summary) and further evaluation of these is required.

Clinical efficacy

The efficacy of ruboxistaurin mesylate (ruboxistaurin; RBX) for the treatment of diabetic retinopathy (DR) was evaluated in 2 randomized, double-masked, placebo-controlled, long-term (3 year) studies (B7A-MC-MBCM and B7A-MC-MBBM). A total of 937 patients with Early Treatment of Diabetic Retinopathy Study (ETDRS)-graded moderately severe to very severe non-proliferative diabetic retinopathy (NPDR) were recruited.

The pivotal therapeutic study for the proposed indication in this application was MBCM (N=685) while study MBBM (N=252) was considered a supportive study. In addition study B7A-MC-MBBK, (N=686) investigated patients with diabetic macular oedema (DME) while study B7A-MC-MBBC (N=29) was a clinical pharmacology study in diabetic patients with no or very limited diabetic retinopathy.

The clinical studies provided in support of the proposed indications are shown in the table below:

Efficacy table 1 **Clinical Studies Pertinent to the Claimed Indication (Ref – Table 2.7.3.1)**

Study Identifier; Title	**Dose[a]:Randomized (Completed [%]) Treatment Duration**	**Diagnosis or Inclusion Criteria**	**Primary Endpoint(s)**
Phase 1b Study			
B7A-MC-MBBC; Safety and Pharmacokinetics of LY333531 in Patients with Diabetes Mellitus: Dose-Ranging Study	RBX 8 mg BID: 7 (6 [85.7]) 16 mg QD: 7 (7 [100]) 16 mg BID: 8 (8 [100]) Placebo 7 (6 [85.7]) 28 days	Type 1 or 2 DM <10 years duration and ETDRS absent to mild NPDR.	Safety[b], pharmacokinetics, pharmacodynamics – retinal blood flow, retinal circulation time, vascular permeability.
Phase 3 Diabetic Retinopathy and Diabetic Macular Edema Studies			
B7A-MC-MBBM; Protein Kinase Cβ Inhibitor - Diabetic Retinopathy Study	RBX (QD) 8 mg: 60 (45 [75.0]) 16 mg: 64 (39 [60.9]) 32 mg: 67 (47 [70.1]) Placebo	Type 1 or 2 DM with ETDRS moderately severe[c] to very severe NPDR without previous PRP and VA	Progression of DR by ≥3(2)[d]steps on ETDRS retinopathy severity scale or PRP for DR.

(PKC-DRS)	61(47 [77.0]) Minimum of 36 months	of ≥45 letters in at least 1 eye.	
B7A-MC-MBBK; Protein Kinase C β Inhibitor – Diabetic Macular Edema Study (PKC-DMES)	RBX (QD) 4 mg: 168 (131 [78.0]) 16 mg: 174 (127 [73.0]) 32 mg: 168 (114 [67.9]) Placebo 176 (122 [69.3]) Minimum of 30 months	Type 1 or 2 DM with ETDRS mild-to-moderately severe[e] NPDR and DME not involving the retina within 300 microns of the center of the macula without previous PRP or focal/grid PC and VA of ≥75 letters in at least 1 eye.	Progression of DME to involve or imminently threaten the center of the macula (within 100 microns of the center of the macula) or focal/grid PC for DME.
B7A-MC-MBCM; Protein Kinase C β Inhibitor – Diabetic Retinopathy Study 2 (PKC-DRS2)	RBX (QD) 32 mg: 345 (258 [74.8]) Placebo 340 (256 [75.3]) Minimum of 36 months	Type 1 or 2 DM with ETDRS moderately severe to very severe NPDR without previous PRP and VA of ≥45 letters in at least 1 eye.	SMVL (occurrence of a ≥15-letter loss in a DR study eye for the 6-month period from 30 months through 36 months or for the last 6 months of study participation).

Abbreviations: BID = twice daily; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; focal/grid PC = focal/grid photocoagulation; PRP = panretinal photocoagulation; LY333531 = ruboxistaurin; NPDR = nonproliferative diabetic retinopathy; RBX = ruboxistaurin mesylate; SMVL = sustained moderate visual loss; VA = visual acuity as determined by the ETDRS protocol (best corrected).
a All regimens were once daily unless otherwise noted. Route of administration was by mouth.
b Safety parameters: Hematology, chemistry, and lipid panel, urine analysis, coagulation studies, acute glycemic control, liver function tests, immunologic markers, and ECG.
c Did not include patients with ETDRS DR severity Level 47A.
d See Clinical Study Report MBBM, Section 7.1.
e Did not include patients with ETDRS DR severity Levels 47B-D.

Additional studies have been conducted in diabetic patients with erectile dysfunction (ED), peripheral neuropathy, peripheral vascular disease and nephropathy. No clinically significant effect of RBX was observed on ED, symptoms of neuropathy or peripheral vascular disease. These studies were not part of the claimed indication, but all 11 completed placebo-controlled studies, regardless of indication, have been integrated to constitute the primary safety database for this application.

Currently, there are 3 additional ophthalmic studies ongoing:

- Study B7A-MC-MBDL (N=900; data expected in 2010) is being conducted to evaluate the effects of RBX on DME in patients with mild to moderately severe NPDR;
- Study B7A-MC-MBCU (N=220; data expected in 2008) is being conducted to evaluate the effect of RBX on CSME in patients with moderate to severe NPDR using Optical Coherence Tomography (OCT) to measure retinal thickening;
- Study B7A-MC-MBDV (data expected in 2007) is the open-label extension phase of Study MBCM. The purpose of this study is to evaluate the effect of RBX on sustained moderate visual loss (SMVL) for an additional 2 years, in patients who completed Study MBCM.

Paediatric development of the therapeutic agent is not relevant for the claimed indication.

Dose Selection

The doses of 16mg and 32mg QD were chosen based on the results of preclinical efficacy and pharmacokinetic studies. In study MBBC, no significant pharmacodynamic effect on the mean RCT was seen with 16mg dose (8mg bid & 16mg QD). Doses higher than 32mg were not used because of non-completion of toxicology studies supporting safety of higher doses. The question whether a higher dose would have been more effective cannot be answered with certainty. There was no clear predictive relationship between response and exposure.
The justification for the 32 mg dose in phase III is unclear because of the following reasons: the phase 1b study B7A-MC-MBBC testing, relative to placebo, the 8mg BID, 16mg QD and 16mg BID doses administered for 28 days, on retinal circulation in a very limited number of diabetic patients (8/group), cannot be considered as a dose determination study for phase III although the Applicant considered these the strongest data for dose selection of phase III. The main pharmacodynamic effect was a marginal, not clinically relevant, reduction of retinal circulation time (RCT) with the 16 mg BID dose, in 8 patients with DR not representative of the phase III programme. Furthermore, the change when adjusted for baseline value was not statistically significant compared to placebo (p=0.066). The other doses did not show relevant effects; no dose-response could be identified. Also, 32 mg/day were given as a BID dosage and not as a once daily dose regimen as administered in the pivotal trial. Thus, these phase I study results do not support the selection of the 32 mg OD for the pivotal trial in patients with moderately severe to very severe NPDR. Doses higher than the daily 32mg dose should have been considered but could not be tested, because of drug substance originating from a batch containing higher levels of impurities than previously used in non-clinical toxicology or clinical studies. Thus the dose selection of 32 mg/day in the pivotal study, was essentially based i) on a non significant trend shown with the 32 mg dose in a different patient population of a previous dose-ranging trial, having lacked to show any dose response and ii) the obligation to use the 32 mg as the maximum dose, because of the lack of any safety margin of a higher dose.

Pivotal study (Study MBCM)
This was a randomised, double-masked, placebo-controlled, long-term (3 year) study which enrolled 685 patients. Patients with type 1 or type 2 diabetes mellitus with ETDRS moderately severe to very severe NPDR without previous PRP and VA of ≥45 letters in at least 1 eye. A total of 685 patients were recruited, 345 in ruboxistaurin group and 340 in placebo group. The number of patients who completed the study was 258/345 (74.8%) in ruboxistaurin group and 256/340 (75.3%) in placebo group.

Population Characteristics at Study Entry
Patients with aged >=18 years, type I or II diabetes mellitus; one or two DR study eyes as defined in study protocol, moderate to very severe NPDR in at least one eye, best-corrected visual acuity score >= 45 letters in at least one DR study eye, no previous pan retinal laser photocoagulation (PRP) in DR study eye.
Protocol-defined uncontrolled diabetes, systolic/ diastolic blood pressure ≥180/105 mmHg, QTc > 500msec on ECG were exclusion criteria from the study.

Baseline Patient Characteristics -All randomized Patients (N=685)

Variable	Placebo N=340	32 mg RBX N=345	Total N=685
Age (yrs)			
Mean (+/- SD)	**59.18 (10.61)**	**59.48 (10.91)**	**59.33 (10.76)**
Origin			
Caucasian	**273 (80.3%)**	**259 (75.1%)**	**532 (77.7%)**
Non-Caucasian	**67 (19.7%)**	**86 (24.9%)**	**153 (22.3%)**
Gender			
Male	**218 (64.1%)**	**215 (62.3%)**	**433 (63.2%)**
Female	**122 (35.9%)**	**130 (37.7%)**	**252 (36.8%)**
Diabetes Type			
Type 1	**40 (11.8%)**	**40 (11.6%)**	**80 (11.7%)**
Type 2	**300 (88.2%)**	**305 (88.4%)**	**605 (88.3%)**
Duration of Diabetes (yrs)			
Mean (+/- SD)	**16.12 (7.77)**	**15.97 (8.47)**	**16.05 (8.12)**

Diabetes Therapy			
D/E	**3 (0.9%)**	**2 (0.6%)**	**5 (0.7%)**
I/P	**94 (27.6%)**	**91 (26.4%)**	**185 (27.0%)**
OAH	**150 (44.1%)**	**144 (41.7%)**	**294 (42.9%)**
OAH I/P	**93 (27.4%)**	**108 (31.3%)**	**201 (29.3%)**
BMI (kg/m2)			
Number of patients	**337**	**345**	**682**
Mean (+/- SD)	**32.81 (6.70)**	**32.76 (8.03)**	**32.78 (7.40)**
Haemoglobin A1c (%)			
Number of patients	**334**	**339**	**673**
Mean (+/- SD)	**8.08 (1.41)**	**8.14 (1.43)**	**8.11 (1.42)**
Median	**7.90**	**7.80**	**7.90**
Maximum	**12.70**	**12.50**	**12.70**
Diastolic Blood Pressure (mmHg)			
Mean (+/-SD)	**77.54 (9.99)**	**77.32 (10.64)**	**77.43 (10.32)**
Median	**78.50**	**78.00**	**78.00**
Systolic Blood Pressure (mmHg)			
Mean (+/-SD)	**138.04 (17.56)**	**136.19 (17.38)**	**137.11 (17.48)**
Median	**138.00**	**136.00**	**138.00**
Maximum	**196.00**	**200.00**	**200.00**

Baseline Diabetic Retinopathy Study Eye Characteristic- All Randomized Patients: N=685

Variable	**Placebo N=340**	**32 mg RBX N=345**	**Total N=685**
Number of DR Study Eyes			
	584	**599**	**1183**
DR level			
<47	**53 (9.1%)**	**62 (10.4%)**	**115 (9.7%)**
47	**353 (60.4%)**	**367 (61.3%)**	**720 (60.9%)**
53	**178 (30.5%)**	**170 (28.4%)**	**348 (29.4%)**
Number of DR Study Eyes per Patient			
Two	**244 (71.8%)**	**254 (73.6%)**	**498 (72.7%)**
One	**96 (28.2%)**	**91 (26.4%)**	**187 (27.3%)**
Visual Acuity Score (letters correct)			
Mean (+/-SD)	**77.38 (11.35)**	**77.24 (12.45)**	**77.31 (11.92)**
Median	**80.00**	**80.00**	**80.00**
Minimum	**22.00**	**6.00**	**6.00**
DME Level			
0-2	**138 (23.7%)**	**141 (23.6%)**	**279 (23.7%)**
3	**119 (20.4%)**	**107 (17.9%)**	**226 (19.2%)**
4	**39 (6.7%)**	**28 (4.7%)**	**67 (5.7%)**
5	**26 (4.5%)**	**33 (5.5%)**	**59 (5.0%)**
6 - 7	**63 (10.8%)**	**79 (13.2%)**	**142 (12.0%)**
8 - 9	**16 (2.7%)**	**11 (1.8%)**	**27 (2.3%)**
10 - 11	**181 (31.1%)**	**198 (33.2%)**	**379 (32.1%)**
Retinal thickening Area Within 3000 Microns of the Centre of the Macula (Disc Areas)			
<0.5	**212 (36.3%)**	**224 (37.4%)**	**436 (36.9%)**
>=0.5, <1	**70 (12.0%)**	**61 (10.2%)**	**131 (11.1%)**
>=1, <3	**147 (25.2%)**	**153 (25.5%)**	**300 (25.4%)**
>=3	**155 (26.5%)**	**161 (26.9%)**	**316 (26.7%)**
Prior focal PC			
Yes	**291 (49.8%)**	**270 (45.1%)**	**561 (47.4%)**

A total of 72 % of patients were included in the study with 2 DR study eyes. Around 60% of DR study eyes had DR level 47 and 30% had DR level 53 on the ETDRS DR severity scale. Average visual acuity was around 77 letters (ETDRS VA protocol) at baseline. Since DME level was not an entry criterion, there was a large range of DME severity levels ranging from steps 0-1 to step 11. Approximately 52 % of eyes had DME severity steps 5-11. Over 50% of eyes had a >= 1 level of retinal thickening area within 3000 microns of macular centre. About 50% of the eyes had already had

focal/ grid photocoagulation. Although DME appeared to have been appropriately categorized in the patient population, no information is available with respect to the ischemic component of maculopathy.

The primary study objective was to test the hypothesis that oral administration of 32 mg per day of ruboxistaurin over 3 years would reduce, relative to placebo, the occurrence of sustained moderate visual loss (SMVL) in at least 1 diabetic retinopathy (DR) study eye. Sustained moderate visual loss was defined as the occurrence of ≥15 letters loss in best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) for the 6-month period from Visit 13 (30 months) through Visit 15 (36 months), or for the last 6 months of a patient's study participation for those patients who discontinued early.

The primary endpoint was changed prior to unmasking of data (see above).

The Primary Efficacy endpoint had been discussed during the Scientific Advice. The CHMP indicated that "*Approval would need to show a clinically significant benefit and a favorable benefit-risk. It would be necessary to relate the primary endpoint of the trial to the occurrence of MVL in terms of percentage of patients who benefit and the magnitude of benefit. A clear definition of magnitude of treatment benefit on visual acuity would be needed. Visual acuity may be complicated by other conditions such as cataract. The endpoint "sustained moderate vision loss" as defined by the Applicant could be acceptable*". Ischaemic maculopathy was investigated neither at baseline nor during study.

The Two Major Secondary Efficacy Endpoints (termed "Gate keeping" by the Applicant) were defined as follows:

- *Gate keeping Group I:* occurrence of DME that involves or imminently threatens the centre of the macula (steps 8 through 11) in patients without such DME in a DME study eye at baseline.

- *Gate keeping Group II:* progression of DR defined as >=3 steps on the ETDRS retinopathy severity person scale for patients with two DR study eyes; or >= 2 steps on the ETDRS retinopathy severity eye scale for patients with only one DR study eye; or the application of PRP

  The DME "Scale for Threat to or Involvement of the Centre of the Macula" has not been referenced as a well-known tool used in previous large DME trials. No information was available with respect to its validation.

There were numerous secondary endpoints including application of PRP in a study eye, development of definite or worse PDR , development of high-risk or worse PDR, occurrence of severe visual loss (VA <5/200), occurrence of MVL, development of DME that involved or imminently threatened the center, progression of DR: ≥3(2)[a] steps or application of PRP, application of focal/grid PC in a study eye, application of focal/grid PC in eye without prior laser therapy and mean changes in categorical changes in VA score.

Results

The primary analysis in ITT population showed significantly less SMVL in patients treated with ruboxistaurin, compared to placebo. The relative risk reduction was 40%.

Efficacy table 3 - Occurrence of Sustained Moderate Visual Loss[a] in Study MBCM. Ref: Table 2.7.3.4

	Placebo (N=340)	32 mg RBX (N=345)	p-value[b]	Relative Risk Reduction
SMVL	9.1%	5.5%	0.034	40%

Primary Efficacy Endpoint (SMVL)Analysis

Primary Analysis of Primary Endpoint: SMVL –All Randomised Patients (N=685) - Patient Level Analysis

Number of DR Study Eyes	DME Level	Placebo		RBX	
		n/N	%	n/N	%
1	0-4	1/56	1.8	0/40	0
	5-11	5/40	12.5	7/51	13.7
2	0-4	2/82	2.4	0/84	0
	5-11	23/162	14.2	12/170	7.1
Result Overall	**0-11**	**31/340**	**9.1**	**19/345**	**5.5**

n=number of patients with Sustained Moderate Vision Loss (SMVL); N= number of patients randomized (N Total=685)

The primary analysis, a CMH test on the ITT population, stratified for the number of DR study eyes and the severity of DME demonstrated that the proportion of patients experiencing SMVL was significantly larger in the placebo than in the BRX group (p=0.034). The global Chi Square test, however, did not show statistical significance (p=0.069). The CMH analyses carried out on the primary endpoint in the "Completers" as well as in the "Per-Protocol" cohorts did not show any statistical significance in either of these cohorts (for completer cohort: p=0.052 and for "per protocol cohort: p=0.066).

Furthermore, when looking at the occurrence of SMVL per stratum i.e. per number of DR eyes and DME level, it is clearly demonstrated that only data from stratum " 2 DR study eyes and DME level 5-11", would support a difference of occurrence of SMVL in the RBX group as compared to placebo. This effect is not shown for the same DME level in patients with only 1 DR eye (nor in any other strata).

It can be concluded that the statistical significance of the primary analysis is actually supported by only the result in the stratum [2 DR study eyes, DME level 5-11]. As already mentioned, with only one single additional occurrence of SMVL in this stratum in the RBX group, the analysis would no longer have been significant.

Subgroup Analyses of Primary Endpoint by Baseline Covariate –All Randomised patients (N=685)
These subgroup analyses show that the primary efficacy result is driven by the effect in women. A large treatment effect for the primary endpoint of SMVL was demonstrated in women but no treatment effect was evidenced in men. In women the occurrence of SMVL was as follows: placebo 14.8% versus RBX 3.8%; and in men: placebo 6.0% versus RBX 6.5% (see also section of effect on gender).

Furthermore, the primary efficacy result was also driven by ethnicity. A large significant effect for the primary endpoint of SMVL was demonstrated in non-Caucasians, no treatment effect was evidenced in Caucasians. In non-Caucasians, the occurrence of SMVL was as follows: placebo: 11.9% versus RBX 3.5% as compared to Caucasians: placebo: 8.4% versus RBX 6.2%. (See also section of effect on gender).

Occurrences of SMVL by Baseline Patient Characteristics

	Variable	Placebo N=340 n/N (%)	32 mg RBX N=345 n/N (%)	Total N=685 n/N (%)	Chi-square p-value
Occurrence of SMVL by Baseline Systolic Blood Pressure					
	> median 138.0	18/183 (9.8%)	8/165 (4.8%)	26/348 (7.5%)	0.077
	< median 138.0	13/157 (8.3%)	11/180 (6.1%)	24/337 (7.1%)	0.440
Occurrence of SMVL by Baseline HbA1c					
	> median of 7.9	16/169 (9.5%)	11/169 (6.5%)	27/338 (8.0%)	0.316
	< median of 7.9	14/165 (8.5%)	6/170 (3.5%)	20/335 (6.0%)	0.056
Occurrence of SMVL by Baseline Body Mass Index					
	< 31.63	17/162 (10.5%)	13/178 (7.3%)	30/340 (8.8%)	0.300
	> 31.63	14/337 (8.0%)	6/167 (3.6%)	20/342 (5.8%)	0.083
Occurrence of SMVL by Baseline Total Cholesterol					
	> median 4.89	22/178 (12.4%)	9/155 (5.8%)	31/333 (9.3%)	0.040
	< median 4.89	9/156 (5.8%)	9/185 (4.9%)	18/341 (5.3%)	0.710
Occurrence of SMVL by Origin					
	Caucasian	23/273 (8.4%)	16/259 (6.2%)	39/532 (7.3%)	0.320
	Non Caucasian	8/67 (11.9%)	3/86 (3.5%)	11/153 (7.2%)	0.045

Occurrence of SMVL by Baseline Concomitant Treatment

	Variable	Placebo	32mg RBX	Total	Chi Square p-value
Occurrence of SMVL by Baseline Use of Insulin					
	Insulin yes	12/187 (6.4%)	11/199(5.5%)	23/386 (6.0%)	0.712
	Insulin no	19/153 (12.4%)	8/146 (5.5%)	22/299 (9.0%)	0.036
Occurrence of SMVL by Baseline Use of Statin					
	Statin yes	13/149 (8.7%)	11/160 (6.9%)	24/309 (7.8%)	0.544
	Statin no	18/191 (9.4%)	8/185 (4.3%)	26/376 (6.9%)	0.051

Considering confounding factors at baseline, such as, systolic blood pressure, total cholesterol, body mass index, the drug effect tended to be less effective in the patient population with values below the median. for these confounding factors. The drug effect tended to be less effective in patients with HbA1c above median value at baseline. Finally,, no drug effect could be shown in patients taking insulin or statins.

Thus the results on primary efficacy endpoint of the B7A-MC- MBCM study do not support the CHMP requirements. They lack robustness, rely on the distribution of one single patient, with an overall p-value of 0.034 i.e. not compellingly stronger than the usual <0.05 threshold and are characterized by a very high rate of patient lost to follow up. In addition, the results relative to the primary efficacy are driven essentially by 1) the subgroup of patients with [2 DR study eyes and DME level 5-11] 2) by women 3) non Caucasians

Effect of treatment (Placebo vs RBX), DME baseline level (5 through 11 vs 0 through 4; stratification level 1 of the CMH test), and number of DR study eyes (2 vs 1; stratification level 2 of the CMH test) on the occurrence of SMVL was evaluated by logistic regression analysis. The estimated odds ratio of greater than 1 was observed for the treatment effect and baseline DME level.

As regards visual acuity (VA), the proportion of patients who noted to have a baseline-to-endpoint increase in VA of ≥15 letters was greater in the ruboxistaurin 32mg group (4.9%) than in the placebo group (2.4%, p=0.027). The proportion of patients experiencing MVL was greater at each time point in placebo group than in the ruboxistaurin 32mg group although it achieved statistical significance only at the 30 months visit.

Many Secondary Analyses of Primary Endpoint were carried out using Eye Level Analyses

All these analyses were based on the eye level. The tests used were statistically inappropriate since they did not take into consideration the correlation of both eyes, for those patients having two study eyes. Thus, no conclusions should be drawn from these results. In addition, the large numbers of analyses performed raise the issue of multiplicity in clinical trials and the risk of false positive conclusions. The proportion of DR study eyes experiencing SMVL by baseline DR severity level (all, < 47, 47, or 53) was significantly different between treatments overall, but was not different for any individual severity level.

Analyses of Secondary Efficacy Endpoints

A very large number of analyses and subgroup analyses were carried out on secondary efficacy endpoints. In the review they were categorized according to their relation with i) visual acuity ii) diabetic macular oedema iii) progression of diabetic retinopathy. Only selected secondary endpoints and analyses have been displayed

Visual Acuity

Mean Change of Visual Acuity (Eye Level Analysis): when all study eyes were analysed, the VA mean change from baseline to endpoint showed a change in placebo group: -2.63±13.33 letters and in 32 mg RBX group: -0.80±12.26 letters; p=0.014.

The aforementioned VA analysis is based on the number of study eyes. Again the test applied is inappropriate, since the analysis does not take into consideration the intra individual correlation of the two eyes for those subjects with two DR study eyes.
Furthermore, irrespective of methodological and statistical considerations, the between treatment group difference of mean VA score of 1.83 letters at endpoint (or grossly 1.83 letters after 36 months) cannot be considered of any clinical relevance. These analyses do not support any favourable effect of RBX on visual acuity or derived variables

Diabetic Macular Oedema (DME)

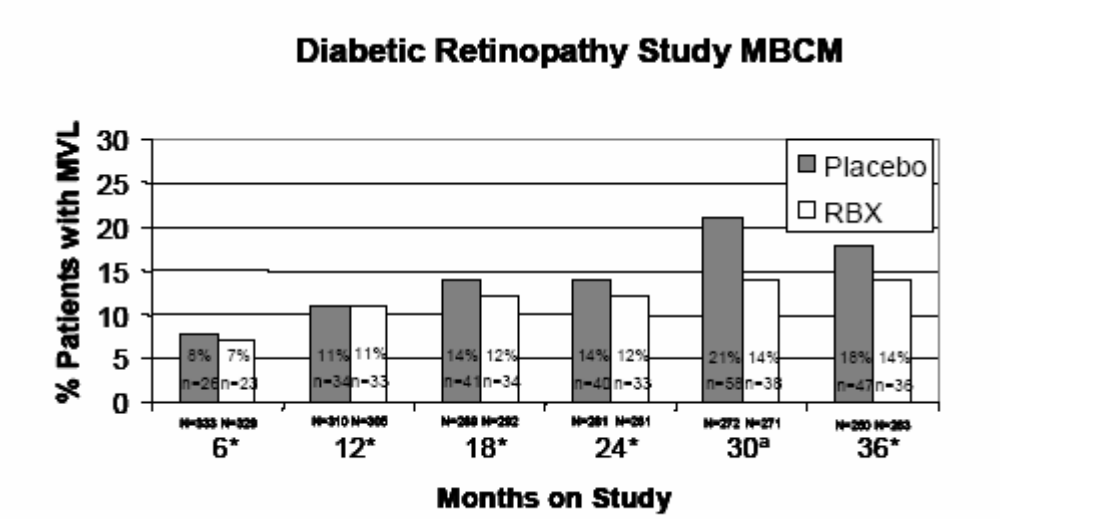
The proportion of patients with centre threatening or less DME at baseline (Steps 0-7), who developed centre involved or imminently centre threatening DME (Steps 8 -11) at any time during the study, was not significantly different between treatment groups (ITT analysis; CMH test: p=0.174; Chi Square: p=0.300).

Patients Developing Centre-Involved or Imminently Centre Threatening DME

DME Level at Baseline	Placebo		RBX	
	n/N	%	n/N	%
0-7	**122/249**	**49.0**	**110/248**	**44.4**
0-3	53/147	36.1	50/132	37.9
4-7	69/102	67.6	60/116	51.7

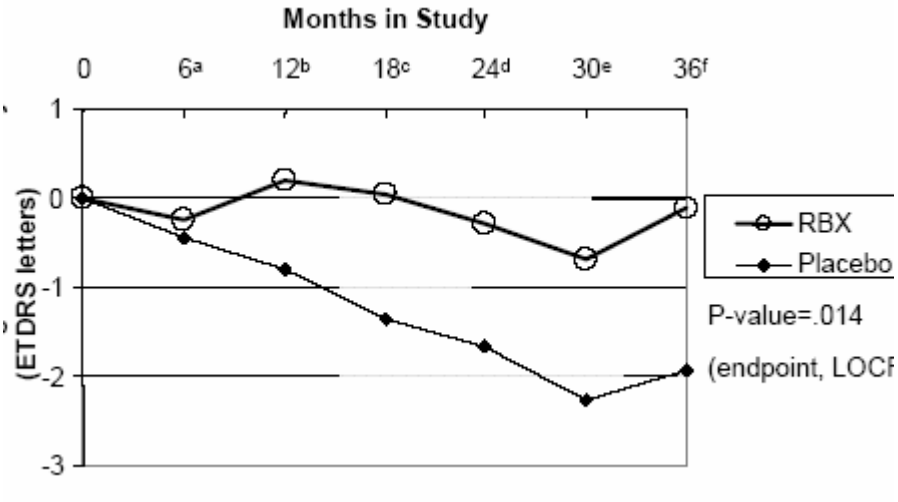
The analyses in the "completer" and "per-protocol" cohorts were also not statistically significant, The non-statistically significant Chi Square and the CMH tests demonstrated that overall the proportion of patients with DME Steps 0-7at baseline and who developed DME Steps 8 -11 during the study, was not different between the treatment groups. The stratum of patients with DME level 4-7 at baseline showed a slightly larger percentage of placebo patients developing DME level 8-11, as compared to the RBX patients. All additional analyses relative to development/ progression of DME proved

negative. These analyses do not provide any support to the primary analysis on primary endpoint. Furthermore, these negative results do not support the proposed mechanistic hypothesis of the drug effect.



Efficacy Fig 1 - Occurrence of MVL in a DR study eye: diabetic retinopathy Studies MBCM (patient level analysis)

Abbreviations: MVL = moderate visual loss of ≥15 letters in visual acuity at any visit; RBX = 32mg ruboxistaurin mesylate
a p=0.026
b p=0.023
c p=0.009
*p-value not significant



Surprisingly no improvement in quality of life was observed.

Statistical Conclusion on study MBCM

Although, the results from the primary endpoint are statistically significant the p-value is only just less than 5% (0.034). As a single pivotal study these results are not considered as providing overwhelming evidence of efficacy. As discussed previously the results from the hypothesis generating study MBBM should not be considered as strong supportive evidence of efficacy. Therefore on the basis of the results from study MBCM it is considered that insufficient evidence of efficacy for Arxxant at a daily dose of 32mg for the treatment of diabetic retinopathy in adult patients with moderate to severe non-proliferative diabetic retinopathy (NPDR) has been provided. The results for the most important secondary endpoint of diabetic macular oedema were not statistically significant (p = 0.174). Other measures of loss of vision mirrored the results of the primary endpoint. No evidence of an effect for delaying progression of diabetic retinopathy was observed.

Study MBBM

Study MBBM was a phase 3, multi-centre, randomised, double-masked, placebo controlled study. Eligible patients were enrolled to receive treatment with placebo or Arxxant at 8, 16 or 32mg once a day. The study consisted of 4 periods: a screening and randomisation period lasting up to 6 weeks, a 24-month treatment period, an extended treatment period of a further 12 months and a long-term treatment period of between 0-10 months. The primary endpoint was the time to progression of diabetic retinopathy.

The results for the primary endpoint were not statistically significant. No pair wise comparison between an Arxxant treatment group and the placebo group was statistically significant for progression of retinopathy (8mg Arxxant vs placebo, p =0.828, 16mg Arxxant vs placebo, p = 0.294, 32mg Arxxant vs placebo, p = 0.541). A Log-rank test to compare survival curves was not statistically significant (p=0.535).

Given the change in primary endpoint in the pivotal study it is relevant to show the results for this endpoint for this study.

Efficacy table 4 - Occurrence of Sustained Moderate Visual Loss (SMVL) in study MBBM

Variable	Placebo	32mg Arxxant
	N=61	N=67
SMVL	10 (16.4%)	6 (9.0%)
CMH*		0.092
Breslow-Day test		0.231
OR**		0.411
95% CI		(0.139,1.215)

* Cochran-Mantel-Haenszel general association statistics, stratified by number of diabetic retinopathy (DR) study eyes (1 versus 2) and diabetic macular oedema level (0-4 versus 5-11) in the worst DR study eye at baseline.

** Odds ratio for Arxxant versus placebo.

Statistical Conclusion on study MBBM

The results for the primary endpoint were not significant for any dose of Arxxant. Subsequent analyses of secondary endpoints were more encouraging for the effect of Arxxant on visual loss. Of the doses studied 32mg showed the most promise. As pointed out in the CPMP Scientific Advice given in 2003 the analyses of the secondary endpoints are considered to be hypothesis generating. Therefore the results for the endpoint used in the pivotal study for this study should be considered as mildly supportive evidence of efficacy. The placebo rate of SMVL is higher in this study than in the pivotal study. On those grounds alone it could be considered inappropriate to pool the results from this study with the results from the pivotal study. Of course, as the SMVL endpoint was not originally defined in study MBBM it would be inappropriate to use the results from this endpoint in this study as part of the pivotal evidence of efficacy for Arxxant.

Study MBBK

Study MBBK was a multi-centre, randomised, double-masked placebo controlled study that compared the efficacy and safety of Arxxant to placebo in patients with diabetes with mild to moderately severe non-proliferative diabetic retinopathy and macular oedema that did not involve the retina within 300 to 500 microns of the centre of the macula. The primary objective of this study was to test the hypothesis that Arxxant would delay the development of diabetic macular oedema. The results from this study did not provide evidence of efficacy. A trend for efficacy was seen in the 32mg dose of Arxxant for a secondary endpoint of progression of diabetic macular oedema. Interestingly no statistically significant, clinically relevant differences among treatment groups in progression to occurrence of moderate visual loss or sustained moderate visual loss were seen. In summary, the results from this study provide limited evidence of efficacy for Arxxant in this patient population. The 32mg daily dose offers the most promise for further evaluation.

This study is not directly relevant as it is in a different patient population to the pivotal study. The results are generally negative and therefore do not provide much, if any, supportive evidence of efficacy for the current application.

Overall clinical conclusion

The evidence for efficacy is based on a single pivotal study (MBCM) in patients with moderately severe to very severe non-proliferative diabetic retinopathy (NPDR).There were two supportive studies MBBM and MBBK. Trial MBBM was in 252diabetic patients and compared the efficacy of 3 different doses (8mg, 16mg and 32mg per day) of RBX against placebo. Study MBBK was in 686 patients with diabetic macular oedema. This study also compared the efficacy of oral doses of RBX 4mg, 16mg and 32mg daily with placebo.

The main therapeutic study MBCM recruited 685 patients (PL – 340, RBX – 345). The primary efficacy objective was to demonstrate that RBX 32mg, compared to placebo, demonstrated reduction in sustained moderate visual loss (SMVL) at 36 months. Based on ITT analysis the results did show that the proportion of patient with SMVL was less in RBX 32mg arm (Pl – 9.1%, RBX – 5.5%. The results from the primary endpoint were statistically significant (p=0.034). The results on secondary endpoint of diabetic macular oedema was not statistically significant.(p=0.174). There was no significant affect on delay in progression of diabetic retinopathy. The mean visual acuity score showed a difference of 1.83 letters in RBX 32mg group when compared to placebo after 36 months of treatment. The clinical relevance of this is questioned.

The pivotal study MBCM had numerous methodological problems (see statistical assessment above).

In conclusion, the modest efficacy shown clinically is not robust enough methodologically .In view of methodological concerns this cannot be accepted as conclusive evidence of efficacy. The clinical relevance of a difference in visual acuity score of 1.83 letters between RBX and placebo after 36 months of treatment should be discussed.

Overall Statistical Conclusion

The results from the single pivotal study MBCM are promising. However, on their own they do not provide sufficient evidence of efficacy. The only supportive evidence of efficacy comes from study MBBM. This study did not meet its primary objective. Further investigation of the secondary endpoints in this study suggested Arxxant may be efficacious for the sustained moderate visual loss endpoint. As such the results from this study can only be considered as hypothesis generating and cannot be considered as strongly supportive evidence of efficacy. The Applicant provides an argument in the Clinical Overview to justify that the results from study MBCM fulfil the requirements laid out in the CPMP Points to consider document on application with 1) meta-analyses and 2) single pivotal study (CPMP/EWP/2330/99). This argument is not supported. In particular, it is argued that the degree of statistical significance seen in this study is sufficient. However, the document states that a level of significance considerably stronger than 5% is required. The observed p-value of 0.034 is not considered to meet this requirement. Therefore, without further confirmatory evidence of efficacy from another clinical study efficacy of a daily dose of 32mg of Arxxant in this indication is not considered to have been established.

Several major methodological issues have been identified in the single pivotal study B7A-MC-MBCM. They are discussed below:

- GCP Aspects

In this single pivotal study, 31 sites were not compliant with GCP principles Because of these GCP deficiencies in the pivotal study, an inspection was requested.

- Dose Selection

The justification for the 32 mg dose is unclear: the phase 1b study (B7A-MC-MBBC) testing, relative to placebo, the 8mg BID, 16mg QD and 16mg BID doses administered for 28 days, on retinal circulation in a very limited number of diabetic patients, cannot be considered as a dose determination study for phase III. This study, considered by the Applicant as the strongest data for dose selection, involved 29 patients who had none or very mild NPDR (ETDRS DR Scale grade ≤ 20). The main pharmacodynamic effect was a marginal, not clinically relevant, reduction of retinal circulation time (RCT) with the 16 mg BID dose, in 8 patients. Furthermore, the change when adjusted for baseline value was not statistically significant (p=0.066) compared to placebo. The other doses did not show relevant effects; no dose-response could be identified. Also, the 32 mg/day were given as a BID dosage and not as a once daily dose regimen as administered in the pivotal trial. Thus, these phase I study results do not support the selection of the 32 mg OD for the pivotal trial in patients with moderately severe to very severe NPDR (ETDRS DR scale grade 47 and 53). Not only were the results of the phase Ib study not statistically significant, but the study was carried out in a very different diabetic population with much less severe diabetic retinopathy.

The two additional phase III studies B7A-MC-MBBM and B7A-MC-MBBK tested a range of daily doses of 8mg-16mg-32mg and 4mg-16mg-32mg respectively for up to 36 months. Both studies showed no significant results on the primary efficacy endpoint. The B7A-MC-MBBM study showed a trend towards a reduction of SMVL. This result was the basis for the efficacy hypothesis in the pivotal B7A-MC-MBCM study. However, the patient characteristics at entry as well as during the study, and the study endpoints were different compared to those of the pivotal study. It should also be noted that studies B7A-MC-MBBM and B7A-MC-MBBK used RBX drug substance from a batch containing higher levels of impurities than previously used in non-clinical toxicology or clinical studies. Since these higher levels of impurities had not been qualified in toxicology studies, a safety margin had not been established at RBX doses higher than 32mg once daily. Therefore, doses higher than the daily 32mg dose could not be tested. Thus the dose selection of 32 mg/day in the pivotal study, was essentially based i) on a non significant trend shown with the 32 mg dose in a different patient population of a previous dose-ranging trial, having lacked to show any dose response and ii) the obligation to use the 32 mg as the maximum dose, because of the lack of any safety margin of a higher dose. During the Scientific Advice, the CHMP requested that the choice of the dose be appropriately justified. The justification of the 32 mg/ day dose for the pivotal trial MBCM has not been adequately addressed.

- Sample Size and Power Estimation

The trial was originally 90% powered to detect a 50% reduction in the rate of DR progression compared to placebo. When the primary end-point was changed, power calculations using the new primary end-point SMVL were performed. The trial was then 80% powered (two-sided Type I error rate of 0.05 overall with 0.001 for the interim analysis) to detect a reduction of 40% in SMVL compared to placebo, assuming an event rate of 22% in the placebo group.
The assumption that 22% of placebo patients would experience SMVL over the 3-year period originated from study B7A-MC-MBBM and was obviously an overestimation in this study B7A-MC-MBCM, in which the rate mounted to only 9.1% over the 3 year period. In the B7A-MC-MBBM study, the post-hoc analysis of SMVL occurrences showed a 22 % rate at Month 30 in the placebo group. The populations of studies B7A-MC- MBCM and B7A-MC-MBBM were quite different from each other, even if patient selection criteria were similar. The baseline study eye characteristics showed that in B7A-MC-MBCM study, the majority of study eyes (60%) had an ETDRS DR severity level of 47 and 30% had a level of 53. In contrast, the B7A-MC- MBBM study recruited patients with more severe diabetic retinopathy: 45% of study eyes had ETDRS DR severity level 47 and 45 % of study eyes had level 53. The number of eyes with DME level Steps 8 through 11 (< 100µ from centre

of macula) was larger in the B7A-MC-MBCM study (35%) as compared to the B7A-MC-MBBM study (26%). In addition, in B7A-MC-MBBM study, patients had higher Hb1Ac and blood pressure levels at baseline, compared to B7A-MC-MBCM study. In conclusion, the pivotal study B7A-MC-MBCM was underpowered for the population tested. To note, the Applicant is not consistent with the level of SMVL used for the sample size calculation in B7A-MC-MBCM; some documents mention a "16.4 % SMVL" instead of 22%. No statistical analysis plan for any study, was included in the application, thus this point could not be reviewed.

- Robustness of the Study Results

The primary efficacy analysis carried out with a CMH test stratified for number of DR study eyes and DME severity, reached statistical significance (p=0.034) in the ITT population. The analysis was not statistically significant however, when carried out in either the "completers" or the "per-protocol" cohort. The analysis was not statistically significant with the unadjusted Chi Square test. These findings clearly highlight a major lack of robustness in the efficacy outcome. The significance threshold of this analysis is so tight, had one SINGLE additional event been reported in the RBX group, the "between -treatment" comparison would no longer have been statistically significant. In fact, had 13 SMVL occurrences been reported , instead of 12, in the RBX group [stratum 2 DR eyes-DME level 5-11], then the CMH test would no longer have been statistically significant (p=0.055).

This comment is to be put in the context of the very large number of patients with missing data. Indeed, the follow up of 25% of patients (n=171 of which 87 were in the RBX group) was unavailable for the SMVL assessment at Month 36 (primary efficacy endpoint). This condition can easily allow for unidentified cases of SMVL. With a categorisation method giving slightly less favorable results, the methodology used (LOCF) would no longer show statistically significant results. This demonstrates the major weakness of the study.

Furthermore, when looking at the occurrence of SMVL per stratum i.e. per number of DR eyes and DME level, it is clearly demonstrated that only data from stratum [2 DR Study Eyes, DME level 5-11], would support a difference of occurrence of SMVL in the RBX group as compared to placebo. Interestingly, this effect is not shown for the same DME level in patients with 1 DR eye (nor in any other strata).
It can be concluded that the statistical significance of the primary analysis is actually supported by only the result in the stratum [2 DR Study Eyes, DME level 5-11].As already mentioned, with only one single additional occurrence of SMVL in this stratum in the RBX group, the analysis would no longer have been significant.
In addition, the primary efficacy result is driven by the effect in women. A large treatment effect for the primary endpoint of SMVL was demonstrated in women but no treatment effect was evidenced in men. In women the occurrence of SMVL was as follows: placebo 14.8% versus RBX 3.8%; and in men: placebo 6.0% versus RBX 6.5%. This topic is more specifically addressed in section" internal consistency".
The primary efficacy result was also driven by race. A large significant effect for the primary endpoint of SMVL was demonstrated in non-Caucasians, no treatment effect was evidenced in Caucasians. In non-Caucasians, the occurrence of SMVL was as follows: placebo: 11.9% versus RBX 3.5% as compared to Caucasians: placebo: 8.4% versus RBX 6.2% (see also discussion in section "special population- effect on race).

During the Scientific Advice the CHMP clearly stated that "A single pivotal trial can be adequate only if it is particularly well designed, well carried out and analysed appropriately. Any ambiguities in the interpretation of the results that may be acceptable in a trial supported by other trials may be problematic in a single pivotal trial" and "if confirmatory evidence is provided by one single pivotal trial only, this trial would have to be exceptionally compelling, and statistical evidence considerably stronger than $p<0.05$ usually required. The trial should also show a homogeneous response across subgroups in terms of benefit and risk. If benefit is confined to one subgroup, then further studies would be necessary to adequately define the target population and confirm the subgroup benefit".

Thus, the results of theB7A-MC- MBCM study do not support the CHMP requirements. They lack robustness, rely on the distribution of one single patient, with an overall p-value of 0.034 i.e. not

compellingly stronger than the usual <0.05 threshold and are characterized by a very high rate of patient missing data. In addition, the results relative to the primary efficacy are driven essentially by 1) the subgroup of patients with [2 DR study eyes and DME level 5-11] 2) by women and 3) non Caucasians, demonstrating a lack of homogeneous response.

The two major secondary efficacy end-point analyses (termed "Gate keeping" by the Applicant were carried out to understand the potential mechanism of action of the drug on SMVL: effect on occurrence of diabetic macular oedema (DME) and progression of DR. Other very numerous secondary and exploratory analyses were carried out to provide corroboration for the primary end-point such as e.g. continuous and categorical analyses of visual acuity and health & vision-related quality of life.

The statistical analysis plan (SAP) was not provided for the pivotal study B7A-MC-MBCM (or for any other study). Therefore it could not be clearly established which secondary end-point analyses had been pre-specified in the final SAP. Some analyses seem to be post-hoc and data driven. Therefore, even if statistically significant, they do not provide compelling evidence for the drug efficacy. In addition, multiple analyses were performed on the eye level basis. Some are statistically significant others are not. It should be stressed that these analyses are statistically inappropriate, since they do not take into consideration the correlation of both eyes for those patients with 2 DR study eyes. In addition, the large numbers of analyses carried out, raise the issue of multiplicity in clinical trials and the risk of false positive conclusions. The results based on eye level analyses are inconclusive and should be considered exploratory. They cannot be supportive of any claim

The two additional phase III studies B7A-MC-MBBM and B7A-MC-MBBK are not supportive of the pivotal study for the claimed indication. Study B7A-MC-MBBM failed to demonstrate significant effects of RBX on the primary and secondary end-points of progression of DR. Furthermore, this study recruited a patient population different from the pivotal study, with more advanced NPDR, higher HbA1c and blood pressure levels. Study B7A-MC-MBBK showed no statistically significant difference between the treatment groups for the primary efficacy end-point of progression of DME. Here again, the patient population was different compared to the pivotal trial. Patients with milder NPDR and much better vision acuity were included.

- Internal Consistency of the Pivotal Study B7A-MC-MCBM

The Applicant performed subgroup analyses on occurrences of SMVL, according to baseline patient demographic characteristics, including glycaemic control (HbA1c), blood pressure, total cholesterol level and baseline concomitant treatment. Interactions were shown with baseline demographics, concurrent disease and concomitant treatment. The most relevant are as follows:

A clear gender by treatment interaction was observed. A large treatment effect for the primary end-point of SMVL was demonstrated in women but no treatment effect was evidenced in men. Overall study primary efficacy endpoint results are only driven by the effect in women. This is to be put in relation to the higher plasma drug exposure in women compared to men as shown in the pharmacokinetic studies in healthy and diabetic patients.

Also a clear ethnic drug effect was shown with a statistically significant reduction of occurrences of SMVL in Non Caucasians and no significant effect in Caucasians.

Considering confounding factors at baseline, such as systolic blood pressure, total cholesterol and body mass index, the drug effect tended to be less effective in the patient population with values below the median for these confounding factors. However the drug effect tended to be less effective in patients with HbA1c above median values (7.9%). In addition, no drug effect could be shown in patients taking insulin or statins. Apart from the HbA1c values, these results would suggest that in the study, the population fairly well cared for their diabetic disease at baseline, no drug effect could be shown or the effect was only minimal as compared to the "uncontrolled" population with values beyond the median.

- External Consistency (generalisability) of Trial Findings

The patient population recruited in the pivotal B7A-MC-MBCM study were diabetic patients with moderately severe to very severe non proliferative diabetic retinopathy with a visual acuity score of at least 45 letters in the eligible diabetic retinopathy study eye. No selection criterion was defined in the study relative to type or severity of maculopathy. Based on the 7 field 30 degree stereoscopic fundus photography technique, the graders at the centralised grading centre evaluated the severity of macular oedema according to a grading scale specific to the centre. The grading evaluation did not differentiate macular oedema between focal or diffuse oedema. In addition, since no fluorescein angiograms had been performed either at baseline or during the study, it was not possible to evaluate the ischaemic component of maculopathy. Thus, the patient population lacked accurate definition at baseline with respect to type and category of diabetic retinopathy and maculopathy. This is of importance, since subsequently the type of responders, if any, could not be clearly determined based on the information available.

The population recruited was composed essentially of type II diabetic patients. Only a very limited number of patients with type I diabetes participated in the trial. Overall, only 80 patients (11% of study participants) were included in the trial: 40 patients in the placebo group and 40 patients in the RBX group. This limited number of patients cannot by no means be representative of the type I diabetic population.

Based on the data shown above, the single pivotal trial B7A-MC-MBCM does not have a homogeneous response across subgroups, since essentially the benefit was limited to patients with [2 DR study eyes and DME level 8-11], women, non Caucasians, patients receiving neither insulin nor statins. The drug effect in the population as described above is of no clinical relevance. No clear target population could be identified. Moreover, since the type of maculopathy has not been investigated, it is not possible to identify a responder, if any, relative to specific lesions of diabetic maculopathy.

To conclude, major methodological deficiencies have been found with the single pivotal study B7A-MC-MBCM which does not comply with CHMP/EWP/2330/99 “Points to Consider on Application with one Pivotal Study”. Major deficiencies relate to the lack of robustness of results, internal and external consistency of the study results. Type I diabetics were not representative in the application nor could any target population be clearly defined. Therefore, this study does not provide compelling evidence for drug efficacy as requested by the CHMP advice.

Clinical safety

The primary safety database comprised 3521 patients with diabetes mellitus plus at least 1 complication of diabetes in 11 placebo-controlled, double-masked clinical trials. A total of 2113 patients had been exposed to RBX and 1408 had been treated with placebo. The doses ranging from 4-64 mg were used in these studies. The therapeutic dose for the proposed indication was 32mg. A total of 1396 patients were exposed to this dose, 1136 for at least 6 months, 815 for at least 1 year and 280 for at least 3 years.

The safety database was categorised as primary safety database including all patients and DR safety database including patients with diabetic retinopathy. - the Diabetic Retinopathy (DR) Database, a subset of the Primary Safety Database, combines the safety data of the two phase III studies: MBCM and MBBM, ie the pivotal trial and an additional long-term phase III study , part of present application. The DR safety database was defined by the Applicant to provide safety data that directly corresponded to the patients involved in the key efficacy analyses of DR. It is unclear however, why the Applicant has not integrated the second supportive long-term phase III study in diabetic patients which is also part of the present application (B7A-MC-MBBK), into the DR Safety Database. It would have been, indeed, of interest to have the three long-term phase III double-blind placebo trials of the present submission, integrated to enable a comparisons with the Primary Safety Database. Since this had not been done, comparisons between the 2 databases are not optimal.

The two subset ECG Databases, categorized as Primary and Secondary were intended for the ECG evaluations. These databases however have not been structured according to the ICH EI4 "Guideline on QT Evaluation". Indeed, ECG interval data should only be pooled with trials of similar rigor with regard to ECG data collection and analysis, but should not be pooled with trials using less rigorous ECG collection, in order to avoid any dilution of signal.

Additional safety assessments not integrated into the primary safety database come from the clinical pharmacology trials, clinical trials not intended for registration and the ongoing studies through data cut-off on 20 January 2006.

In the clinical study reports, the Applicant mentions that safety was analysed with the Intention-to-Treat approach. A secondary analysis with the population "on treatment" was not displayed. This point needs to be clarified by the Applicant. Indeed, if the incidence rates are calculated with the ITT approach, they are underestimated by the fact that the denominators are not accurate. This comment would be valid for the calculation of incidence rates of TEAEs, serious adverse events, deaths and laboratory findings.

A total of 78 deaths have been reported with RBX and 31 with placebo. The majority of death originate from the studies of the present application. The majority of patients died of a cardiovascular cause which is expected in this diabetic population. There does not seem to be an imbalance between the two treatment groups. With respect to the other serious adverse events, no particular previously unidentified SAEs and no striking differences in the SAE profile have been observed between the RBX and placebo groups in the Primary and in the DR safety databases.

The safety database was adequate. The number of patients exposed for more than 12 months and number of elderly subjects in the database is acceptable although number of patients >75 years of age was small.. The number of subjects exposed to long-term is in line with the ICH requirement from the safety point of view. Approximately 20% of patients in primary safety database had type I diabetes.

Exposure

Safety table 1 **Summary of Patient Exposure to Ruboxistaurin**

All Randomized Patients (N=3521)
Primary Safety Database: Placebo-Controlled Studies (Ref table 2.5.5.1)

Cumulative Months in a Study	Placebo N=1408	4/8 mg RBX N=283	16 mg RBX N=329	32 mg RBX N=1396	64 mg RBX N=105	Pooled RBX N=2113
≥6	1151	210	210	1138	68	1626
≥12	809	198	186	815	53	1252
≥24	433	171	167	437	0	775
≥36	275	112	100	280	0	492

Abbreviations: N = total number of patients in a treatment group; RBX = ruboxistaurin mesylate.

Age related exposure is shown in the table below. The number of subjects elderly subjects ≥ 65 years of age is fairly small.

Safety table 2 - Patient Exposure to Study Drug in Months by Age. All Patients Randomised to 32 mg RBX, Primary Safety Database and Diabetic Retinopathy Database (Ref Table 2.7.4.5)

Months Studies	Age group	Any Exposure	≥ 6 Months Exposure	≥ 12 Exposure
Primary Safety Database	All Ages	1396	1138	815
	< 65 Years	1160	948	675
	≥65 Years	236	190	140
	65 to 74 years	189	155	112
	≥ 75	47	35	28
DR Safety Database	All Ages	412	370	356
	< 65 Years	283	255	251
	≥ 65 years	129	115	105
	65 – 74 years	100	90	82
	≥ 75	29	25	23

DR = diabetic retinopathy, RBX = ruboxistaurin

Exposure of elderly subjects is limited for a condition which is common in this age group. The number of subjects ≥75 years of age was even smaller. This, however, is not considered a major issue provided a positive risk:benefit is established in final analysis.

The overall adverse events and the incidence are shown in the table below:

Safety table 3 - Overview of Adverse events, Number and Percentage of Subjects, All randomised subjects, Primary Safety Database and DR Safety Database (Ref table 2.5.5.2)

Adverse Event[a]	Number (%) of Patients PL	32 mg RBX	Pooled RBX
Number of Subjects			
Primary Safety Database	1408	1396	2113
DR Safety Database	401	412	536
Deaths			
Primary Safety Database	30 (2.1)	21 (1.5)	31 (1.5)
DR Safety Database	23 (5.7)	18 (4.4)	22 (4.1)
Serious adverse events			
Primary Safety Database	327 (23.2)	290 (20.8)	477 (22.6)
DR Safety Database	178 (44.4)	168 (40.8)	227 (42.4)
Discontinuations due to an adverse event			
Primary Safety Database	54 (3.8)	39 (2.8)	68 (3.2)
DR Safety Database	11 (2.7)	19 (4.6)	30 (5.6)
Treatment-emergent adverse events			
Primary Safety Database	1137 (80.8)	1118 (80.1)	1762 (83.4)
DR Safety Database	384 (95.8)	384 (93.2)	504 (94.0)
Adverse reactions[b]			
Primary Safety Database	183 (13.0)	174 (12.5)	325 (15.4)
DR Safety Database	69 (17.2)	55 (13.3)	83 (15.5)

Abbreviations; DR = diabetic retinopathy, N = number of patients; PL = placebo; RBX = ruboxistaurin.
a Patients may be counted in more than 1 category.
bAdverse reactions refer to adverse events that were considered possibly, probably, or definitely related to study drug as judged by the investigator.

Discontinuations due to Adverse Events: In the primary safety data base, discontinuations due to AEs were 2.8% in 32 mg RBX and 3.2% in pooled RBX group versus 3.8% in placebo without statistical significance. In the DR database, there were 4.6% discontinuations with 32mg RBX, 5.6% in the pooled RBX group versus 2.7% in the placebo group. The difference was not statistically significant between 32mg RBX and placebo (p=0.158) but reached significance with the pooled RBX group (p=0.035). Upon assessment of the types of AEs that led to discontinuations, the only AE in which a statistically significant difference was observed across the treatment groups was cerebrovascular accidents (p=0.048) in the DR safety base.

The key safety findings and concerns were as follows:

Immuno-suppression was studied in a pharmacodynamic setting on a very limited number of patients. No effect on immuno-suppression could be shown, but no conclusion can be drawn from these data, the number of patients being too small(8 patients exposed to the 32 mg RBX dose) . No significant imbalance was found overall relative to infection between placebo and RBX. Minor infections however, such as nasopharyngitis, sinusitis, chalazion, blepharitis were seen with a higher incidence in the RBX groups. In addition, in the primary safety data base, tooth infection was reported with a statistically significantly greater frequency and >=2% in the 32mg RBX group versus placebo(p=0.017).
Since in animal studies RBX produced effects on immune functions in mice , this issue will need close scrutiny

Cerebrovascular accident: Although no clear signal can be identified in the Primary Safety Database, in study MBBM a larger number of patients in the RBX groups experienced "cerebrovascular accidents" compared to placebo. Since "cerebrovascular accident" is a very unspecific term, it would be important to investigate whether these events are of ischemic or haemorrhagic origin and to identify all cases related to cerebral ischemia/haemorrhage in the Primary Safety Database.

Diabetic Nephropathy: the incidence of Treatment-emergent diabetic nephropathy was significantly higher in the 32 mg RBX group (p=0.031; 11, 0.8%) than the placebo group (3; 0.2%) in the Primary Safety Database. The 32-mg RBX-treated patients (versus placebo) observed a greater number of acute renal failure events in the primary (3.3% versus 3.1%) and DR safety databases (8.5% versus 8.2%). These differences were not statistically significant.
A mean change in serum creatinine over time analysis for creatinine was conducted for patients with renal-related secondary conditions at baseline. The analyses revealed no clinically significant differences between the placebo and 32 mg RBX treatment groups in the Primary and DR Safety Databases. The 64 mg RBX treatment group appeared to have a significantly higher mean change in creatinine in the Primary Safety Database. In addition, the 4/8 mg RBX treatment group appeared to have a significantly higher mean change in creatinine in the DR Safety Database.

The baseline-to-endpoint change in glomerular filtration rate (GFR) in the Primary Safety Database was not significantly different between the placebo and 32 mg RBX treatment groups (-7.27 versus -8.42 mL/min/1.73m^2, respectively; p=0.123). In the DR Safety Database, patients decreased more GFR, but the difference between the placebo and 32 mg RBX treatment groups was not significant (-11.1 versus -10.1 mL/min/1.73m^2, respectively; p=0.605). For patients with baseline GFR ≥70 ml/min/1.73m^2, the baseline-to-endpoint change in GFR in the primary safety database was not significantly different between the placebo and 32 mg RBX treatment groups (-4.22 versus -2.97 ml/min/1.73m^2, respectively; p=0.226. In the DR Safety Database, patients decreased more GFR but the difference between the placebo and 32 mg RBX treatment groups was not significant (-6.74 versus -4.95 ml/min/1.73 m^2, respectively; p=0.353).
Of note, the 4/8mg RBX grouping the DR safety database, showed a deterioration of renal function with marked mean increases of BUN and creatinine and important reductions of GFR .The reason why this group deteriorates renal function more than the other groups, including the 32 mg RBX group is not clear.
Renal impairment and renal failure are of concern, in particular in these diabetic patients who most often have already compromised renal function. The Applicant is requested to provide a comprehensive analytical review of all patients with renal events focusing not only on "diabetic nephropathy", but any renal impairment reported in the primary safety database.

Asthma: in an interim integrated analyses involving 7 studies (MBBM, MBBK, MBCC, MBCI, MBBS, MBBO, and MBBQ), a possible dose relationship between RBX intake and asthma was observed. The incidence of patients experiencing asthma-related events is higher in the RBX groups (16.2%) as compared to placebo (11.7%) in the Primary Safety Database. Since a possible effect of PCK-β on bronchi is unknown, drug-induced asthma cannot be ruled out. The Applicant has been requested to further investigate and provide a comprehensive review on these events. The incidence of cough is also higher in the RBX patients (12%) compared to placebo (9%)in the Primary Safety Database.

Liver Impairment: No biliary tree-related adverse events in the Primary or DR Safety Databases had a >=2% statistically significant incidence for the 32 mg RBX group. No statistically significant differences in the incidences of ALT and total bilirubin values were observed between the 32 mg RBX and placebo treatment groups.
However, a few patients in the RBX groups were reported with hepatic failure (1 patient: 32mg; jaundice (1 patient: 32mg), liver disorder (2 patients: 4/8mg and 32mg). The applicant is requested to provide the narratives of these patients.

Angioedema: in the Primary Safety Database**,** the occurrence of "face oedema" has been reported in 4 RBX treated patients (2 patients with 16mg and2 patients with 32mg). None was reported with placebo, in the Primary Safety Database. Since "face oedema" is evocative of Quincke angioedema, the Applicant has been requested to retrieve from the Primary safety database all reports evocative of angioedema such as "swollen tongue, tongue oedema, oedema mouth, oedema mucosal, angiooedema, face oedema", scattered over several SOCs. No further information is presently available relative to the severity of these events, the actions taken and outcome.

Skin discoloration: In the Primary Safety Database, the TEAE term "skin discoloration" encompasses a variety of skin-related TEAEs, not necessarily associated with discoloration. The rate of patients with skin discoloration -related events is higher in the RBX groups (11.3%) compared to placebo.(8.9%). No particular trend of events was seen. Of note, 10 patients with photosensitivity and 4 patients with urticaria were identified with RBX in the Primary Safety Database.No such event was reported with placebo

Effect on Glycemic Control: the investigation of this event is of paramount importance, since it is essential that the drug is neutral vis-à-vis glycaemic control and has no detrimental effect on glycemia and its biomarker haemoglogin A1c (HbA1c) long-term. The Applicant defined "Potential clinically significant (PCS) laboratory abnormalities" as follows: for HbA1c >12.0%; blood glucose: L< 50mg/dL; H> 600mg/dL.

In the Primary Safety Database, the number of patients with hyperglycemia-related events (TEAEs) was higher in the RBX groups (2.3%) compared to placebo (1.5%).

In the DR Safety Database, there was a significant higher number of patients with a PCS value in the 32 mg RBX group (27; 7.2%) compared to placebo (13; 3.6%) (p=0.034).No statistically significant differences were observed between the placebo and 32 mg RBX treatment groups in baseline-to-endpoint mean change in both non-fasting and fasting glucose levels in the DR Safety Database. This Safety Database however, does not include the phase III study MBBK, one of the longterm phase III studies of the present application. Importantly, results of study MBBK show a different pattern. For fasting plasma glucose, the difference in baseline to endpoint changes between the 32mg RBX and the placebo groups was significant (p=0.042).This was essentially the result of a mean decrease of 0.56 mmol/L in the pacebo group compared with a mean increase of 0.40 mmol/L in the 32mg RBX group. Moreover, when categorical changes in laboratory values post-baseline were considered, a significantly larger number of patients with normal fasting glucose was in the placebo group compared to the RBX 32mg group (p=0.017). Consistent with this detrimental effect on the glycemic profile, the difference in HbA1c level in baseline-to-endpoint changes between the two groups approached statistical significance (P=0.052). This was the result of a mean decrease in HbA1C levels, less important in the RBX 32mg group (0.3%) compared to placebo (0.6%).

In the Primary Safety Database, there was a higher number of patients with a PCS values for HbA1c >12% in both the 32mg RBX group (61; 4.9%), and the pooled RBX groups (98; 5.2%) compared to placebo (48; 3.8%). These results however, did not reach statistical significance (32mg RBX vs placebo p=0.203; pooled RBX vs placebo: p=0.083). In this database, the number of PCS value for blood glucose (H>6OOmg/dL) was higher in the 32mg RBX group (10;1%) than with placebo (4; 0.4%).

The change in diabetes mellitus therapy (oral hypoglycemic agents and insulin) post-baseline was assessed. No significant overall differences between all treatment groups were observed in either Primary or DR Safety Databases.

Regarding a gender effect, in the Primary Safety Database, after excluding patients with a baseline HbA1c >=12.0%, a statistically significantly higher percentage of women in the 32 mg RBX treatment group versus placebo was observed for a PCS value of HbA1c >12.0%, (7.6% and 2.8%, respectively;

p=0.003). For men, these percentages were 3.7% in the 32 mg RBX group and 4.0% in the placebo group (p=0.806).

In addition, when the PCS value was redefined for HbA1c > 11.2%, a statistically significant difference in the occurrence of the PCS value > 11.2% was noted in women with the 32 mg RBX group compared with placebo (11.0% and 6.4%, respectively; p=0.029). In men, the occurrence of the redefined PCS value mounted to 9.5% in the 32 mg RBX and 8.8%, placebo groups (p=0.550). There were no statistically significant differences for either men or women when comparing the 32 mg RBX and placebo treatment groups in the mean change from baseline to endpoint for HbA1c.

In the DR Safety Database, after excluding patients with a HbA1c >=12.0% at baseline, a statistically significantly higher percentage of women with an HbA1c >=12.0% in the 32 mg RBX treatment group versus placebo (12.9% and 3.2%, respectively; p=0.006) were seen over time. For men, these percentages were 4.5% in the 32 mg RBX group and 3.7% in the placebo group (p=0.820). There were no statistically significant differences when mean changes from baseline to end-point were considered. Analyses of other measures of glucose levels or glycemic control in the DR Safety Database demonstrated a statistically significant difference in fasting glucose in the baseline-to-endpoint analysis for men between the 32 mg RBX and placebo treatment groups (0.26 and -2.15, respectively; p=0.043). For women, these values were 0.07 in the 32 mg RBX treatment group and -0.35 in the placebo treatment group (p=0.822).

To conclude, as evidenced in the Primary and DR Safety Databases, analyses of the occurrence of HbA1c values that met PCS criteria (>12%) suggest a detrimental influence of RBX on glycemic control in diabetic patients. Individual results of study MBBK which was not pooled in the DR Safety Database showed a consistent adverse signal on glycemic control in the 32 mg RBX patient group compared to placebo. Furthermore, this detrimental effect was more pronounced in women compared to men, which is consistent with the known higher drug exposure in women. This safety signal is confounded when analyses on mean changes from baseline to end point are performed. These analyses are not reassuring relative to lack of impact of RBX on glycaemic control, as was stated by the Applicant. The analyses do not address this very important issue for diabetic patients. The Scientific Advice had specifically requested that this issue be addressed in depth.
No effect on serum total cholesterol was shown. Many confounding factors such as e.g. new cholesterol-lowering treatments did not allow for any conclusive results.

Hypothyroidism: in rat studies, moderate accumulation of radiocarbon (approximately 7-fold) was observed in the thyroid. The rate of patients with hypothyroidism-related TEAEs was higher in the RBX groups (2.6%) compared to placebo (1.6%) in the Primary Safety Database (p= 0.037). Although the Applicant does not consider this a safety concern, the Applicant should further investigate and provide a comprehensive review of these reports, so that a more conclusive medical evaluation can be made.

QT prolongation/Risk of Ventricular arrhythmia
Ruboxistaurin and N-desmethyl ruboxistaurin have been shown to block hERG potassium channel in preclinical studies. An integrated statistical analysis of ECGs in 6 clinical pharmacology studies in healthy subjects did not show any effect of RBX on QT. This however could be questioned, as the basis of collection of ECG data in these trials is not detailed.

A thorough QT study, in line with ICH E14 was conducted by the applicant (Study B7A-LC-MBDT) with 256 mg Ruboxistaurin, a dose much higher than the recommended dose. The study was a randomised, double-masked, placebo- and active – (oral moxifloxicin therapeutic dose of 400 mg), controlled, three-way, crossover study in 86 healthy subjects (46 men, 40 women) aged 18 to 70 years. The largest time-matched mean effect occurred at 6 hours with a mean increase in QTc relative to placebo of 6.10 msec (upper limit of one-sided 95% CI = 7.74), allegedly indicating no clinically relevant increase in the QT interval adjusted for the RR interval according to corrected formula. Although it is claimed that the thorough QT study was negative, it should be considered positive, since RBX was associated with a mean QTc change of >5msec, 6 hours post-dose, and close to the

prolongation observed with the positive control moxifloxicin. A gender effect was observed with women having a significantly greater QT interval prolongation.

When mean changes from baseline to maximum QT prolongation were analysed in the Primary ECG Safety Database, an increase of 11 ms QTcB and QTcF prolongations were shown, with doses of 4/8 and 16mg. With the 32mg dose, the mean prolongation was only 6.5ms but statistically significant (p=0.021). This apparent discrepancy in magnitude between groups, might be explained by the shorter term studies with more frequent ECGs for the 4/8 mg and 16mg groups. In the short term ECG database 8(2.3%) patients were experiencing an "abnormal change" from baseline to end-point (change in QTc >=30 ms and <60ms) in the placebo group compared to 23(6.5%) in the 32mg RBX group.

In the Primary Safety Database, there was no increase relative to placebo in arrhythmia-related TEAEs. One case of Torsade de Pointes (TdP) however, was reported with the 32mg RBX dose in a 70-year-old women.

Risk of AV block: the TEAE data related to AV block is suggestive of a significant effect of RBX on AV conduction. Since patients with 2nd and greater AV block were excluded from the study protocols and the subsequent data analyses excluded patients with abnormal values, it is not possible to fully evaluate the effect of RBX on AV conduction. Further investigation has been requested to the Applicant

There is clear indication to suggest that RBX prolongs QT interval. This requires that the product is contraindicated in congenital or drug-induced QT prolongation. This in addition to evidence of 1st degree A-V block raises serious concern regarding risk:benefit of the product. Possibility of PKC inhibition leading to down regulation of potassium and sodium channels should be addressed.

Diabetic retinopathy and consequential effect on vision is a slow process and takes many years to develop. The consequence of QT prolongation is immediate and life-threatening. Phase 2 and 3 studies also show an increase of 2.4 msec (placebo subtracted value).

The applicant has put undue emphasis on 10 msec as the safety cut off level for QTc. This is not so. The criteria of 10 msec in ICH E 14 document was intended to define the upper limit beyond which there will be clinical concern. When the confidence limit is narrow but the baseline is well clear of placebo, it is possible that the upper limit is well within 10 msec but there may still be concern regarding QT prolongation (ICH E 14 Q & A document).

With clear indication of hERG blockade in preclinical data, prolongation of QTc in thorough QT study and evidence of 1st degree A-V block and QT prolongation in primary safety database, there is a concern regarding this issue. The applicant should address this in terms of clinical data. Positivity or negativity of thorough QT study does not in itself signal safety of the product but dictates the need for further evaluation of QT analysis and safety analysis in phase III study.

Cataract Formation: cataractous changes of the ocular lens in the repeat-dose dog studies were considered by the Applicant, to be the most serious finding in nonclinical toxicology studies.The Applicant considers these findings species specific

Although Cataract scores were not significantly different between placebo and the 32 mg dose in the DR studies , this result is inconclusive: for the time being too few patients have been followed up for a too small duration. In the Primary Safety Database a statistically significant higher frequency of posterior capsule opacification was reported in the 32 mg RBX group (7; 0.5%) as compared to placebo (1; 0.1%) (p=0.033). The Applicant is requested to further investigate and provide a detailed report on the patients having experienced cataract during RBX treatment

CPK
There is a concern regarding rise in CPK with ruboxistaurin. The applicant should provide further reassurance regarding this.

In clinical pharmacology studies, isolated incidences of abnormally elevated serum CPK following RBX or placebo administration were observed in 12 subjects (RBX: 11, placebo: 1). Of the 11 RBX subjects, 7 experienced small increases in CPK that seemed to be associated with assay and biological variability. RBX effect could not be ruled out on the remaining 4 subjects, 1 of whom was discontinued from the study by the investigator because the subject reported a mild case of skeletal muscle injury. None of the CPK results were linked to renal damage.

In addition, in the clinical pharmacology studies there was a higher incidence of the adverse event myalgia in placebo subjects (4/111) than in RBX subjects (2/313) reported following 72 hours of study drug administration.

In the Primary Safety Database, no statistically significant difference was observed between treatment groups for patients who experienced an increase in CPK >=3 times the ULN (placebo: 7/1408, 0.5% and 32 mg RBX: 5/1396; 0.4%; p=0.774).

In the Primary Safety Database, a review of TEAE reports "blood CPK increased" revealed a statistically significant difference between the placebo and 32 mg RBX groups (placebo: 4/1408 [0.3%], 32 mg RBX: 14/1396 [1.0%]; p=0.017). When muscle-related TEAE terms were analysed in the Primary Safety Database, no statistically significant difference was observed in the frequency of the events between the placebo and 32 mg RBX treatment groups (placebo: 52 [3.7%], 32 mg RBX: 66 [4.7%]). Women consistently reported TEAEs more often than males in both the placebo and 32 mg RBX groups in the Primary Safety Database. Women (n=21, 5.1%) reported more cases of myalgia than males (n=23, 2.3%) in the 32 mg RBX treatment group (p=0.006). Creatinine Phosphokinase increase is an identified drug related event. In order to avoid complications such as rhabdomyolysis and renal impairment, it will need close attention.

As regards ophthalmic safety, posterior capsular opacification (0.5%) has been identified as a potential safety risk and has been addressed in the risk management plan. Chalazion (0.4%) is reported more frequently with RBX but this is not considered a major health issue and has been included in the SPC. Other events identified were dyspepsia (4.3%), skin discolouration (0.5%), micturition urgency (0.4%) and CPK increase (1%). At present it is not possible to determine the exact frequency and severity of these events dur to fairly limited number of patients exposed. The applicant is also requested to provide a review of the incidence of events according to the ICH recommendations.

There is a suggestion that RBX therapy could cause hypothyroidism. It is difficult to come to any conclusion based on the analysis provided. The data related to this should be re-analysed.

The laboratory data show increase in non-fasting blood sugar and HbA1C in RBX 32mg group compared to placebo. This is a matter of concern, particularly in view of the fact that effective control of diabetes in itself delays progression of diabetic retinopathy. Assessor does not concur with the clinical expert's conclusion in the clinical overview that ruboxistaurin does not affect the glycaemic control. There is a clear difference between the placebo and the RBX 32mg as well as pooled group with non-fasting blood sugars and HbA1C levels in RBX group. This is in spite of the fact that the cut off level for potentially clinically significant HbA1c was taken at 12% which is rather generous. In clinical practice that would be a matter of concern. Further reassurance is required on this point.

The possibility causal association of RBX 32 mg to increased CPK could not be ruled out. There were no safety data in hepatically and renally impaired patients. There were some safety concerns particularly detrimental effects on the kidneys with a higher occurrence of renal impairment.

The QT issue is considered a major public health concern

Death in the majority of reports was due to a cardiovascular cause, expected in the diabetic population studied in the application. There did not seem to be a difference in the occurrence of deaths between RBX and placebo, with the exception of cerebrovascular accident. A comprehensive review of all cardiovascular reports is necessary to get a clear picture of the impact, if any, of RBX on the cardiovascular system.

Although the applicant has submitted a risk management plan the concern here is the balance between benefit for diabetic retinopathy which is a slow developing process and the sudden risk associated with conditions related to QT prolongation.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

The benefit:risk of the product at the time of assessment was considered negative. The modest benefit based on the primary endpoint could not be considered robust in view of methodological issues. The main efficacy data of this submission were provided by one single pivotal trial carried out in diabetic patients with moderately severe to severe non- proliferative diabetic retinopathy (NPDR). The selection of the 32 mg RBX dose for this pivotal trial was not supported by an adequate data base and rationale. The primary efficacy analysis showed that RBX reduced the proportion of sustained moderate vision loss (SMVL) compared to placebo with a marginal statistical significance. Statistical significance was only confined to the ITT population and not in the completers or per-protocol cohorts. In addition to this lack of robustness of the pivotal study, there was a non homogenous drug response across important patient subgroups. The drug effect was demonstrated in only one patient stratum of NPDR(2 DR Study Eyes, DME level 5-11). Moreover, the primary efficacy result was driven by women and non-caucasian populations. No significant effect could be shown in men, Caucasians and patients on insulin or statins. The patient population recruited in the pivotal trial lacked accurate definition at baseline with respect to type and category of diabetic retinopathy and maculopathy. Therefore, the potential type of responder or target population could not be clearly determined based on the available clinical information. Only 40 patients with type I diabetes were randomised on RBX . This very limited number of type I diabetic patients does not allow assessment of drug effect in this patient population whose maculopathy is not identical to that of type II diabetic patients. The pivotal study and the two additional phase III study provided in the application, failed to demonstrate any significant drug effect on DME and progression of diabetic retinopathy.
In overall, there was no compelling evidence for drug efficacy based on the current clinical data.

There were a number of concerns related to safety. The QTc related issues were considered major safety concern. The development of diabetic retinopathy is a slow process and takes many years while adverse implications of drug prolonging QT is immediate (VT and sudden death). RBX has shown strong blockade of the potassium ion current. In addition there is evidence of an increase in A-V block.

This, in addition to other safety concerns including posterior lens opacity, raised CPK, hypothyrodism and suggestion of increased blood sugar and HbA1c, cerebro-vascular accidents, diabetic nephropathy and phototoxicity made the benefit:risk negative. These needed further investigation.

A marketing authorisation was not recommended at that stage.