The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Darapladib

Study Number: DM2115403

Title: A phase 2, multi-national, multi-centre, double masked, randomized, placebo controlled, parallel-group study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of darapladib administered for 3 months to adult subjects with diabetic macular edema with centre involvement

Rationale: The purpose of this study was to characterize the systemic and ocular safety and tolerability, pharmacokinetics (PK), and efficacy/pharmacodynamics of 3 months of repeat administration of oral darapladib in subjects with diabetic macular edema (DME) with centre involvement.

Phase: II

Study Period: 27 February 2012 to 21 February 2013

Study Design: This was a randomized, double-masked, placebo-controlled, parallel-group study of repeat oral administration of 160 mg darapladib once daily for 3 months in adult subjects with DME with centre involvement. Subjects (N=54) were randomized to receive darapladib:placebo in a 2:1 ratio, respectively. Subjects were stratified based on baseline visual acuity for balance between groups: >50 letters and ≤50 letters. Eligibility for each subject was based only on one eye, which was designated as the study eye. If both eyes qualified for the study, the study eye was determined by the Investigator. The study eye was examined for changes over the life of the study. As this investigational treatment is systemic, the fellow eye was examined in tandem to provide additional safety data.

Centres: This study was conducted at 16 centres in 5 countries in Europe and Australia.

Indication: Diabetic macular edema

Treatment: Subjects were assigned to 160 mg of darapladib or matched placebo (2:1 ratio) in accordance with the randomization schedule generated by GSK, prior to the start of the study, using validated internal software.

Objectives: The primary objective was to determine the effect of darapladib administered as oral once daily doses for 3 months on best-corrected visual acuity (BCVA) and spectral domain optical coherence tomography (SD-OCT) centre subfield of the study eye in adult subjects with centre-involved DME.

Primary Endpoints: Mean change from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA and SD-OCT centre subfield retinal thickness in the study eye.

Secondary Endpoints:

- Changes in retinal anatomy as assessed by fluorescein angiography (leakage area), fundus photography (retinal thickening area) and SD-OCT (macular volume, subretinal fluid, intraretinal cysts) in the study eye
- Safety and tolerability assessed by complete ophthalmic examination, visual acuity, vital sign measures (heart rate and blood pressure), clinical laboratory tests, clinical monitoring and adverse event (AE) reporting
- Plasma PK parameters (Cmax, $AUC_{0-\tau}$, apparent volume of distribution and apparent clearance, etc) of darapladib as data permitted

Statistical Methods:

Analysis Populations:

- Efficacy/Pharmacodynamic Population: any randomized subjects who received at least one month of study medication and completed Day 30 visit assessments.
- Safety Population: any randomized subjects who received at least one dose of study medication.
- Pharmacokinetic Population: subjects in the safety population for whom a pharmacokinetic sample was obtained and analysed.

Efficacy and Pharmacodynamic (PD) analysis: For primary analysis, the change from baseline in BCVA and OCT central subfield and center point at month 3 for darapladib arm were analyzed by Bayesian probability model. Normal distributions were assumed. Mildly informative prior distributions for the mean and standard deviation were assumed. The posterior probabilities of month 3 mean BCVA change greater than 0 letter, less than 4 letters, and greater than 6 letters and mean OCT central subfield change, center point change less than 65 μm and greater than 120 μm were computed at interim analyses 1 and 2 when 10 subjects and 20 subjects in darapladib arm completed 3 months treatment of darapladib and at final reporting when all subjects completed the study. For secondary analysis, the change from baseline in BCVA and SD-OCT endpoints of center point, central subfield and total volume were separately analyzed using mixed model repeated measures (MMRM) method fitting visit, treatment, and visit by treatment interaction as fixed effects, baseline data as covariate. Within each subject, the observations across visits

were treated as repeated measures. The variance/covariance for observations across visits within a subject was assumed to be the same for all subjects and have an unspecified (UN) structure. Point estimates with 95% confidence intervals (CIs) were provided by visit for darapladib arm, placebo arm and the difference darapladib – placebo.

Pharmacodynamic analysis: For fluorescein angiography (FA) and fundus photography (FP) data, no formal statistical analyses were performed. These FA and FP data were descriptively summarized.

Safety analysis: No formal statistical analyses were performed. These safety data were descriptively summarized.

Pharmacokinetic (PK) analysis: No formal statistical analyses for PK concentration data or PK parameters were performed. These PK data were descriptively summarized.

Study Population:

- Healthy male and female (non-childbearing potential) subjects ≥18 years of age
- Diagnosis of diabetes mellitus (type 1 or type 2) with HbA1c ≤10% at screening
- Confirmation of DME in the study eye by investigator-determined fluorescein angiography (FA)
- Retinal thickening (DME) involving the centre of the fovea in the study eye as defined by investigator-determined SD-OCT central subfield thickness > 330 μm for Heidelberg Spectralis and >310 μm for Zeiss Cirrus. If both eyes were eligible, the eye with the greater OCT centre subfield score was selected as the study eye.
- BCVA score of 78-24 letters (Snellen equivalent ~20/32 to 20/320) in the study eye

Subject Disposition

Number of Subjects	**Placebo**	**Darapladib 160 mg QD**	**Total**
Number of subjects randomized, N:	18	36	54
Number of subjects completed as planned, n (%):	16 (89%)	36 (100%)	52 (96%)
Number of subjects completed Day 90 visit	17 (94%)	36 (100%)	53 (98%)
Number of subjects completed Day 90 visit without rescue	14 (78%)	34 (94%)	48 (89%)
Number of subjects withdrawn (any reason), n (%):	2 (11%)	0	2 (4%)
Number of subjects rescued [1]	3 (17%)	2 (6%)	5 (9%)
Number of subjects rescued and withdrawn	0	0	0
Number of subjects withdrawn for AE, n (%):	1 (6%)	0	1 (2%)
Number of subjects withdrawn for SAE, n (%):	1 (6%)	0	1 (2%)
Reasons for subject withdrawal, n (%)			
Adverse events	1 (6%)	0	1 (2%)
Lost to follow-up	1 (6%)	0	1 (2%)

1. Rescue was defined as receiving rescue medication (intravitreal anti-VEGF) in the study eye before assessments of Day 90 visit.

Demographics

Number of Subjects	**Placebo N=18**	**Darapladib 160 mg QD N=36**
Age in Years, Mean (Range)	64.8 (51 – 79)	63.6 (44 – 80)
Sex, n (%)		
Female:	6 (33%)	11 (31%)
Male:	12 (67%)	25 (69%)
BMI,(kg/m^2) Mean (Range)	27.4 (21 – 36)	30.2 (19 – 42)
Height, (cm) (Mean and Range)	166.9 (153 – 180)	170.3 (140 – 191)
Weight, (kg) (Mean and Range)	76.9 (64 – 93)	87.7 (62 – 152)

Ethnicity, n (%)		
Hispanic or Latino:	0	1 (3%)
Not Hispanic or Latino:	18 (100%)	35 (97%)
Race, n (%)		
White	17 (94%)	33 (92%)
Asian	1 (6%)	2 (6%)

Primary Efficacy Results:

Summary of Bayesian Analysis Results for BCVA and SD-OCT Endpoints at Day 90—Study Eyes

	OC[1]
N	34
Mean BCVA Change	4.25
95% Credible Interval	(2.39, 6.15)
Probability (BCVA<4 | data)	0.3980
Probability (BCVA>6 | data)	0.0347
Center Point	
N	33
Mean Decrease	83.33
95% Credible Interval	(45.60, 121.2)
Probability(decrease <65 | data)	0.1686
Probability(decrease >120 | data)	0.0290
Central Subfield	
N	33
Mean Decrease	64.33
95% Credible Interval	(33.66, 94.76)
Probability(decrease <65 | data)	0.5164
Probability(decrease >120 | data)	0.0004

[1] OC: Observed case data. For these data, a missing assessment at any scheduled visit was not imputed or included in data analysis. If a subject received a rescue therapy, the data after rescue therapy was not included.

Summary of Statistical Analysis of Change from Baseline in SD-OCT Endpoints at Day 90 Visit—Study Eyes (OC[1])

	Darapladib			**Placebo**			**Difference**	
Endpoint	**N**	**LS mean**	**95% CI**	**N**	**LS mean**	**95% CI**	**LS mean**	**95% CI**
BCVA	34	4.06	(2.31, 5.80)	14	1.67	(-0.99, 4.34)	2.38	(-0.81, 5.57)
SD-OCT Endpoints								
Central Subfield (µm)	33	-57.0	(-84.1, -29.9)	14	-34.1	(-75.0, 6.8)	-22.9	(-72.1, 26.2)
Center Point (µm)	33	-74.3	(-110.5, -38.1)	14	-58.5	(-112.9, -4.1)	-15.8	(-81.1, 49.6)

[1] OC: Observed case data. For these data, a missing assessment at any scheduled visit was not imputed or included in data analysis. If a subject received a rescue therapy, the data after rescue therapy was not included.

Pharmacokinetic Results:

Summary of Pharmacokinetic Parameters in DME Subjects Following Repeat Once Daily Dosing of 160 mg Darapladib

	AUC(0-τ) (ng.h/mL)	**Cmax (ng/mL)**	**Tmax (hour)**
N=36	555.6	39.2	4

	(56.9%) Range: (187-1867)	(61.5%) Range: (8.12-133)	Range: (0-8)

AUC and Cmax are presented as geometric mean (CV%) and range
Tmax is presented as median and range

Safety Results:

Summary of Number of Subjects with Ocular Adverse Events in more than One Subject in any Treatment Group—Both Eyes (Safety Population)

Adverse Events **Preferred Term, n (%)**	**Placebo** **N=18**	**Darapladib** **160 mg QD** **N=36**
Study Eye		
Number of subjects with any ocular AE	4 (22%)	8 (22%)
Diabetic retinal edema	2 (11%)	2 (6%)
Eye pain	2 (11%)	0
Macular edema	1 (6%)	1 (3%)
Fellow Eye		
Number of subjects with any ocular AE	1 (6%)	6 (17%)

Summary of Number of Subjects with Non-Ocular Adverse Events in more than One Subject in any Treatment Group—(Safety Population)

Adverse Events **Preferred Term, n (%)**	**Placebo** **N=18**	**Darapladib** **160 mg QD** **N=36**
Number of subjects with any non-ocular AE	9 (50%)	14 (39%)
Influenza	1 (6%)	2 (6%)
Nasopharyngitis	1 (6%)	2 (6%)
Urinary tract infection	1 (6%)	2 (6%)
Diarrhoea	1 (6%)	1 (3%)
Blood creatinine increased	0	2 (6%)
Vomiting	2 (11%)	0
Blood urea increased	0	2 (6%)

Serious Adverse Events - No fatal SAEs were reported during the study. One subject on darapladib was reported with a non-fatal SAE of myocardial infarction and remained on investigational product and completed the study. One subject on placebo was reported with a non-fatal SAE of severe diarrheoa and was withdrawn from the study.

Conclusion:

- Bayesian analysis results showed a 60.2% probability of mean BCVA change from baseline ≥ 4 letters and an 83.14% probability of mean SD-OCT center point decrease from baseline ≥ 65µm at Day 90 visit for darapladib arm given study eye OC data.
- Administration of darapladib 160 mg for 3 months resulted in statistically significant improvements from baseline at Day 90 in BCVA, SD-OCT center subfield and center point.
- PK parameters in DME subjects (n=36) showed that the geometric mean of AUC(0-24) and Cmax were 555.6 ng.h/mL (CV%= 56.9%) and 39.2 ng/mL (CV% = 61.9%), respectively.
- Administration of darapladib 160 mg for 3 months was safe and well tolerated.