

Study No: P1A114919	
Title : An open label, randomized, crossover study to assess the relative bioavailability of different 2mg formulations of GSK2018682 (S1P1 agonist) in healthy volunteers	
Rationale: GSK2018682 is a potent and selective agonist for the sphingosine-1-phosphate receptor subtype 1 (S1P1) with the potential to be an effective treatment for multiple sclerosis (MS). A tablet formulation is desired for progression into future clinical safety and efficacy studies as the existing capsule formulation (CD2) is not suited to large scale manufacture. Therefore, it was important to assess the relative bioavailability of three oral formulations of GSK2018682, including CD2 capsule, CD3 non-micronised tablet and CD3 micronised tablet. The effect of food on the pharmacokinetics of the CD3 non-micronised tablet was explored as it is the most likely to be used in a future Phase II study. A 2 mg dose was used in the study based on the following reasons: 1) PK can be well quantified at this dose; 2) significant (in excess of 100%) changes in PK parameters will be detectable; 3) PK will be below level of quantification by 7 days after dosing; 4) S1P1-mediated PD effects on lymphocytes and heart rate have not been detected; 5) there is at least a 2 fold cover to exposures that do have PD effects on lymphocytes and heart rate; 6) it is very likely to be a dose used in a future Phase II study (given the predicted accumulation ratio and exposure at steady state	
Phase: I	
Study Period: 22 Dec 2010 to 15 Feb 2011	
Study Design: This study investigated single doses of GSK2018682 in a cohort of 16 healthy male subjects according to a randomized, open-label, 4 way crossover design. The effect of food on the pharmacokinetics of the CD3 tablet formulation will be explored	
Centres: Q-Pharm Pty Limited Clive Berghofer Cancer Research Centre (CBCRC) Level D, 300 C Herston Road Herston, Queensland, 4006, Australia	
Indication: multiple sclerosis	
Treatment: NA	
Objectives: Safety and Tolerability Objectives -Investigation of the safety and tolerability of different oral formulations of GSK2018682 in healthy volunteers Pharmacokinetic Objectives - Assessment of the pharmacokinetics of different oral formulations of GSK2018682 in healthy volunteers - Investigation of the effect of food on the pharmacokinetic parameters of the CD3 non-micronised tablet formulation of GSK2018682 Pharmacodynamic Objectives - Evaluation of the effect of different oral formulations of GSK2018682 on lymphocytes in healthy volunteers	
Statistical Methods: The pharmacokinetic parameters C _{max} , t _{max} , AUC(0-t), AUC (0-∞), (t _{1/2}) and CL/F were derived from the plasma GSK2018682 concentration data. In addition, a formal statistical analysis of C _{max} , AUC(0-t) and AUC (0-∞) was conducted to assess the relative bioavailability of the formulations along with a food effect comparison using a mixed model analysis of variance (ANOVA) with treatment and period as a fixed effects and subject as a random effect. Following loge-transformation, the primary endpoints, AUC(0-inf), AUC (0-t) and C _{max} were separately analysed using a mixed effects model with fixed effect terms for period and treatment. Subject was treated as a random effect in the model. Point estimates and their associated 90% confidence intervals were constructed for the following ratios by back transforming the difference between the treatment least squares means (LS-means) and the associated 90% confidence interval for the following: CD3 Non-micronised tablet (B) – CD2 capsule (A) [B-A] CD3 Micronised tablet (C) – CD2 capsule (A) [C-A] CD3 Micronised tablet (C) - CD3 Non-micronised tablet (B) [C-B] CD3 Non-micronised tablet under fed conditions (D) – CD3 Non-micronised tablet (B) [D-B] Pharmacodynamic data was summarised and graphically presented.	
Study Population: healthy volunteers	
Number of Subjects:	All subjects
Planned N	16
Dosed N	16
Completed n (%)	14

Total Number Subjects Withdrawn N (%)	2
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	NA
Withdrawn for Other Reasons n (%)	2 (12.5) (One met the stopping safety criterion for heart rate; one was due to personal commitments)
Demographics	All subjects
N (ITT)	16
Females: Males	0:16
Mean Age in Years (sd)	25 (5.05)
Mean Weight in Kg (sd)	79.18 (9.10)
White n (%)	15 (93.75)
Pharmacokinetics (PK) Endpoint(s):	
<ul style="list-style-type: none"> • Peak blood concentration (C_{max}) • Time of peak blood concentration (t_{max}) • Area under the blood concentration-time curve up to the last quantifiable time point (AUC(0-t)) and extrapolated to infinite time (AUC (0-∞) • Terminal half-life (t_{1/2}) • Apparent oral clearance (CL/F) 	
Pharmacodynamics (PD) Endpoint(s):	
<ul style="list-style-type: none"> • Reduction from baseline in lymphocyte counts 	
Safety results:	
<p>The period for the collection of 'on therapy' AEs and SAEs was from the start date of study medication but not later than the follow-up visit.</p> <p>No deaths or serious AEs were reported. No drug-related AEs were reported. The most frequently reported AE irrespective of causality was headache, which occurred in 4 subjects (25%). Heart rate reductions were observed between 1 hour and 4 hour post dosing. The magnitude of heart rate reduction was less in the subjects administered with the CD3 non-micronised tablet under fed conditions.</p>	
Adverse Events:	All subjects
N (ITT)	16
No. subjects with AEs n (%)	4 (25%)
Most Frequent AEs	headache
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:	
No serious AEs were reported.	

Conclusions

All adverse events were classified as mild and moderate in intensity. The most frequently reported AE irrespective of causality was headache, which occurred in 4 subjects. Reductions of heart rate were observed between 1 hour and 4 hour post dosing. The magnitude of heart rate reduction was less in the subjects administered with the CD3 non-micronised tablet under fed conditions. The GSK2018682 pharmacokinetic parameters including AUC(0-inf), AUC (0-t) and C_{max} did not differ between the CD2 capsule, CD3 non-micronised tablet or the CD3 micronised tablet, with the exception of C_{max} for CD3 non-micronised tablet which was 30% higher than C_{max} for the CD2 capsule. There was no food effect observed with the CD3 non-micronised tablet for the pharmacokinetic parameters AUC(0-inf), AUC (0-t) and C_{max}.