TITLE PAGE

Protocol Title: Phase I, Open-Label, Multi-Center Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of GSK2798745 after 28 Day Repeat Oral Administration to Adults with Diabetic Macular Edema

Protocol Number: 212669/Amendment 05

Compound Number: GSK2798745

Study Phase: Phase 1

Short Title: Study 212669: A Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK2798745 in Participants with Diabetic Macular Edema

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information: In the Study Reference Manual (SRM)

Regulatory Agency Identifying Number(s):

Registry	**ID**
United States	154168

Approval Date: 02-Feb-2022

SPONSOR SIGNATORY:

Protocol Title: Phase I, Open-Label, Multi-Center Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of GSK2798745 after 28 Day Repeat Oral Administration to Adults with Diabetic Macular Edema

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	Date

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Group Leader
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order**.**		
Document	**Date**	**DNG Number**
Amendment 05	*02-Feb-2022*	*TMF-14377129*
Amendment 04	*11-NOV-2021*	*TMF- 14073254*
Amendment 03	*24-MAR-2021*	*TMF-11874499*
Amendment 02	*28-OCT-2020*	*2019N404030_02*
Amendment 01	*11-MAY-2020*	*2019N404030_01*
Original Protocol	*19 SEP 2019*	*2019N404030_00*

Amendment 05 02-Feb-2022

Overall Rationale for the Amendment: Protocol Amendment 05 is implementing modifications to the Inclusion and Exclusion criteria and study assessments, including removal study visit Day 7. The majority of changes focus on relaxing criteria to ease the study burden on the participant during the ongoing COVID-19 pandemic. The other changes clarify or correct the wording in the risk:benefit table and have Inclusion / Exclusion changes based on new modelling and for clarification.

Where the Amendment Applies:

This protocol Amendment 5 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
1.3.1: 28 Day – 4 Week Treatment Period SoA	**Previous Text:** Current SoA **Revised Text:** Addition of the following footnote to Screening column: Any laboratory or ECG assessments completed within the 28 days prior to the start of screening may be used to determine eligibility. These assessments must not have been collected for the purposes of this study, but for the routine care of the participant. Any assessments with abnormal values may be re-tested within the screening window and post-consent collection would be considered the first assessment of that lab/ECG. Additional guidance is contained within the SRM.	Feedback from Investigators is that through routine diabetic care, participants may have had recent lab or ECG assessments. To help decrease the need to go out in public for clinical assessments, during continued COVID pandemic we are looking to use incidentally collected labs or ECG within the 28 days prior to screening in lieu of collecting at screening. This is only if the assessments were collected as part of routine care and independent of study considerations. Note that the allowed assessments are also being collected within the study itself for Baseline.

Section # and Name	Description of Change	Brief Rationale
1.3.1: 28 Day – 4 Week Treatment Period SoA	Changing Visit 3, Day 7 from all participants to only the intensive PK Subset **Previous Text:** Current SoA **Revised Text:** Addition of the following footnote to Visit 3, Day 7: *Day 7 for Participants in the PK Subset only. Removed the "X" for PK – Trough Sampling and greying out the box for Visit 3, Day 7 Column.	Based on the continued COVID pandemic and subsequent restrictions and lockdowns, removal of this visit for most study participants will decrease the need to go out in public to get to the clinic for assessments. Prior dosing in completed clinical studies have been through 7 days in Heart Failure and Chronic Cough patients and through 14 days in healthy subjects. No clinical safety findings of concern have been noted.
5.3.2: Caffeine, Alcohol and Tobacco	**Previous Text:** Participants participating in the PK subset and for all participants on Day 7 and Day 28 will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 8 hours before the start of dosing until after collection of the final pharmacokinetic sample **Revised Text:** Participants participating in the PK subset on Day 7 and Day 28 and for all participants on Day 28 will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 8 hours before the start of dosing until after collection of the final pharmacokinetic sample	For general participants, deferring 12-Lead ECG, CSSRS, VS, Clinical Chemistry, Hematology & UA (including Cardiac Troponin, CPK), Compliance Check for Study Medication, AE-SAE Assessments, and Concomitant Medical Assessment should not increase the risk to the patient relative to the risk of going out in public during the continued pandemic. Evaluation of pharmacokinetics (Trough Sampling) is being done on Day 28. Removal of Day 7 pharmacokinetic sampling will not have significant impact on data evaluation. Visit 3, Day 7 will remain for participants in the Intensive PK Subset as detailed in Section 1.3.2 PK Subset - Intensive PK Sampling Day 7 and Day 28 SoA

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	**Previous Text:** 7. Body weight ≥50 kg and body mass index (BMI) within the range 18 to 40 kg/m^2 (inclusive) at screening. **Revised Text:** 7. Body weight ≥50 kg and body mass index (BMI) within the range 18 to <u>43</u> kg/m^2 (inclusive) at screening.	Preliminary physiologically-based pharmacokinetic modelling and simulations indicate minimal impact on systemic exposure to GSK2798745 for BMI up to 43 kg/m^2. The expansion of the BMI limit is being changed to reflect this new information.
5.2 Exclusion Criteria	**Previous Text:** 13. Uncontrolled diabetes as indicated by HbA1c >10% at screening. **Revised Text:** 13. Uncontrolled diabetes as indicated by HbA1c ><u>12%</u> at screening.	Feedback from investigators and recent publications (Fragala, 2021) indicate that HbA1c has increased even amongst otherwise controlled patients due to the COVID pandemic and subsequent restrictions and lockdowns. The increase is attributed to the inability to continue close monitoring of HbA1c and the inability to intensify diabetes therapy (Fragala, 2021). This can lead to an increase of up to 11% from diminished monitoring and up to 18.6% from failure to intensify actionable diabetes treatment (Samuels, 2008). These increases, if applied to the prior HbA1c cut-off of 10%, would result in HbA1c of 11.1% and 11.9%, respectively. The change in the criterion reflects this.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	**Previous Text:** 14. Active ulcer disease or gastrointestinal bleeding at the time of screening (positive FOBT at screening). **Revised Text:** 14. Active ulcer disease or gastrointestinal bleeding <u>by history within 6 months of screening or by exam</u> at the time of screening.	By expanding the history of ulcer/gastrointestinal disease, confirmation by positive FOBT is no longer required to determine subject eligibility.
Section 1.3.1 28 Day – 4 Week Treatment Period	**Previous Text:** Fecal Occult Blood Test (FOBT) assessment schedule **Revised Text:** Removal of Fecal Occult Blood Test (FOBT) assessment schedule	By expanding the history of ulcer/gastrointestinal disease, confirmation by positive FOBT is no longer required to determine subject eligibility.
8.1.5 Fecal Occult Blood Test	**Previous Text:** 8.1.5 Fecal Occult Blood Test Based on the preclinical finding of gastric erosions (Section 2.3.1), FOBT will be performed at screening to determine eligibility. **Revised Text:** Section Removed	By expanding the history of ulcer/gastrointestinal disease, confirmation by positive FOBT is no longer required to determine subject eligibility.
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 4 Protocol-Required Safety Laboratory Assessments	**Previous Text:** Remove Fecal Occult Blood Test (Screening only) **Revised Text:** Section removed	Per above, the Fecal Occult Blood Test is no longer required

Section # and Name	**Description of Change**	**Brief Rationale**
Section 10.6 Appendix 6: Abbreviations and Trademarks	**Previous Text:** FOBT Fecal Occult Blood Test **Revised Text:** Abbreviation removed	The Fecal Occult Blood Test is no longer required and FOBT wording is being removed from the protocol, so the abbreviation definition is no longer necessary.
Section 2.3.1 Risk Assessment	**See Risk Tables below for Previous and Revised text**	Clarifying that the mucosal findings in the oral 4-week dog and 13-week rat studies were not adverse effects and do not impact exposure considerations in the Gastrointestinal Section. The original wording did not clearly reflect the conclusions of these two animal studies. Also changed was the wording for Exclusion 14 in the Gastrointestinal and Mortality and General Health Sections to reflect the revision of that criterion being completed in this amendment.

Section # and Name	Description of Change	Brief Rationale
Section 9.5	Old text: **9.5. Interim Analyses** No interim analyses are planned for this study. New text: **9.5. Interim Analyses** As this is an open-label study, data will be reviewed on an ongoing basis and may be shared externally to support discussion with regulatory agencies. After approximately 8 participants completed the Day 28 visit, OCT and [redacted] data will be analysed on an ongoing basis to assess futility and the study may be terminated early if the futility criteria are met. Additional endpoints may be reviewed as well if necessary. Full details will be provided in the interim analysis charter.	Interim analysis was added to support development discussions of GSK2798745 and allow early termination of current study if the interim data is negative.

Previous Text:

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Gastrointestinal: Oral 4-wk repeat dose dog study: Mucosal erosion/ulceration in the stomach and/or duodenum was observed at doses of 3 mg/kg/day and higher. Oral 4-wk repeat dose rat study: Mucosal erosion/ulceration in the stomach and/or duodenum was observed at 300 mg/kg/day. Oral 13-wk repeat dose rat study: Mucosal erosion in the stomach was observed at 60 mg/kg/day.	Exclusion criterion #14: Active ulcer disease or gastrointestinal bleeding at the time of screening (positive fecal occult blood test [FOBT] at screening). Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs, including hemoglobin and hematocrit. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.
Mortality and General Health: Oral 4-wk repeat dose dog study: One male dog at 30 mg/kg/day was terminated from the study on Day 6 due to poor clinical condition. Two additional male dogs at 30 mg/kg/day were terminated from the study on Day 10 due to extremely reduced food consumption and body weight loss. Another high dose male dog had transient whole body shaking on Days 8 and 9. Oral 13-week repeat dose dog study: One female at 10 mg/kg/day was euthanized on Day 74 for welfare reasons. Elevated body temperature (39.6°C), slightly decreased skin turgor, bright/dark red/irregular surface of tongue and inner lips, as well as friable skin lesions on the limb and tail were noted. Oral 4-wk repeat dose rat study: Decreased food consumption was observed at 300 mg/kg/day without correlated deceases in body weights. Rat micronucleus and comet study: Mortality was observed following 1 to 3 doses at ≥600mg/kg/day.	Exclusion criterion #14: Active ulcer disease or gastrointestinal bleeding at the time of screening (positive FOBT at screening). Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs, including hemoglobin and hematocrit. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

Revised Text:

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Gastrointestinal: Oral 4-wk repeat dose dog study: Minimal grade mucosal erosion/ulceration in the stomach and/or duodenum was observed at doses of 3 mg/kg/day and higher. The observations were not considered to be adverse. Oral 4-wk repeat dose rat study: Mucosal erosion/ulceration in the stomach and/or duodenum was observed at 300 mg/kg/day. Oral 13-wk repeat dose rat study: Minimal grade mucosal erosion in the stomach was observed at 60 mg/kg/day. The observations were not considered to be adverse.	Exclusion criterion #14: Active ulcer disease or gastrointestinal bleeding by history within 6 months of screening or by exam at the time of screening. Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs, including hemoglobin and hematocrit. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Mortality and General Health: Oral 4-wk repeat dose dog study: One male dog at 30 mg/kg/day was terminated from the study on Day 6 due to poor clinical condition. Two additional male dogs at 30 mg/kg/day were terminated from the study on Day 10 due to extremely reduced food consumption and body weight loss. Another high dose male dog had transient whole body shaking on Days 8 and 9. Oral 13-week repeat dose dog study: One female at 10 mg/kg/day was euthanized on Day 74 for welfare reasons. Elevated body temperature (39.6°C), slightly decreased skin turgor, bright/dark red/irregular surface of tongue and inner lips, as well as friable skin lesions on the limb and tail were noted. Oral 4-wk repeat dose rat study: Decreased food consumption was observed at 300 mg/kg/day without correlated deceases in body weights. Rat micronucleus and comet study: Mortality was observed following 1 to 3 doses at ≥600mg/kg/day.	Exclusion criterion #14: Active ulcer disease or gastrointestinal bleeding by history within 6 months of screening or by exam at the time of screening. Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs, including hemoglobin and hematocrit. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Diabetic Retinopathy (DR), a complication of diabetes in which high blood sugar levels cause damage to retinal blood vessels, is the main cause of all vision loss from age 20-74 years and is detectable in one third of all diabetics worldwide (one-third of 285 million diabetics in 2010). DR is a continuum with Non-Proliferative DR (NPDR) and Proliferative DR (PDR) as the two sub-types. Diabetic Macular Edema (DME) may be present in either NPDR or PDR and is the main cause for vision loss while PDR is the main cause of blindness, in diabetics.

The pathophysiology of DME is multifactorial involving key pathways, including protein kinase C, advanced glycation end production, polyol and hexosamine pathways. The common result in the eye is the breakdown of the Blood-Retinal-Barrier (BRB). The BRB is the tight junctions between the retinal capillary endothelial cells (internal BRB) and the retinal pigmented epithelial cells (external BRB).

Current treatments focus on addressing BRB breakdown. Non-pharmacologic intervention includes laser photocoagulation. Pharmacologic intervention includes intraocular corticosteroid implants and intraocular anti-Vascular Endothelial Growth Factor (VEGF) injection. Steroid treatments may decrease inflammation and regulate endothelial junction proteins and adhesion molecules to have a beneficial effect on the BRB. Anti-VEGF treatments may restore cellular junctions and may partially act via blockage of calcium influx into endothelial cells caused by activation of VEGF Receptor.

Transient Receptor Potential Vanilloid 4 (TRPV4) is a non-selective Ca^{2+} channel that is associated with modulation of vascular permeability and is expressed on retinal vascular endothelial cells. TRPV4 activation increases endothelial barrier permeability via the reorganization of actin cytoskeleton, microtubule disassembly, and disruption of cell-cell and cell-matrix adhesion and enhances BRB leak. Conversely, TRPV4 blockers can reverse BRB leakiness, as measured by Evans' blue extravasation, in a diabetic rat model. GSK2798745 is a potent and selective oral TRPV4 channel blocker and has the potential to reverse BRB leak and treat DME.

Protocol Title: Study 212669: Phase I, Open-Label, Multi-Center Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of GSK2798745 after 28 Day Repeat Oral Administration to Adults with Diabetic Macular Edema

Short Title: Study 212669: A Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK 2798745 in Participants with Diabetic Macular Edema

Rationale:

GSK2798745 is a potent and selective oral TRPV4 channel blocker being investigated for the treatment of DME. GSK2798745 can block *in vitro* recombinant human TRPV4 channels with an IC_{50} of 1.6 to 2.0 nM and can block native human endothelial TRPV4 channels (in the presence of human whole blood) with an IC_{50} of 6.5nM.

To date, oral GSK2798745 has been administered to healthy participants as single doses up to 12.5 mg and for up to 14 daily doses of 5 mg. Oral GSK2798745 has been administered to patients with heart failure as a single 2.4 mg dose or as daily 2.4 mg doses for 7 days. An oral dose of 4.8 mg followed by a 2.4 mg once daily for an additional 6 days (7 days total) has be administered in patients with chronic cough.

Review of data in healthy participants indicates that there were no clinically significant safety concerns with single or repeat administration of GSK2798745. Review of data in participants with heart failure and chronic cough indicates that there are no clinically significant safety signals or concerns with lab values of potential clinical importance with repeat GSK2798745 administration up to 7 days. Of note, 15 participants in the heart failure studies were also diabetic and 2 had diabetic retinopathy. There was no impact of GSK2798745 on a glucose challenge test in healthy participants.

Further information regarding GSK2798745 pre-clinical and clinical data is available in the Investigator brochure (IB).

The present study will be the first to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of repeat oral doses of 3.2 mg GSK2798745 administered to participants with DME.

Administration of GSK2798745 will be for 28 days. The PD change of interest will be change from baseline (CFB) in macular edema as measured by Spectral-Domain Optical Coherence Tomography (SD-OCT).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To characterize the safety and tolerability of GSK2798745 following 28 days of daily oral dose administration to adult participants with confirmed Diabetic Macular Edema. To evaluate the pharmacodynamics of 28 daily oral doses of GSK2798745 in the study eye of adult participants with DME.	Safety parameters including: complete ophthalmic examination, visual acuity, physical examination findings, vital sign measurement, clinical lab tests, 12-lead ECG, clinical monitoring and observation and adverse event reporting. Mean change from baseline in center subfield retinal thickness in the study eye as measured by SD-OCT.
Secondary	
To evaluate the pharmacokinetics of 28 daily oral doses of GSK2798745 in adult participants with DME.	Plasma concentrations of GSK2798745, major metabolite M1, and derived PK parameters, as data permit

Objectives	Endpoints
Exploratory	
CCI [redacted]	

Overall Design:

Study 212669 is a multi-center, open-label, single arm, 28-day treatment study. Each participant enrolled will receive a single daily 3.2 mg oral dose of GSK2798745 for 28 days. The study will be composed of 3 periods for all participants (Screening, Treatment, and Follow-up).

Disclosure Statement: This is a single arm, un-masked treatment study.

Number of Participants:

This is a study in participants with diagnosed Diabetic Macular Edema. At least 20 participants will be screened and enrolled to ensure 20 evaluable participants can be achieved at the end of the 28-day treatment period. Subjects that are screened and meet eligibility criteria will be enrolled in the study. A maximum of 30 participants may be enrolled. A minimum of 5 enrolled participants will be consented to partake in the PK subset for intensive PK sampling on Day 7 and Day 28 (Section 1.3.3).

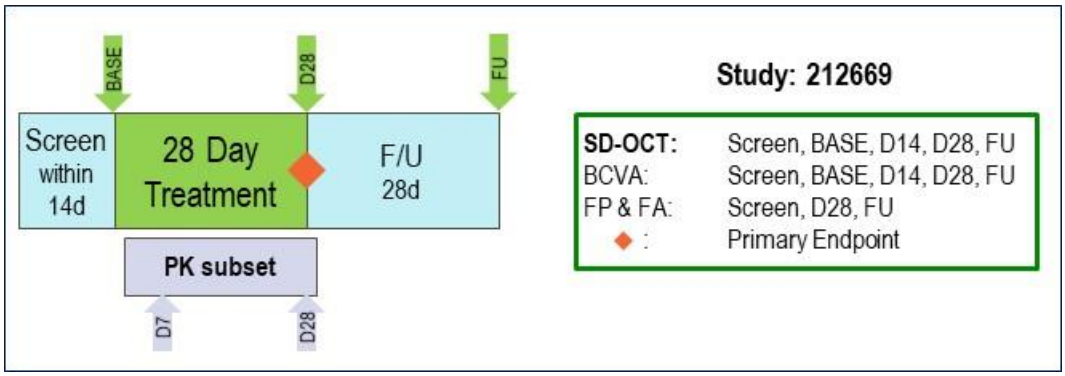
Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

The study will be composed of 3 periods for all participants (Screening, Treatment, and Follow-up). The screening period may occur across two visits but should be completed within 14 days from the Baseline visit. The treatment period is 28 days. Participants enrolled into the study will receive GSK2798745. The maximum days a participant will be in the study is approximately 70.

Data Monitoring or other Committee: No

1.2. Schema



1.3. Schedule of Activities (SoA)

1.3.1. 28 Day – 4 Week Treatment Period

Procedure / Study Day:	Screening	Baseline	Treatment Period				Early Withdrawal (WD)	Follow-up Day 56 Week 8	Notes
			Day 1 Week 0	Day 7[1] Week 1 PK-Subset Visit Only	Day 14 Week 2	Day 28 Week 4			
Visit Window	-1 to -14	-3 to -1	1	6 – 8	13 – 16	27 – 30		54 - 58	Visit window relative to Day 1 (first day of dosing at home). Screening assessments may be conducted across multiple visits, if required, but all samples for laboratory safety tests to be collected at one visit (unless repeats).
Informed Consent	X								
Outpatient Visit	X	X		X[1]	X	X	X	X	[1] Day 7 for participants in PK Subset only – see PK SoA Section 1.3.3
Demography	X								
Medical History (include substance usage & medication history)	X	X							Substances: Drugs, Alcohol, tobacco. Review & update at baseline visit. See Section 5.3.2
Complete Physical Examination	X						X	X	Including height and weight. See Section 8.1.1
Brief Physical Exam		X			X	X			See Section 8.1.1
12-Lead ECG	X[2]	X		X[1]	X	X[1]	X	X	Single ECG required at Screening, Baseline, Treatment periods, and follow-up; Triplicate ECG required at WD [2]Any ECG assessments completed within the 28 days prior to the start of screening may be used to determine eligibility. These assessments must not

Procedure / Study Day:	Screening	Baseline	Treatment Period				Early Withdrawal (WD)	Follow-up Day 56 Week 8	Notes
			Day 1 Week 0	Day 7[1] Week 1 PK-Subset Visit Only	Day 14 Week 2	Day 28 Week 4			
									have been collected for the purposes of this study, but for the routine care of the participant. Any assessments with abnormal values may be re-tested within the screening window and post-consent collection would be considered the first assessment of that ECG. Additional guidance is contained within the SRM. [1] Day 7 for participants in PK Subset only – see PK SoA Section 1.3.3 See Section 8.1.3
Columbia Suicidality Severity Rating Scale (CSSRS)	X			X	X	X	X	X	Use 'Baseline' CSSRS at Screening. Use the 'Since Last Visit' CSSRS all other visits including Follow-up. See Section 8.1.5
Vital Signs	X	X		X	X	X	X	X	See Section 8.1.2
Clinical Chemistry, Hematology & UA (including Cardiac Troponin, CPK)[2]	X	X		X	X	X	X	X	UA baseline, WD and Follow-up only [2]Any laboratory assessments completed within the 28 days prior to the start of screening may be used to determine eligibility. These assessments must not have been collected for the purposes of this study, but for the routine care of the participant. Any assessments with abnormal values may be re-tested within the screening window and post-consent collection would be considered the first assessment of that lab. Additional guidance is contained within the SRM.

Procedure / Study Day:	Screening	Baseline	Treatment Period				Early Withdrawal (WD)	Follow-up Day 56 Week 8	Notes
			Day 1 Week 0	Day 7[1] Week 1 PK-Subset Visit Only	Day 14 Week 2	Day 28 Week 4			
HbA1c	X								Fasting
FSH / Estradiol	X								As needed in women of non-childbearing potential only. See Section 10.2 and Section 10.4
Inclusion / Exclusion Criteria	X								
Dispense Study Medication		X							Open label.
Compliance Check for Study Medication				X	X	X	X		
First Day of Study Treatment			X						Site staff will contact each participant (or caregiver) on the first dosing day (Day 1) to review dosing, to: 1) verbally confirm that the participant has begun dosing; 2) review and verbally confirm proper storage of treatment; 3) remind the participant to save all treatment containers; 4) inquire about adverse events; and 5) answer any other questions the participant may have. Additional guidance on Day 1 dosing can be found in the SRM.
Dosing in Clinic				X	X	X			
PK – Trough Sampling						X			All participants pre-dose trough D28. On the PK day, participants may have light meal prior to visit (see SRM). Participants will be dosed at the clinic & must not take treatment at home.
PK – Intensive Sampling				X		X			PK subset only see PK SoA Section 1.3.3.
Spectral Domain Optical Coherence Tomography (SD-OCT)	X	X[3]			X	X	X	X	[3]If the date of the screening SD-OCT is within 3 days of baseline, the screening SD-OCT can be considered as baseline SD-OCT

Procedure / Study Day:	Screening	Baseline	Treatment Period				Early Withdrawal (WD)	Follow-up Day 56 Week 8	Notes
			Day 1 Week 0	Day 7[1] Week 1 PK-Subset Visit Only	Day 14 Week 2	Day 28 Week 4			
CCI [redacted]									
General Ophthalmic Exam	X	X[3]				X	X	X	[3]If the date of the screening general ophthalmic exam is within 3 days of baseline; the screening exam can be considered as baseline
CCI [redacted]									
AE - SAE Assessment	X	X	X	X	X	X	X	X	SAEs collected from the time of consent. AEs collected from the time of first dose (see Section 8.2.1).
Concomitant Medication	X	X	X	X	X	X	X	X	

1.3.2. PK Subset - Intensive PK Sampling Day 7 and Day 28

This SoA details the intensive PK sampling schedule on Day 7 and Day 28. All other assessments detailed on the 28 Day SoA (Section 1.3.1). The intensive PK sampling is for the PK subset participants only. A minimum of 5 enrolled participants will participate in the PK subset. Participants will be evaluated and dosed in the clinic on PK days.

Day 7 and 28	Pre-Dose	0h	0.5h	1h	2h	3h	4h	6h	8h	Notes
Study Drug Dose		X								On PK days, participant to be dosed at the clinic and must not take study treatment at home on that day.
Plasma PK / M1 Metabolite Sampling	X		X	X	X	X	X	X	X	PK subset only. Timepoints relative to dosing
12-Lead ECG	X									See Section 8.1.3
Vital Signs	X									See Section 8.1.2
Clinical Chemistry, Hematology (including cardiac troponin, CPK)	X									

1.3.3. Additional SoA Notes

- Study Day 7 is for Participants in the PK Subset only.
- Doses should be taken in the morning with or without food, except on specified PK days when participants may consume a light meal prior to the clinic visit.
- The timing of assessments should allow PK samples to be taken as close as possible to the nominal time-point. The actual data and time of dose and sampling should be recorded in the electronic case report form (eCRF).
- Participants should agree to and plan to complete all study visits. However, in the exceptional instance where a visit is missed, participants should be encouraged to reschedule as soon as possible in order to ensure careful monitoring of participant safety. If it is not feasible to reschedule prior to the next planned study visit, then site staff should make extra effort to ensure that the participant comes in for that next visit.
- With the exception of PK sampling days where the treatment dose will be taken at the clinic, participants will self-administer the study treatment, or obtain dosing assistance from a caregiver, for the duration of the study. The oral tablet should be taken once daily in the morning ±2 hours from the Day 1 dose with or without food.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF). These changes will be approved by the IRB/IEC before implementation.

2. INTRODUCTION

2.1. Background

Diabetic Retinopathy (DR), a complication of diabetes in which high blood sugar levels cause damage to retinal blood vessels, is the main cause of all vision loss from age 20-74 years and is detectable in one third of all diabetics worldwide (one-third of 285 million diabetics in 2010) [Lee, 2015]. DR is a continuum with Non-Proliferative DR (NPDR) and Proliferative DR (PDR) as the two sub-types. Diabetic Macular Edema (DME) may be present in either NPDR or PDR and is the main cause for vision loss while PDR is the main cause of blindness, in diabetics [Lee, 2015].

DME has a worldwide estimated prevalence of 21 million and is expected to increase with increased incidence of diabetes [Yau, 2012]. The pathophysiology of DME is multifactorial with complications of diabetes interacting with and modulating key pathways, including protein kinase C, advanced glycation end production, polyol and hexosamine pathways [Haritoglou, 2018, Fogli, 2016]. The common result in the eye is the breakdown of the Blood-Retinal-Barrier (BRB). The BRB is the tight junctions between the retinal capillary endothelial cells (internal BRB) and the retinal pigmented epithelial cells (external BRB) [Haritoglou, 2018, Fogli, 2016].

Current treatments focus on addressing BRB breakdown. Non-pharmacologic intervention includes laser photocoagulation of microaneurysms (focal) and general edematous tissue (grid) [Singer, 2016]. Pharmacologic intervention includes intraocular corticosteroid implants and intraocular anti-Vascular Endothelial Growth Factor (VEGF) injections [Dugel, 2015, Singer, 2016]. Steroid treatments may decrease inflammation and regulate endothelial junction proteins and adhesion molecules to have a beneficial effect on the BRB [Dugel, 2015]. Anti-VEGF treatments may restore cellular junctions and may partially act via blockage of calcium influx into endothelial cells caused by activation of VEGF Receptor [Bates, 2010].

The dexamethasone and fluocinolone acetonide implants have a long durability of effect (6m and 24-36m, respectively) [Dugel 2015]. However, there are side effects including implantation complications, increased intraocular pressure (IOP), and cataract formation that may necessitate their removal and discontinuation of treatment [Dugel, 2015]. Ranibizumab and aflibercept anti-VEGF intraocular injections are approved for monthly dosing and also have side effects including increased IOP, ocular pain, floaters, and subconjunctival hemorrhage [Blinder, 2017].

Although current treatments have efficacy compared to laser or no treatment, 55% of patients receiving anti-VEGF treatment and ~80% patients with a steroid implant fail to achieve ≥15 letter improvement after 2 or 3 years, respectively [Gonzalez, 2016, Boyer, 2014]. There is still an opportunity to explore treatments with a better safety and efficacy profile, potentially with a route of administration other than intravitreal.

Transient Receptor Potential Vanilloid 4 (TRPV4) is a non-selective Ca^{2+} channel that is associated with modulation of vascular permeability and is expressed on retinal vascular endothelial cells. TRPV4 activation increases endothelial barrier permeability via the

reorganization of actin cytoskeleton, microtubule disassembly, and disruption of cell-cell and cell-matrix adhesion and enhances BRB leak [Phuong, 2017; Arredondo, 2017]. Conversely, TRPV4 blockers can reverse BRB leakiness, as measured by Evans' blue extravasation, in a diabetic rat model [Arredondo, 2017]. Additionally, TRPV4 modulation can regulate human retinal capillary endothelial cell migration and tube formation *in vitro*, two processes essential to neovascularization associated with BRB leak [Wen, 2018].

2.2. Study Rationale

GSK2798745 is a potent and selective oral TRPV4 channel blocker being investigated for the treatment of DME. GSK2798745 can block *in vitro* recombinant human TRPV4 channels with an IC_{50} of 1.6 to 2.0 nM and can block native human endothelial TRPV4 channels (in the presence of human whole blood) with an IC_{50} of 6.5 nM.

To date, oral GSK2798745 has been administered to healthy participants as single doses up to 12.5 mg and for up to 14 daily doses of 5 mg. Oral GSK2798745 has been administered to patients with heart failure as a single 2.4 mg dose or as daily 2.4 mg doses for 7 days. An oral dose of 4.8 mg followed by a 2.4 mg once daily for an additional 6 days (7 days total) has be administered in patients with chronic cough.

Review of data in healthy participants indicates that there were no clinically significant safety concerns with single or repeat administration of GSK2798745. Review of data in participants with heart failure and chronic cough indicates that there are no clinically significant safety signals or concerns with lab values of potential clinical importance with repeat GSK2798745 administration up to 7 days. Of note, 15 participants in the heart failure studies were also diabetic and 2 had diabetic retinopathy. There was no impact of GSK2798745 on a glucose challenge test in healthy participants.

Further information regarding GSK2798745 pre-clinical and clinical data is available in the Investigator brochure (IB) [GSK Document Number 2013N162862_07].

The present study will be the first to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of repeat oral doses of 3.2 mg GSK2798745 administered to participants with DME.

Administration of GSK2798745 will be for 28 days. The PD change of interest will be change from baseline (CFB) in macular edema as measured by Spectral-Domain Optical Coherence Tomography (SD-OCT).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2798745 may be found in the Investigator's Brochure [GSK Document Number 2013N162862_07].

2.3.1. Risk Assessment

All potential risks of GSK2798745 are based on pre-clinical data. No risks have been identified in the clinical studies of GSK2798745 conducted prior to the effective date of this protocol.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Cardiovascular: Oral 4-wk repeat dose dog study: Arterial lesions in 2 male dogs at 30 mg/kg/day. One with coronary artery inflammation and thymic arteriole inflammation with fibroplasia; one with epididymal artery degeneration/necrosis with inflammation. Cardiac myofiber degeneration/necrosis and inflammation was observed in one dog at 30 mg/kg/day. Oral 13-wk repeat dose dog study: Arterial lesions in 1 male and 1 female dog at 10 mg/kg/day. Male dog with epididymal arteriole degeneration/necrosis with lymphocytic inflammation; female dog with bladder arteriole degeneration/necrosis with lymphocytic inflammation.	Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study. Exclusion criterion #22: QTc >450 msec or QTc > 480 msec in participants with bundle branch block. Exclusion criterion # 32: Cardiac troponin at screening > ULN for the assay.	As the nonclinical observations are not monitorable in the clinical, general safety and tolerability will be monitored and the participant may be withdrawn at any time at the discretion of the Investigator for safety. Cardiac troponin will be monitored through the study to assess general cardiac status. The GSK2798745 dose was selected to maintain an exposure 30-fold or greater below the no effect exposure of AUC 513 ng*hr/mL and Cmax 50 ng/mL (observed at 3 mg/kg/day in the dog 13-wk repeat dose study)

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Gastrointestinal: Oral 4-wk repeat dose dog study: Minimal grade mucosal erosion/ulceration in the stomach and/or duodenum was observed at doses of 3 mg/kg/day and higher. The observations were not considered to be adverse. Oral 4-wk repeat dose rat study: Mucosal erosion/ulceration in the stomach and/or duodenum was observed at 300 mg/kg/day. Oral 13-wk repeat dose rat study: Minimum grade mucosal erosion in the stomach was observed at 60 mg/kg/day. The observations were not considered to be adverse.	Exclusion criterion #14: Active ulcer disease or gastrointestinal bleeding by history within 6 months of screening or by exam at the time of screening. Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs, including hemoglobin and hematocrit. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Hepatic: Oral 4-wk repeat dose dog study: In one male dog, focal hepatocellular degeneration was observed at 30 mg/kg/day. Oral 7-day repeat dose rat study: Biliary epithelial hypertrophy/hyperplasia and periductal mixed inflammatory cell infiltrate into the liver was observed at 300 mg/kg/day.	Exclusion criterion #15: Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study. Exclusion criterion #19: Alanine transferase (ALT) >1.5x upper limit of normal (ULN). Exclusion criterion #20: Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).	Scheduled assessments of safety labs, including LFTs. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Mortality and General Health: Oral 4-wk repeat dose dog study: One male dog at 30 mg/kg/day was terminated from the study on Day 6 due to poor clinical condition. Two additional male dogs at 30 mg/kg/day were terminated from the study on Day 10 due to extremely reduced food consumption and body weight loss. Another high dose male dog had transient whole body shaking on Days 8 and 9. Oral 13-week repeat dose dog study: One female at 10 mg/kg/day was euthanized on Day 74 for welfare reasons. Elevated body temperature (39.6°C), slightly decreased skin turgor, bright/dark red/irregular surface of tongue and inner lips, as well as friable skin lesions on the limb and tail were noted. Oral 4-wk repeat dose rat study: Decreased food consumption was observed at 300 mg/kg/day without correlated deceases in body weights. Rat micronucleus and comet study: Mortality was observed following 1 to 3 doses at ≥600mg/kg/day.	Exclusion criterion #14: Active ulcer disease or gastrointestinal bleeding by history within 6 months of screening or by exam at the time of screening. Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs, including hemoglobin and hematocrit. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Musculoskeletal: Oral 4-wk repeat dose rat study: Skeletal myofiber necrosis, myofiber degeneration/regeneration, and fibroplasia was observed at 300 mg/kg/day. Oral 13-wk repeat dose rat study and dog 4- and 13-week studies: No test article related skeletal muscle abnormality was noted.	Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	Scheduled assessments of safety labs including CPK. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.
Neurologic: Rat micronucleus and comet study: Convulsions were observed at ≥600mg/kg/day, though not related to Cmax nor to predictable time from dose administration. Rat and dog neurobehavioral function and repeat dosing toxicity studies: No test article related and consistent effects on neurobehavioral functions were observed.	Exclusion criterion #16: History of stroke or seizure disorder within 1 year of screening. Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on Eligibility Criteria	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Genitourinary: Oral 4-wk repeat dose rat study: Spermatid retention at ≥60 mg/kg/day. There were no associated degenerative changes in the testes or epididymis. Oral 13-wk repeat dose rat study: No spermatogenic abnormalities were observed. Oral 4-wk and 13-wk repeat dose dog studies: No spermatogenic abnormalities were observed.	Inclusion criterion #8: Male participants must agree to use of contraceptives and refrain from donating sperm from first dose until after the follow-up visit.	General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety. The GSK2798745 dose was selected to maintain an exposure 30-fold or greater below the no effect exposure of AUC 513 ng*hr/mL and Cmax 50 ng/mL (observed at 3 mg/kg/day in the dog 13-wk repeat dose study). The exposure will be 40-fold or greater below the rat no effect dose.
Immunologic: Oral 4-wk repeat dose rat study: Phospholipid accumulation in alveolar macrophages at ≥ 60 mg/kg/day. Increased cellularity of sinus macrophages in the mesenteric lymph node and macrophage vacuolation in the thymus and increased thymus weight at 300 mg/kg/day. Ultrastructural appearance of mesenteric lymph nodes consistent with phospholipidosis at 300 mg/kg/day. The findings were not associated with degenerative changes. Oral 13-wk repeat dose rat study: No test article related immunologic changes. Oral 4- and 13-wk repeat dose dog studies: No test article related immunologic changes.	Exclusion criterion #18: History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study. Exclusion criterion #21: Evidence of abnormal clinical laboratory finding prior to enrollment that, in the opinion of the Investigator, makes the subject unsuitable for the study.	Scheduled assessments of safety labs, including CBC. General safety and tolerability will be monitored, and the participant may be withdrawn at any time at the discretion of the Investigator for safety. The GSK2798745 dose was selected to maintain an exposure 30-fold or greater below the no effect exposure of AUC 513 ng*hr/mL and Cmax 50 ng/mL (observed at 3 mg/kg/day in the dog 13-wk repeat dose study). The exposure will be 40-fold or greater below the rat no effect dose.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Phlebotomy	Fainting, mild pain, bruising, irritation or redness at a phlebotomy site may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Pupil dilation for Ophthalmologic Exam, CCI	Potential for brief stinging with eye drop application. Small risk for transient eye pressure increase, nausea, and eye pain. Vision may become temporarily blurred. Dilated eyes may become temporarily more sensitive to light.	Experienced site staff will follow standard approaches for managing events related to exam Driving or any other activities where vision is impacted is not recommended. Consider avoiding bright light or wearing sunglasses
CCI [redacted]		

2.3.2. Benefit Assessment

Participants with DME are not expected to receive any direct benefit as the study drug has not been proven to have efficacy. The participants may benefit from the general medical data collected through study assessments such as ophthalmologic exams, retinal imaging, clinical laboratory tests and electrocardiograms (ECGs). Participation in the study may provide societal benefit through advancing development of new oral treatments in this area of disease.

2.3.3. Overall Benefit: Risk Conclusion

The population for the current study, DME patients with center involvement, was selected to allow for exploration of the effects of oral GSK2798745 on retinal thickness. Due to the slow rate of progession of disease, a significant loss of vision is not expected during the length of this Phase I study. In the [redacted] approximately 5% of patients with untreated clinically significant diabetic macular edema with center-involvement lost ≥15 letters of vision over 3 months [redacted] Reseach Group, 1987].

Furthermore, significant spontaneous improvement in visual acuity is not expected during this study, since improvements are uncommon. Less than 3% of the participants overall in the [redacted] had improvements of 15 letters over 3 years [redacted] Research Group, 1985].

Participants will be monitored frequently for evidence of disease progression. At each of the study visits, clinical safety measures, have been incorporated to monitor participants, including, OCT imaging and visual acuity measurement at Visits 4 and 5 (Section 1.3.1) . Should the disease progress significantly, the Investigator may choose to withdrawal the subject from study participation to administer standard of care treatment see Section 6.5.3.

Taking into account the measures taken to minimise risk to participants in this study (e.g., dose selection, careful participant selection and risk monitoring), the potential risks identified in association with GSK2798745 are justified by the anticipated benefits that may be afforded to participants with DME.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To characterize the safety and tolerability of GSK2798745 following 28 days of daily oral dose administration to adult participants with confirmed Diabetic Macular Edema. To evaluate the pharmacodynamics of 28 daily oral doses of GSK2798745 in the study eye of adult participants with DME.	Safety parameters including: complete ophthalmic examination, visual acuity, physical examination findings, vital sign measurement, clinical lab tests, 12-lead ECG, clinical monitoring and observation and adverse event reporting. Mean change from baseline in center subfield retinal thickness in the study eye as measured by SD-OCT.
Secondary	
To evaluate the pharmacokinetics of 28 daily oral doses of GSK2798745 in adult participants with DME.	Plasma concentrations of GSK2798745, major metabolite M1, and derived PK parameters, as data permit
Exploratory	
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

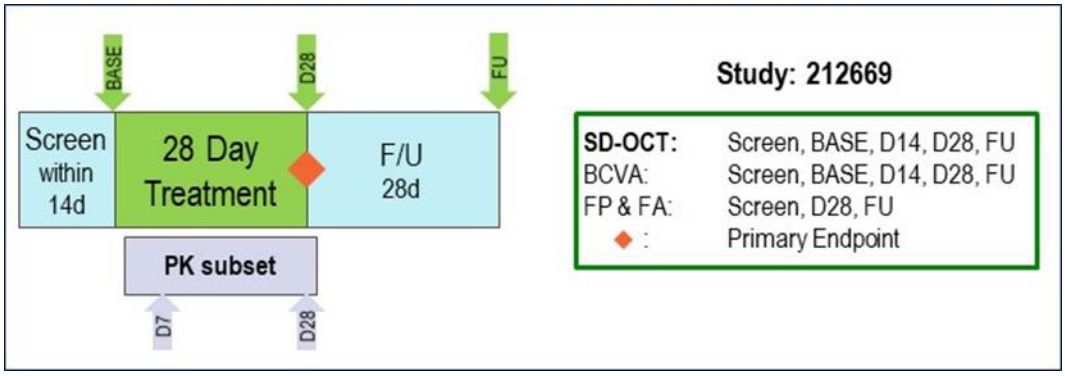
This is a multi-center, open-label, single arm, 28-day treatment study. The study will be composed of 3 periods for all participants (Screening, Treatment, and Follow-up).

Each participant will:

- be screened (screening may be conducted across more than 1 visit);
- have a 28-day treatment period;
- and, have a follow-up visit (approximately 28 days after the final dose).

Each participant enrolled will receive a single daily 3.2 mg oral dose of GSK2798745 for 28 days.

Figure 1 Study Design Overview



4.2. Scientific Rationale for Study Design

This is a multi-center study of repeat oral administration of 3.2 mg of GSK2798745 daily for 28 days.

The study will be open label. Placebo is not needed for powering the primary endpoint of SD-OCT. Additionally, initial participant safety and tolerability has previously been assessed in multiple placebo-controlled trials. The populations assessed included subjects with diabetes and diabetic retinopathy. There is no specific safety signal we are anticipating that would require discrimination between an active and placebo population.

The primary objectives are to determine 1) safety and tolerability of GSK2798745, and 2) the effect of GSK2798745 on the mean change from baseline in macular thickness as measured by SD-OCT after 28 days of dosing. Measurements will be taken at specified study visits as detailed in the SoA (Section 1.3). At a minimum the screening, baseline and 28-day SD-OCT images will be read by a central reading center.

Eligible participant must start treatment within 14 days of screening. Eligibility for each participant will be based only on one eye, which will be designated as the study eye. If both eyes qualify for the study, the study eye will be determined by the Investigator based on macular thickness and visual acuity as outlined in the SRM.

The study eye will be examined for changes over the life of the study. As this investigational treatment is systemic, the fellow eye will be examined in tandem to provide additional safety data. The same assessments will be performed for the study eye and fellow eye. The duration of treatment will be 28 days. Participants will return for a follow-up visit approximately 28 days after the last dose of study medication.

Safety will be assessed by complete ophthalmic examination, vital sign measurement, clinical laboratory tests, clinical monitoring and adverse event reporting.

Pharmacodynamic assessments will include SD-OCT measurements of the central retinal thickness, during screening, on-treatment and follow-up visits.

Visual acuity using [redacted] chart reading will be measured at specified visits as per the SoA (Section 1.3). Retinal morphology will be assessed by SD-OCT, [redacted]

4.3. Justification for Dose

4.3.1. Dose Rationale

Once daily dosing with 3.2 mg tablet GSK2798745 will be administered in this study. The average systemic exposure (Cav) over the once daily dosing interval with 3.2 mg is expected to be around 8 ng/mL [95%CI: 3.5 – 17.5] which would be associated with systemic target TRPV4 inhibition of ~70% [95%CI: 46%-85%]. The TRPV4 potency (IC50) of GSK2798745 range from 2.1 to 3.2 ng/mL based on in vitro human cell lines, an in vivo PK-PD rat pulmonary edema model and ex vivo human umbilical vein endothelial cell (HUVEC) assays using blood from heart failure patients dosed with GSK2798745 [GSK Document Number 2013N162862_07]. As GSK2798745 is highly lipophilic ($logD_{7.4} = 3.14$) with good permeability, a relatively high tissue-to-plasma ratio of the drug is expected in the choroid and retinal epithelial barriers into the ocular vascular endothelial capillaries.

Evidence for translational TRPV4 target engagement in diabetic macular edema has been demonstrated using a potent tool TRPV4 inhibitor. TRPV4 blockade using the potent and selective inhibitor GSK2193874 given intravitreally reversed BRB leak in diabetic rats [Arredondo, 2017]. It is notable per GSK internal data that GSK2193874 is approximately 10-times less potent than GSK2798745 for systemic TRPV4 inhibition using rat PK-PD pulmonary edema model. Further evidence of translational TRPV4 target engagement is provided with the TRPV4 inhibitor HC-067047 given intra-peritoneally (10mg/kg daily for over 1 month) in a mouse model of glaucoma and showed sustained inhibition of intra-ocular pressure comparable to baseline levels [Ryskamp, 2016]. HC-067047 is ~ 10-fold less potent than GSK2798745 in cell lines expressing mouse and human recombinant TRPV4 [Everaerts, 2010], however no systemic PK data with HC-067047 are available to allow for translational cross-species comparison to GSK2798745.

The intended dosing regimen also limits the daily ceiling human exposure at individual participant level to 30-fold below the exposure observed at the no observed adverse effect level (NOAEL) dose of 3 mg/kg/d from the 3-month dog safety study. The proposed clinical dose of 3.2mg once daily GSK2798745 is selected so that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng/mL. The likelihood of one or more participants of the 20 participants to be dosed with this regimen exceeding the threshold is listed in Table 1 below:

Table 1 Predicted exposure, probability of exceeding threshold and predicted TRPV4 inhibition after oral doses of 3.2 mg daily administered to 20 participants

Percentage systemic TRPV4 blockade over 24 h (median [95% PI])	Predicted exposure (median [95% PI])		% Probability that ≥1 of 20 participants will exceed the toxicokinetic limit[1]	
	AUC0–24 h (ng.h/mL)	Cmax (50 ng/mL)	AUC0–24 h (513 ng.h/mL)	Cmax (50 ng/mL)
70% [46% – 85%]	195 [85–420]	15 [8–25]	0.94	0

PI: predicted interval.

1. The percentage of the 500 simulated studies (of 20 subjects each) in which ≥1 subject exceeds the toxicokinetic limit.

NOTE: Recruitment is planned to ensure that 20 participants will be evaluable after 28 days of dosing. Should 30 participants be recruited and all complete, the % probability of exceeding the limit goes down for the AUC to 0.84% and remains 0% for Cmax.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the follow-up visit and last scheduled procedures shown in the Schedule of Activities.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Adherence to the entry criteria and the study design requirements, including those specified in the SoA (Section 1.3) are essential.

5.1. Inclusion Criteria

Participants and the participants' study eye are eligible to be included in the study only if all of the following criteria apply:

AGE
1. At least 18 to 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Diagnosis of diabetes mellitus (type 1 or type 2).
3. Confirmation of DME with center involvement in at least one eye, including those with focal or diffuse DME as determined by Investigator-determined CCI [redacted] CCI

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
4. Retinal thickening (DME) involving the center of the fovea in the study eye as defined by Investigator-determined SD-OCT central subfield thickness >340 microns for Heidelberg Spectralis or >320 for Zeiss Cirrus; if both eyes are eligible, the eye with the greater OCT center subfield score is selected as the study eye if all other criteria are met. SD-OCT assessments for individual patients must be taken with the same machine throughout the duration of the study. 5. CCI letter score of 80 letter or worse (Snellen equivalent ~20/25) or worse in the study eye. 6. Safe to withhold treatment of the study eye with laser photocoagulation, intravitreal steroid injection, or intravitreal VEGF inhibitor for the duration of the study. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigator in consultation with the Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

WEIGHT
7. Body weight ≥50 kg and body mass index (BMI) within the range 18 to 43 kg/m^2 (inclusive) at screening.

SEX
8. Male or Female a. **Male participants:** Male participants are eligible to participate if they agree to the following first dose of study treatment until the follow-up visit. • Refrain from donating sperm PLUS either: • Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent OR • Must agree to use contraception/barrier as detailed below: • Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 • Should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

SEX
b. **Female participants:** A female participant is eligible to participate if she is not pregnant, not breastfeeding and **not of childbearing potential** as defined in Appendix 4. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

INFORMED CONSENT
9. Subject is willing and able to return for all study visits and to comply with all protocol requirements and procedures. 10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS – OCULAR
1. Additional eye disease in the study eye that in the opinion of the Investigator could compromise assessment of SD-OCT, CCI [redacted] or imaging of the posterior pole by CCI [redacted], CCI [redacted] or is likely to require intervention during the study (e.g., cataract, glaucoma with documented visual field loss, ischemic optic neuropathy, retinitis pigmentosa). 2. History of choroidal neovascularization in the study eye, or current choroidal neovascularization in the fellow eye requiring treatment. 3. Active PDR in the study eye or untreated active PDR in the fellow eye. 4. Ischemic maculopathy on CCI [redacted] defined as a total area of capillary loss greater that 2-disc areas (>5mm^2) within the ETDRA macular grid or a foveal avascular zone greatest linear diameter of >1000 microns. 5. Intraocular surgery or laser photocoagulation in the study eye within 90 day of dosing which might compromise assessment of SD-OCT, CCI [redacted] or imaging of the posterior pole by CCI [redacted] Allowed in fellow eye. 6. Use of intravitreal ranibizumab or bevacizumab within 42 days (6 weeks), or aflibercept within 56 days (8 weeks) of dosing in the study eye. Allowed in fellow eye. 7. Use of intraocular steroids in the study eye within 180 days of dosing. Allowed in

MEDICAL CONDITIONS – OCULAR
fellow eye. 8. Use of or expected need for intravitreal or intraocular treatment in the study eye during course of the study. Allowed in fellow eye. 9. Use of any systemically administered anti-angiogenic agent (e.g., bevacizumab, sunitinib, cetuximab, sorafenib, pazopanib), approved or investigational, within 6 months of dosing. 10. Evidence of vitreomacular traction as determined by the Investigator. 11. Uncontrolled intraocular pressure >22 mmHg in the study eye despite treatment with glaucoma medication. 12. Within 6 months prior to the Screening Visit, use of medications known to be toxic to the retina, lens or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, chlorpromazine, phenothiazines, tamoxifen, interferons and ethambutol) or are implicated in the development of macular edema (e.g. thiazolidinediones, fingolimod).

MEDICAL CONDITIONS - NON-OCULAR
13. Uncontrolled diabetes as indicated by HbA1c >12% at screening. 14. Active ulcer disease or gastrointestinal bleeding by history within 6 months of screening or by exam at the time of screening 15. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 16. History of stroke or seizure disorder within 1 year of screening. 17. Participant who, in the Investigator's opinion, poses a significant suicide risk. Evidence of serious suicide risk may include any history of suicidal behaviour and/or any evidence of suicidal ideation on any questionnaires e.g., Type 4 or 5 on the CSSRS in the last 6 months (assessed at screening). 18. History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic, infectious or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study. 19. Alanine transferase (ALT) >1.5x upper limit of normal (ULN). 20. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 21. Evidence of abnormal clinical laboratory finding prior to enrollment that, in the opinion of the Investigator, makes the subject unsuitable for the study. 22. QTc >450 msec or QTc >480 msec in participants with bundle branch block. *NOTES: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either*

MEDICAL CONDITIONS - NON-OCULAR
machine-read or manually over-read. *The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.*

PRIOR / CONCOMITANT MEDICATIONS
23. Unless permitted per Section 6.5, use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise participant safety. Note: *Stable use of some medications and standard multi-vitamins (with only vitamins and minerals, and no plant extracts or herbal additives) may be permitted if the dose is stable for at least 3 months prior to Day 1, and the medication was prescribed for an indication other than DME. The dose should remain constant throughout the study. Changes in dose are not permitted, unless required for safety or tolerability. Paracetamol at doses of ≤2 grams/day is permitted for use any time.* 24. Use of a listed precluded medication, including strong inhibitors or inducers of cytochrome P450 (CYP) 3A or p-glycoprotein (Section 6.5.2), within the restricted timeframe relative to the first dose of the study treatment.

PRIOR / CONCURRENT CLINICAL TRIAL EXPERIENCE
25. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months from screening. 26. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 27. Current enrollment, or past participation within the last 60 days, of any clinical study involving an investigational study intervention, or any other type of medical research, before signing of consent for this study.

DIAGNOSTIC ASSESSMENTS
28. Positive human immunodeficiency virus (HIV) antibody test. 29. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention. 30. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study intervention.

DIAGNOSTIC ASSESSMENTS
NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained 31. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. *NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing* 32. Cardiac troponin at screening > ULN for the assay.

OTHER EXCLUSIONS
33. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study. 34. Regular substance abuse including drug and/or alcohol consumption within 6 months prior to the study. Alcohol consumption is defined as: An average weekly intake of > 14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants are not permitted to consume red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before the start of study treatment until the end of study treatment. The exception to this is that regular orange juice is allowed anytime except 2 hours prior through 2 hours after study treatment dose.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants participating in the PK subset on Day 7 and Day 28 and for all participants on Day 28 will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 8 hours before the start of dosing until after collection of the final pharmacokinetic sample.
- Participants who use tobacco products (including alternate delivery devices such as vaporizers) or alcohol will be instructed that use of such tobacco products or alcohol will not be permitted while they are in the clinical unit. Stable use of nicotine patches will be allowed at all times.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., walking).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Participants may be rescreened once only after consultation and agreement with the Medical Monitor. If rescreening is performed, participants must be assigned a different unique subject identification number for the rescreening, and all screening procedures must be repeated. See the study reference manual (SRM) for more details.

In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the Investigator and GSK Medical Monitor, the subject will be considered a screen failure.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered

Study Treatment Name:	**GSK2798745**
Dosage formulation:	White to almost white, round, film-coated tablet.
Unit dose strength:	3.2 mg
Route of Administration:	Oral
Dosing instructions:	One tablet to be taken per day. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).
Packaging and Labelling:	GSK2798745 tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.
Manufacturer:	GSK

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions as detailed in SRM have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorised site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

- This is a single arm, open-label study.
- Assessments are objective measures and should have limited risk of bias.
- The PD endpoints are based on studies with the same population and will also minimize bias.
- The study will use Pre-Coded numbers provided to the site.
- Participants will be assigned a unique number in ascending numerical order at each study site. The number encodes the participant's assignment to the single arm study, according to the schedule generated prior to the study by the Statistics Department at GSK. Each participant will be dispensed study intervention, labeled with his/her unique number, throughout the study.

6.4. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person

administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

- When participants self-administer study intervention(s) at home, compliance with GSK2798745 will be assessed by direct questioning and counting returned tablets/capsules, etc. during the site visits and documented in the source documents and CRF.
- A record of the number of GSK2798745 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, some vitamins, and/or herbal supplements), approved by the Investigator, in consultation with the GSK Medical Monitor, that the participant is receiving at the time of enrolment, or receives during the study, must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medications

Paracetamol at doses of ≤2 grams/day is permitted for use any time during the study.

Other concomitant medication will be considered on a case by case basis by the Investigator in consultation with the GSK Medical Monitor. An exception is that rescue treatment is allowable in the fellow eye at any time during the study, see Section 6.5.3.

Stable use of some medications may be permitted if the dose is stable for at least 3 months prior to Day 1, and the medication was prescribed for an indication other than DME. The dose should remain constant throughout the study. Changes in dose are not permitted, unless required for safety or tolerability. These will be considered on a case by case basis by the Investigator in consultation with the GSK Medical Monitor.

6.5.2. Prohibited Medications

Except for the permitted medication noted above and those approved by the Investigator in consultation with the GSK Medical Monitor (Section 6.5.1, participants must abstain from taking prescription and non-prescription drugs (including some vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study.

During the study, participants should not use drugs that are strong inhibitors or inducers of Cytochrome P450 (CYP) 3A4 or p-glycoprotein (P-gp), because they may alter GSK2798745 concentrations. The list of background therapy/drugs may be modified based on emerging data. These include, but are not limited to, those listed in Table 2.

Table 2 Strong Inducers/Inhibitors of CYP3A4 and P-gp

Antiretrovirals:	atazanavir, danoprevir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir, boceprevir
Antibiotics:	clarithromycin, telithromycin, troleandomycin, rifampin
Oral antifungals:	ketoconazole, itraconazole, voriconazole
Antidepressant	nefazadone
Immunosuppressant	Cyclosporine
Anti-Epileptic	carbamazepine, phenytoin

GSK2798745 has weak CYP3A4 inhibition potential. It is possible that concentrations of drugs that are substrates of CYP3A4 may be increased. HMG-CoA reductase inhibitors, such as atorvastatin and simvastatin, are examples of CYP3A4 substrates that might be taken by the eligible participants. Participants being treated with simvastatin will be allowed to participate in the study, as long as their dose is ≤20 mg once daily. Participants being treated with >20 mg once daily simvastatin will be considered on a case basis by the Investigator in consultation with the GSK Medical Monitor. Participants being treated with atorvastatin of any therapeutic dose are allowed to participate in the study. Pharmacokinetic data in three patients with refractory cough on GSK2798745 co-administered with chronic oral atorvastatin 20 mg dose under steady state condition did not reveal any clinically relevant pharmacokinetic interactions for both atorvastatin and its major metabolite para-hydroxyatorvastatin [GSK Document Number 2018N386129_00]. The Investigators may also consider substitutions of these medications.

It is strongly recommended that participants avoid using drugs that are sensitive substrates of Cytochrome P450 (CYP) 3A4 and/or P-gp or that have a low therapeutic index because concentrations of these substrates may be increased by GSK2798745. If co-administration of medications with interaction potential with GSK2798745 is necessary, Investigators should monitor participants for safety risks or consider substitutions of these medications.

All concomitant medications may be reviewed by the Medical Monitor and it will be up to the discretion of the Investigator in consultation with the GSK Medical Monitor, whether the medication can be continued, and/or the participant can participate in the study.

6.5.3. Ophthalmic Safety Rescue Medicine

At any time during the study, including the follow-up period, the subject may be withdrawn and rescue treatment (standard of care) administered based on the clinical judgment of the Investigator.

Rescue treatment should strongly be considered for participants who have experienced in the study eye:

- A loss of greater than 5 letters from baseline in visual acuity maintained at 2 consecutive visits and/or
- An increase from baseline in SD-OCT center subfield thickness >60 microns or >15%

Intervention in the fellow eye with rescue medication is allowable at any point and does not require withdraw from the study.

The study site will institute and supply rescue medication at the discretion of the Investigator or physician treating the patient. GSK will not supply the rescue medication.

Subjects requiring rescue treatment in the study eye will be withdrawn from the study and follow early withdraw procedures as per the SoA (Section 1.3).

6.6. Dose Modification

No dose modifications are permitted without submission of an amendment to the protocol.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study, because the indication being studied is not life threatening or seriously debilitating.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will not remain in the study except to complete with early withdraw visit assessments (see the SOA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed). If subjects are prematurely discontinued from the study prior to completing the primary endpoint 28-day dosing period, additional replacement

participants may be enrolled at the discretion of the Sponsor in consultation with the Investigator. Replacement participants may be enrolled until the protocol defined sample size is achieved.

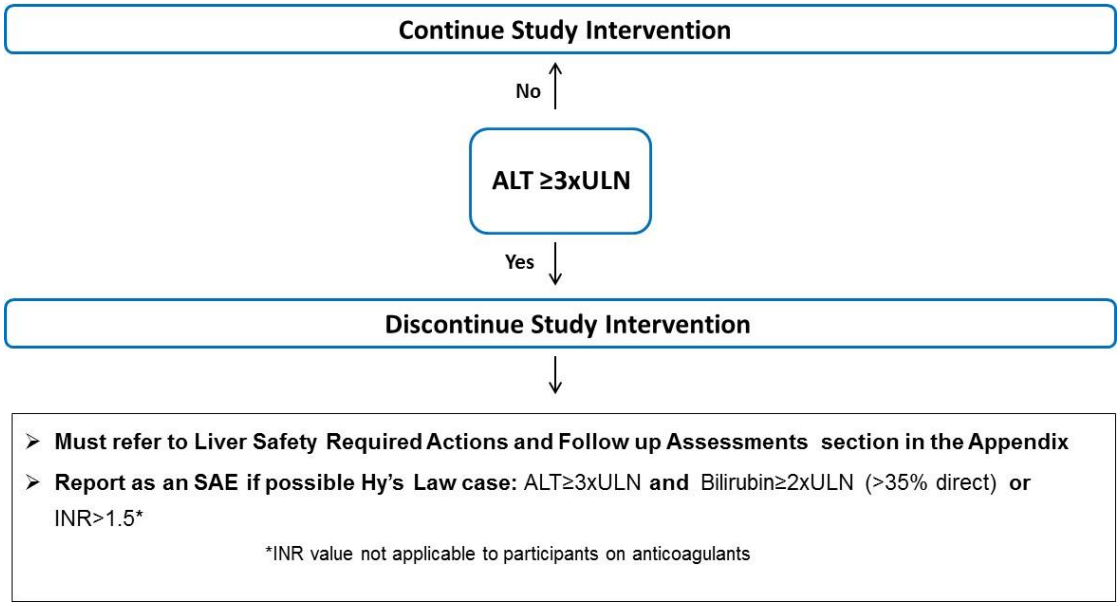
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the Investigator believes study intervention discontinuation is in the best interest of the participant.

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Section 10.5 for required Liver Safety Actions and Follow up Assessments

7.1.2. QTc Stopping Criteria

If a participant meets either bulleted criterion below, two further ECG recordings should be done (obtained over a brief [e.g. 5 to 10 minute] recording period). A participant who meets either bulleted criterion, based on the average of the triplicate ECG readings, will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT >600 msec

- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
<450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

7.1.3. Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria

7.1.3.1. Symptomatic Participant:

If a participant experiences symptoms of cardiac ischemia, (e.g. chest pain, increased shortness of breath, and diaphoresis), cardiology consultation should be obtained immediately. GSK2798745 should be discontinued permanently. The participant should be evaluated by a cardiologist and undergo any clinically appropriate testing. The participant should be followed up until symptoms are resolved.

7.1.3.2. Asymptomatic Participant:

Cardiac troponin will be measured pre-dose and at specific time points during the treatment period as specified in the SoA (Section 1.3). If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (Day -1), the participant should be assessed for symptoms of cardiac ischemia (as above). If the participant is asymptomatic, the participant can continue in the study after discussion with the Medical Monitor and close monitoring for symptoms.

7.1.3.3. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.4. General Stopping Criteria

If the same or identifiably similar moderate or severe AE, considered reasonably attributable to study intervention in the opinion of the Investigator, occur in more than 4 participants, then dosing will be temporarily halted, and no further participants will be enrolled or dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant site personnel, and the IRB/IEC will take place before resumption of enrollment or dosing.

If the same or identifiably similar SAE, considered reasonably attributable to study intervention in the opinion of the Investigator, occurs in more than 2 participants, then dosing will be temporarily halted, and no further participants will be enrolled or dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the Medical Monitor, relevant site personnel, and the IRB/IEC will take place before resumption of enrollment or dosing.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3) See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the SoA (Section 1.3) and SRM, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA (Section 1.3) and SRM.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    - 12-lead ECG
    - vital signs
    - blood draws
- Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study Sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC and Investigators will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.1.1. Physical Examinations

- A complete physical examination will include, at a minimum, measuring weight, and assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, measuring weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height will be measured at screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.1.2. Vital Signs

- Vital signs include systolic and diastolic blood pressure and pulse and will be measured in semi-supine position after 5 minutes rest. Manual techniques will be used only if an automated device is not available.
- Temperature will also be measured as a vital sign but will not require positioning or rest prior to measuring.

- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.1.3. Electrocardiograms

- 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- Single 12-lead ECGs will be obtained for trial eligibility and will be obtained as outlined in the SoA (Section 1.3).
- Withdrawal of participants is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the participant should be discontinued from the study.

8.1.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 to 10 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the Investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the aetiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.1.5. Columbia Suicidality Severity Rating Scale (CSSRS)

Based on preclinical studies that have been conducted, GSK2798745 is considered to be a central nervous system (CNS)-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although GSK2798745 has not been shown to be associated with an increased risk of suicidal thinking or behaviour, GSK considers it important to monitor for such events.

Participants being treated with GSK2798745 should be assessed and monitored appropriately for suicidality and unusual changes in behaviour. Consideration should be given to discontinuing GSK2798745 in participants who experience signs of suicidal ideation or behaviour. Families of participants being treated with GSK2798745 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour, and to report such symptoms immediately to the study Investigator.

The CSSRS is a measure of suicidal ideation and behaviour, with demonstrated predictive validity and reliability. Sections of the CSSRS include suicidal ideation, intensity of ideation, suicidal behaviour, and actual suicide attempt(s). The CSSRS assesses lifetime and current suicidal thoughts and behaviours across these categories based on an increasing severity of a 1- to 5-rating scale. The semi-structured questionnaire is completed by a trained and experienced neurologist, psychiatrist, or neuropsychologist, or another trained and experienced person approved by the Sponsor, who may be the Principal Investigator or a sub-Investigator for the study. See SRM for details of the scale.

At screening, the 'Baseline' CSSRS questionnaire will be completed. At all other time-points, the 'Since Last Visit' CSSRS questionnaire will be used (see Section 1.3, SOA).

Should suicidality or unusual changes in behaviour occur, the Investigator will refer the participant for appropriate evaluation and treatment.

8.1.6. Ophthalmic Safety Assessments

8.1.6.1. Refraction and Visual Acuity

- Refraction and visual acuity will be measured using electronic CCI visual acuity charts (eVA with CCI or standard CCI visual acuity charts (light box with CCI charts).
- Refraction and visual acuity assessments must be taken with the same method of assessment (i.e. CCI) throughout the duration of the study. See the SRM for more details.
- Refraction and visual acuity measurements must be performed by an examiner that has been appropriately trained.
- CCI including refraction, will be determined at defined study visits (see Section 1.3, SOA).

8.1.6.2. General Ophthalmic Examination

A complete eye exam will be performed per the SoA (Section 1.3) and will include the following:

- Examination of eye color (screening only), eyelids and lashes (including Meibomian glands)
- Pupil motility and confrontation visual field examination

- Slit lamp evaluation of anterior ocular structures (including conjunctiva, tear film, cornea and fluorescein staining, anterior chamber, iris, lens and anterior vitreous)
- Intraocular pressure measurement
- Dilated Fundus Examination (Indirect ophthalmoscopy and slit lamp biomicroscopy)

CCI

[redacted]

8.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention and study (see Section 7).

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she

considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.2.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent IRB/IEC Committees (IEC), and Investigators.
- For all studies except those utilizing medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until the follow-up visit.
- If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.2.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.3. Treatment of Overdose

For this study, any dose of GSK2798745 greater than 3.2 mg (i.e., ≥2 tablets of 3.2 mg) within a 24-hour time period ± 4 hours will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The Investigator (or physician in charge of the participant at the time) will use clinical judgment to treat any overdose.

In the event of an overdose, the Investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2798745 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 24 h from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.4. Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2798745 and its metabolite GSK3526876 as specified in the SoA (Section 1.3). Details of sample collection, processing, storage and shipping procedures are provided in the SRM.

- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of

sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK2798745 and GSK3526876. samples collected for analyses of GSK2798745 and GSK3526876 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- PK analysis will be performed under the control of In Vitro/In Vivo Translation (IVIVT)/ and Third-Party Resourcing (TPR) /GlaxoSmithKline. Plasma concentrations of GSK2798745 and GSK3526876 will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

8.5. Pharmacodynamics

8.5.1. Optical Coherence Tomography

- SD-OCT images/scans will be collected at specified visits (see Section 1.3, SoA).
- Quantitative and qualified assessments will be obtained by an appropriately trained photographer/technician using SD-OCT equipment that has been approved by a central reader.
- Images will be evaluated by the Investigator for protocol inclusion/exclusion criteria and safety monitoring. Images will be sent to and evaluated by a central reading center at the end of the study for pharmacodynamic effect.

CCI [redacted]

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GlaxoSmithKline.

Reporting of study data will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards.

Complete details of the planned statistical analyses will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

The co-primary objective of this study is to estimate the treatment effect on mean change from baseline in center subfield retinal thickness in the study eye as measured by SD-OCT at 28 days.

To ensure high probability of accurate decision making around the change at Day 28 in SD OCT, the decision criteria are defined as:

- "Positive" if Prob[CFB in OCT @ 28 days > 70 µm decrease |data] > 80% and
- "Negative" if Prob[CFB in OCT @ 28 days < 95 µm decrease |data] > 90%.

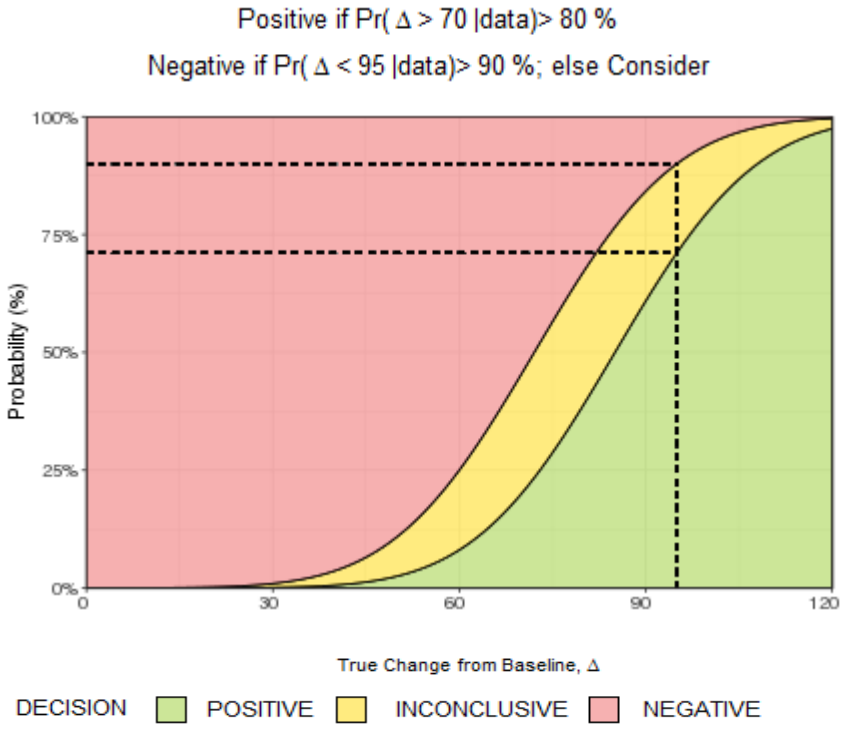
If neither Positive nor Negative criterion are meet, an evaluation of the [redacted] will be performed. A positive outcome will be concluded if the [redacted] after completing 28 days of dosing is 3 letters or greater as reviewed in the context of all available PD data.
Further details of the analysis will be included in the reporting and analysis plan document (SAP).

9.2. Sample Size Determination

A minimum 20 participants will be screened and enrolled such that 20 evaluable participants can be achieved at end of 28 days.

A standard deviation of 75 µm in SD-OCT mean change from baseline at 28 days has been considered based on the variability observed in the Placebo arm from Darapladib study [GSK Document Number 2011N112198_01]. The statistical operating characteristics of the criteria given these assumptions are presented in Figure 2.

Figure 2 Operating Characteristics curves for SD-OCT (µm)



From the above Figure 2, considering 20 subjects and standard deviation of 75 µm,

- if the true mean change from baseline in SD-OCT at 28 days as 95 µm then, the probability of a positive study outcome is 74.2%.
- if the true mean change from baseline in SD-OCT at 28 days as 0 µm (no change) then, the study outcome is always negative.
- the minimum observed value of change from baseline in 28 days that would meet the criteria for a positive outcome is 84 µm and the maximum observed value of change that would meet the criteria for a negative outcome is 73.3 µm.
- If the true mean CFB is less than 70 µm then the maximum risk of getting a false positive outcome is 20%. If the true mean CFB is greater than 95 µm then the maximum risk of getting a false-negative outcome is 10%.

9.2.1. Sample Size Sensitivity

The sensitivity of different variability estimates and sample sizes on the probabilities of study outcomes such as Positive, Negative and Inconclusive were evaluated in Table 3 below:

Table 3 Sample Size Sensitivity Calculations

Standard deviation (µm)	Sample Size	True Change (µm)	Probability of Positive outcome[1]	Probability of Negative outcome[2]	Probability of neither positive nor negative outcome
75	15	0	0%	100%	0%
		70	20%	50.4%	29.6%
		95	67.3%	10%	22.7%
	20	0	0%	100%	0%
		70	20%	58.3%	21.7%
		95	74.2%	10%	15.8%
	25	0	0%	100%	0%
		70	20%	65%	15%
		95	79.5%	10%	10.5%
	30	0	0%	100%	0%
		70	20%	70.7%	9.3%
		95	83.7%	10%	6.3%
80	15	0	0%	100%	0%
		70	20%	47.2%	32.8%
		95	64.4%	10%	25.6%
	20	0	0%	100%	0%
		70	20%	54.6%	25.4%
		95	71.1%	10%	18.9%
	25	0	0%	100%	0%
		70	20%	61.1%	18.9%
		95	76.5%	10%	13.5%
	30	0	0%	100%	0%
		70	20%	66.6%	13.4%
		95	80.8%	10%	9.2%

1 - Positive if Prob[$\Delta > 70$ | data] > 80%

2 - Negative if Prob[$\Delta < 95$ | data] > 90%

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who passed screening and entered the study. Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.
Safety	All enrolled participants who received at least one dose of study treatment.
PD	All participants in the Safety population who had at least 1 post-baseline non-missing PD assessment.
PK	All participants in the Safety population who will have intensive PK sampling on Day 7 and Day 28 per Section 1.3.3 (PK Subset).

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Endpoints

9.4.1.1. Safety Analyses

The primary analyses are to evaluate safety and tolerability of GSK2798745 following 28 days of daily oral dose administration to adult participants with confirmed Diabetic Macular Edema. The safety population will be used for the primary analyses.

Endpoint	Statistical Analysis Methods
Primary	Safety and tolerability data comprising of • complete ophthalmic examination • visual acuity • physical examination findings • adverse events (clinical monitoring and observation) • clinical laboratory safety data

Endpoint	Statistical Analysis Methods
	• vital signs • 12 lead ECGs Will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.1.2. Pharmacodynamics (PD) Analysis

All PD analyses will be performed on the PD Population.

Endpoint	Statistical Analysis Methods
Primary	Mean change from baseline in center subfield retinal thickness in the study eye as measured by SD-OCT at 28 days PD data will be presented in graphical and/or tabular form and will be summarized descriptively by days/weeks. A Bayesian probability model will be used to analyse the mean change from baseline in OCT at Day 28. Normal distribution is assumed for the change in OCT. Let x_i, i=1, 2, …., n, denotes i.i.d observations of mean change from baseline at Day 28 of the i^{th} subject, such that $x_i \sim N(\mu, \sigma^2)$, i=1, 2, …, n, where μ is the mean, σ^2 is the known variance, therefore $\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i \sim N(\mu, \frac{\sigma 2}{n})$ and let σ=75 μm. A non-informative prior distribution of μ will be considered as $\mu \sim N(\mu_0, \sigma_0^2)$, where $\mu_0=0$ and $\sigma_0^2=10^{10}$. The study decision criteria will be evaluated based on the following posterior distribution of $\mu|\bar{x}, \sigma 2$: $$\mu|\bar{x}, \sigma^2 \sim N\left(\frac{\frac{1}{\sigma_0^2}\mu_0 + \frac{n}{\sigma^2}\bar{x}}{\frac{1}{\sigma_0^2}+\frac{n}{\sigma^2}}, \frac{1}{\frac{1}{\sigma_0^2}+\frac{n}{\sigma^2}}\right) \approx N\left(\bar{x}, \frac{\sigma 2}{n}\right)$$ Evidence of an effect on 28-day OCT will be evaluated based on the posterior probabilities. Details of the final analysis will be included in the SAP.

9.4.2. Secondary Endpoint

9.4.2.1. Pharmacokinetic (PK) Analyses

All PK analyses will be performed on the PK Population.

Endpoint	Statistical Analysis Methods
Secondary	Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, (CPMS), GlaxoSmithKline. Non-linear mixed effect methods will be used to analyse all the plasma GSK2798745 drug levels based on the combined intensive and sparse PK sampling schedules in this patient population. Individual participant PK parameters (including absorption rate, oral clearance and oral volume of distribution) with the associated inter-and intra-individual variability will be estimated. Population PK parameter simulation will be applied to estimate the individual patient Cmax and AUC over dosing interval. Plasma M1 metabolite concentration-time data will be analyzed by non-compartmental methods.

Full description and technical details of planned PK analysis will be described either as add-on to the statistical analysis plan or as a stand-alone population PK, PK-PD analysis plan.

9.4.3. Other Analyse(s) Exploratory Endpoint(s)

CCI [redacted]

9.5. Interim Analyses

As this is an open-label study, data will be reviewed on an ongoing basis and may be shared externally to support discussion with regulatory agencies.

After approximately 8 participants completed the Day 28 visit, OCT and CCI [redacted] ata will be analysed on an ongoing basis to assess futility and the study may be terminated early if the futility criteria are met. Additional endpoints may be reviewed as well if necessary. Full details will be provided in the interim analysis charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the study intervention approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining images for optional further research. The Investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate tick box will be required to document a participant's agreement to allow any participant data and/or images to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR) / equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.7.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant is screened in the clinical study.

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

All protocol required laboratory assessments, as defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol SoA. Laboratory requisition forms must be completed, and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy Testing
    - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count WBC Count (absolute) Reticulocyte Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC)		WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Chloride	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Uric Acid
	Glucose (fasting/non-fasting)[2]	Bicarbonate	Gamma-Glutamyl Transferase (GGT)	Albumin
	Sodium	Calcium	Alkaline phosphatase	Total Protein
	Bile Acids	Creatinine phosphokinase (CPK)		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Cardiac troponin			
Other Screening Tests	• HbA1c (Screening only. Fasting) • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) or Hepatitis C Virus RNA test (either quantitative or qualitative) should be reflexively performed on the same sample to confirm the result) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)			

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Glucose will be fasting for all screening only. Glucose can be non-fasting for all other time points.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

Events NOT Meeting the AE Definition
convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
○ Results in death
○ Is life-threatening
The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

A SAE is defined as any untoward medical occurrence that, at any dose:
jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before

AE and SAE Recording
submission to GSK. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to GSK. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

Assessment of Causality
assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the GSK Medical Monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of participant's medical records, medical examination, or medical history interview.
2. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) and estradiol level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH and estradiol measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1
    - Are abstinent from heterosexual or homosexual intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal

intercourse with a woman of childbearing potential and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 5.1.

- In addition, male participants must refrain from donating sperm from the time of first dose of study treatment until the follow-up visit.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

10.4.2. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be 12 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) OR international normalized ratio (INR)>1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event case report form (CRF), and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver chemistry event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge participant with study intervention unless allowed per protocol and GSK Medical Governance approval is granted (see below).
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within 24h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE case report form (CRF)
• Record use of concomitant medications on the concomitant medications CRF page including acetaminophen, herbal remedies,</td></tr>
</table>

MONITORING: **<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>If</u> ALT≥3xULN <u>AND bilirubin</u> < 2xULN <u>and INR</u> ≤1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	other over the counter medications. • Record alcohol use on the liver event alcohol intake CRF page **<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A Immunoglobulin M (IgM) antibody; HbsAg and HBcAb; Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to pk blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6. Appendix 6: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
CCI [redacted]	
BMI	Body mass index
BRB	Blood-Retinal-Barrier
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
Cav	Average plasma concentration
CFB	Change from baseline
CI	Confidence Interval
C_{max}	Maximum observed plasma concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
CSSRS	Columbia Suicidality Severity Rating Scale
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DNA	Deoxyribonucleic acid
DR	Diabetic Retinopathy
ECG	Electrocardiogram
eCRF	Electronic case report form
CCI [redacted]	
EVA	Electronic Visual Acuity
CCI [redacted]	
FDA	Food and Drug Administration
CCI [redacted]	
FSH	Follicle Stimulating Hormone
FU	Follow-up
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma Glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HbA1c	Glycated Hemaglobin

HBsAg	Hepatitis B surface antigen
hCG	Human Chorionic Gonadotropin
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
h/hr	Hour(s)
HR	Heart Rate
HRT	Hormonal replacement therapy
HUVEC	Human umbilical vein endothelial cell
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IOP	Intraocular pressure
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
IVIVT	In Vitro/In Vivo Translations
Kg	Kilogram
KO	Knockout
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
mmHg	Millimeter of Mercury
MSDS	Material Safety Data Sheet
Msec	Milliseconds
NOAEL	No observed adverse effect level
nM	Nano Molar
OCT	Optical Coherence Tomography
PD	Pharmacodynamic
PDR	Proliferative diabetic retinopathy
P-gp	p-glycoprotein
PK	Pharmacokinetic
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RBC	Red Blood Cells
RNA	Ribonucleic Acid

SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TPR	Third Party Resourcing
TRPV4	Transient receptor potential vanilloid 4
UA	Urinalysis
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cells
WD	Withdrawal
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
SAS

10.7. Appendix 7: Protocol Amendment History

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 04	*11-NOV-2021*	*TMF- 14073254*
Amendment 03	*24-MAR-2021*	*TMF-11874499*
Amendment 02	*28-OCT-2020*	*2019N404030_02*
Amendment 01	*11-MAY-2020*	*2019N404030_01*
Original Protocol	*19 SEP 2019*	*2019N404030_00*

Amendment 04 11-NOV-2021

Overall Rationale for the Amendment: The fellow eye CCI inclusion criterion was included in the original protocol where an 8 week opt-in period was allowed, resulting in a total potential dosing duration of 3 months. The criterion was to ensure the fellow eye was unlikely to progress over that 3 months period. The criterion is being removed since minimal disease progression is expected within the current 28-day dosing period. Note that treatment for DME is allowable at any time while on study in the fellow eye. A single ECG replaces mandatory triplicate ECG measurement at screening to determine eligibility. If a subject is withdrawn for a clinically significant QTc value, ECG withdrawal measurements will still require collection in triplicate per protocol.

Where the Amendment Applies:

This protocol Amendment 4 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
Page 1	Added US IND number (#)	IND number was missing from the title page

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Previous Text: CCI [redacted] CCI [redacted] letter score of 80 letter or worse (Snellen equivalent ~20/25) or worse in the study eye. The non-study fellow eye should be equivalent or better at Baseline, pre-dose. Revised Text: CCI [redacted] CCI [redacted] letter score of 80 letter or worse (Snellen equivalent ~20/25) or worse in the study eye.	The non-study, fellow eye criterion is being removed since minimal disease progression is expected within the current 28 days dosing period. Treatment for DME in the fellow eye remains allowable at any time while on study.
Section 1.3 Section 8.1.3	Previous Text: Triplicate ECG required at Screening & WD Revised text: Single ECG required at Screening, Baseline, Treatment periods, and follow-up; Triplicate ECG required at WD Previous Text Bullet 2: • Triplicate 12-lead ECGs will be obtained for trial eligibility. Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. • Single 12-lead ECG will be obtained as outlined in the SoA (Section 1.3). Revised Text Bullet 2: • Single 12-lead ECGs will be obtained for trial eligibility and will be obtained as outlined in the SoA (Section 1.3).	The triplicate ECG measurement at screening to determine eligibility and for monitoring throughout the study are reduced to a single ECG reading. If a subject is withdrawn for a clinically significant QTc value, ECG withdrawal measurements will still require collection in triplicate per protocol. (Bullet 2)

Section # and Name	Description of Change	Brief Rationale
Section 10.3.2	Previous Text: A SAE is defined as any untoward medical occurrence that, at any dose: Revised Text: An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:	As per latest protocol template following SAE definition has been updated
Section 10.3.5	Removed the requirement of SAE reporting in Electronic case form (eCRF) within 72 hours	Removal of additional step of eCRF check.

DOCUMENT HISTORY

List dates of original protocol and all amendments in reverse chronological order**.**

Document	Date	DNG Number
Amendment 03	*24-MAR-2021*	*TMF-11874499*
Amendment 02	*28-OCT-2020*	*2019N404030_02*
Amendment 01	*11-MAY-2020*	*2019N404030_01*
Original Protocol	*19 SEP 2019*	*2019N404030_00*

Amendment 03

Overall Rationale for the Amendment: This Protocol Amendment 03 is being implemented to remove the 8-week Opt-in period as well as address several administrative revisions.

Where the Amendment Applies:

This protocol Amendment 3 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
Multiple Sections: 1. Protocol Summary 2. Introduction 3. Objectives and Endpoints 4. Study Design 8. Study Assessments and Procedures 9. Statistical Considerations	Removal of 8-week opt-in period body text, tables and schematics. This includes protocol content that solely supports the conduct of the 8-week opt-in period.	The Protocol 212669 was designed to be a 28-day Phase 1b safety study with an opt-in 8-week extension to explore pharmacodynamics and safety/tolerability beyond 28 days. The primary endpoints were at the 28-day visit. Removal of the 8-week opt-in period retains focus on the primary objectives, safety, tolerability and pharmacodynamics at 28-days and better aligns with a Phase 1b safety study design. The change was prompted, in part, by feedback during regulatory review when opening an investigational new drug (IND) in the United States.
Objectives and Endpoints Tables 1.1 Synopsis 3 Objectives and Endpoints	Removal of Exploratory Endpoint. PREVIOUS TEXT: CCI [redacted]	CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Assessments	Reference and linking to protocol sections pertaining to confirmation of non-childbearing status for women. PREVIOUS TEXT: As needed in women of non-childbearing potential only REVISED TEXT: As needed in women of non-childbearing potential only. See Section 10.2 and Section 10.4	Administrative change.
4.3.1. Dose Rationale	Correction of unit C_{max} unit to ng/mL PREVIOUS TEXT: The proposed clinical dose of 3.2mg once daily GSK2798745 is selected so that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng.hr/mL. REVISED TEXT: The proposed clinical dose of 3.2mg once daily GSK2798745 is selected so that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng/mL 50 ng.hr/mL	Administrative correction in text body.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses	Changed the context of review to 28-day data. PREVIOUS TEXT: If neither Positive nor Negative criterion are meet, an evaluation of the CCI [redacted] CCI [redacted] will be performed. A positive outcome will be concluded if the CCI [redacted] after completing 3-months of dosing is greater than 6 letters. REVISED TEXT: If neither Positive nor Negative criterion are meet, an evaluation of the CCI [redacted] CCI [redacted] will be performed. A positive outcome will be concluded if the CCI [redacted] after completing 28 days 3-months of dosing is 3 letters or greater is greater than 6 letters as reviewed in the context of all available PD data.	With the removal of the 8-week opt-in period, the criteria to review CCI [redacted] CCI [redacted] letter score was adjusted to reflect a 28-day threshold. Given the large variability expected for 28-day CCI [redacted] the entirety of the 28-day PD data will be used in addition to the CCI [redacted] for decision making should neither Positive nor Negative criterion be met.
9.2 Sample Size Determination	Correction of probability of a positive study outcome value to align with Figure 2 and Table 3 PREVIOUS TEXT: • if the true mean change from baseline in SD-OCT at 28 days as 95 µm then, the probability of a positive study outcome is 71.1%. REVISED TEXT: • if the true mean change from baseline in SD-OCT at 28 days as 95 µm then, the probability of a positive study outcome is 71.1% 74.2%.	Administrative correction. Previous text corresponded with a standard deviation of 80 µm for a sample size of 20. Updated to standard deviation of 75 µm for a sample size of 20 to align with Figure 2

Section # and Name	Description of Change	Brief Rationale
11. References	Publication date correction. PREVIOUS TEXT: Dugel, PU, et al. 2016. "Dexamethasone intravitreal implant in the treatment of diabetic macular edema." Clinical Ophthalmology, 9: 1321–1335. REVISED TEXT: Dugel, PU, et al. 2015 2016. "Dexamethasone intravitreal implant in the treatment of diabetic macular edema." Clinical Ophthalmology, 9: 1321–1335.	Administrative correction of reference publication date.

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY

List dates of original protocol and all amendments in reverse chronological order.

Document	Date	DNG Number
Amendment 02	*28-OCT-2020*	*2019N404030_02*
Amendment 01	*11-MAY-2020*	*2019N404030_01*
Original Protocol	*19 SEP 2019*	*2019N404030_00*

Amendment 02 28-OCT-2020

Overall Rationale for the Amendment: This Protocol Amendment 02 is being implemented to adjust specific inclusion and exclusion criteria and clarify the assessment window for Baseline Spectral-Domain Optical Coherence Tomography (SD-OCT), CCI [redacted] CCI and Ophthalmic exams.

Where the Amendment Applies:

This Protocol Amendment 2 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
1.3.1: 28 Day – 4 Week Treatment Period	Clarification of Baseline assessment window for SD-OCT in Schedule of Assessments (SoA) Notes column NEW TEXT If the date of the screening SD-OCT is within 3 days of baseline, the screening SD-OCT can be considered as baseline SD-OCT	Providing clarity to SoA. Minimal biological changes expected within a 3-day timeframe.
1.3.1: 28 Day – 4 Week Treatment Period	Clarification of Baseline assessment window for CCI in SoA Notes column NEW TEXT If the date of the screening CCI is within 3 days of baseline, the screening CCI can be considered as baseline CCI	Providing clarity to SoA. Minimal biological changes expected within a 3-day timeframe.
1.3.1: 28 Day – 4 Week Treatment Period	Clarification of Baseline assessment window for General Ophthalmic Exam in SoA Notes column NEW TEXT If the date of the screening general ophthalmic exam is within 3 days of baseline, the screening exam can be considered as baseline	Providing clarity to SoA. Minimal biological changes expected within a 3-day timeframe.
5.1: Inclusion Criteria, CCI, #5	Updated Inclusion Criteria to allow participants with better vision to enrol in the study PREVIOUS TEXT CCI letter score of 68 letter or worse (Snellen equivalent ~20/50) or worse in the study eye. The non-study fellow eye should be ≥ 73 letters or better at Day 1 pre-dose. REVISED TEXT CCI letter score of 80 letter or worse (Snellen equivalent ~20/25) or worse in the study eye. The non-study fellow eye should be equivalent or better at Baseline, pre-dose.	The original rational for this criterion was to ensure sufficiently impacted vision in the study eye to have a better opportunity to observe improvement. It was also to ensure approximately equal or better vision in the fellow eye. As the CCI is not the primary endpoint, changing the criterion will enable a better opportunity to enrol patients for the primary endpoint of OCT. The new wording maintains that the fellow eye has equal or better vision than the treatment eye.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria, anti-VEGF SOC, #6	Updated Exclusion Criteria to decrease anti-VEGF washout period PREVIOUS TEXT Use of intravitreal ranibizumab, bevacizumab or aflibercept in the study eye within 90 days of dosing. Allowed in fellow eye. REVISED TEXT Use of intravitreal ranibizumab or bevacizumab within 42 days (6 weeks), or aflibercept within 56 days (8 weeks) of dosing in the study eye. Allowed in fellow eye.	Decreasing the required anti-VEGF wash-out period to better align with prescribing labels and treatment practices.

Amendment [01]: 11-May-2020

Overall Rationale for the Amendment

In relation to the Coronavirus SARS-CoV-2 (COVID-19) pandemic, this Protocol Amendment 01 serves to clarify exclusion criteria and include the allowance of replacement participants, add protocol defined laboratory tests, as well as address several administrative revisions.

Where the Amendment Applies:

This protocol Amendment 1 applies to all sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
1.3.1: 28 Day – 4 Week Treatment Period	Added wording to Day 1 Dosing Notes section. NEW TEXT: Additional guidance on Day 1 dosing can be found in the SRM.	Updated Notes section to direct sites to Study Reference Manual (SRM) for guidance on how to conduct Day 1 dosing.
1.3.2: 8-Week Opt-in Treatment Period	Troponin Laboratory test added to Week 6 (Day 42) and Week 10 (Day 70) to monitor troponin levels.	The additional troponin collections were added for the opt-in period to keep the maximum between-testing interval as 2 weeks, consistent with the 28-day primary dosing period

Section # and Name	Description of Change	Brief Rationale
		maximum interval.
1.3.2: 8-Week Opt-in Treatment Period	Added 12-Lead ECG assessment at the Day 112 Follow-up to align with the Day 56 Follow-up assessments.	Typographical error in the original protocol.
4.2: Scientific Rationale for Study Design	Updated section to allow visual acuity assessment via either CCI [redacted] CCI [redacted] PREVIOUS TEXT: Visual acuity using CCI [redacted] CCI [redacted] chart reading will be measured at specified visits as per the SoA REVISED TEXT: Visual acuity using CCI [redacted] CCI [redacted] chart reading will be measured at specified visits as per the SoA	Administrative change per Protocol Note to file dated 03 FEB 2020 providing clarification to protocol wording to allow Clinical Sites to measure visual acuity per current standard of care.
5.2: Exclusion Criteria, Medical Conditional – Non-Ocular, # 18	Updated exclusion criteria to specifically prohibit eligibility of infectious participants. PREVIOUS TEXT 18. History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study. REVISED TEXT: 18. History or current evidence of any serious or clinically significant cardiac, gastrointestinal, renal, endocrine, neurologic, hematologic, infectious or other condition that is uncontrolled on permitted therapies or	The existing phrase 'or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study' does have infection within its scope. However, given the current pandemic, infection is being emphasize as a specific category.

Section # and Name	Description of Change	Brief Rationale
	that would, in the opinion of the Investigator or the Medical Monitor, make the participant unsuitable for inclusion in this study.	
5.2: Exclusion Criteria, Medical Other Exclusions, # 34	Updated exclusion criteria to clarify exclusion of participants with history of regular substance abuse including drug and/or alcohol. PREVIOUS TEXT: 34. Regular alcohol consumption within 6 months prior to the study defined as: An average weekly intake of > 14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. REVISED TEXT: 34. Regular substance abuse including drug and/or alcohol consumption within 6 months prior to the study. Alcohol consumption is defined as: An average weekly intake of > 14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.	Administrative change to align wording with assessments in Schedule of Activities (SoA).
7.1: Discontinuation of Study Intervention	Updated section to allow for replacement participants. NEW TEXT: If subjects are prematurely discontinued from the study prior to completing the primary endpoint 28-day dosing period, additional replacement participants may be enrolled at the discretion of the Sponsor in consultation with the Investigator. Replacement participants may be enrolled until the protocol defined sample size is achieved.	Given the current pandemic and higher risk of drop-out, the section is modified to allow for replacement participants to ensure sufficient participants are available for evaluation of the primary 28-day endpoint.
8.1.7.1: Refraction and Visual Acuity	Updated section to allow visual acuity assessment via either CCI [redacted] CCI	Administrative change per Protocol Note to file dated 03 FEB 2020, providing clarification to protocol wording to allow Clinical Sites to

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted] PREVIOUS TEXT: • Refraction and visual acuity will be measured using electronic CCI [redacted] visual acuity charts (eVA). REVISED TEXT: • Refraction and visual acuity will be measured using electronic CCI [redacted] visual acuity charts (eVA with CCI [redacted]) or standard CCI [redacted] visual acuity charts (light box with CCI [redacted] charts). • Refraction and visual acuity assessments must be taken with the same method of assessment (i.e. CCI [redacted] or CCI [redacted] throughout the duration of the study. See the SRM for more details.	measure visual acuity per current standard of care.
10.2: Clinical Laboratory Tests	Updated section to remove reference to serum or urine pregnancy testing per SoA. PREVIOUS TEXT: Serum or urine pregnancy tests should be performed as per the SoA (Section 1.3). Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study. REVISED TEXT: Additional Serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.	Administrative change to align requirement for routine pregnancy testing to the Schedule of Assessments. Women of Childbearing potential are not eligible to participate in the study; therefore, routine pregnancy testing is not required per the SoA. Pregnancy testing may be performed as determined necessary by the Investigator or local regulations to establish absence of pregnancy.
10.2: Clinical	Updated Appendix 2, Table 4: Protocol-Required Safety Laboratory	Correction due to incomplete

Section # and Name	Description of Change	Brief Rationale
Laboratory Tests	Assessments to detail additional protocol required laboratory tests.	template table.
10.6 Abbreviations and Trademarks	Updated Appendix 6: Abbreviations and Trademarks to include additional abbreviations and remove irrelevant abbreviations and trademarks.	Administrative change
11: References	Updated Arrendondo reference to correct author name. PREVIOUS TEXT: Arredondo, ZD, et al. (2017). "Dual contribution of TRPV4 antagonism in the regulatory effect of vasoinhibins on blood-retinal barrier permeability: diabetic milieu makes a difference." Scientific Reports, 7: 13094. REVISED TEXT: Arredondo, Zamarripa D, et al. (2017). "Dual contribution of TRPV4 antagonism in the regulatory effect of vasoinhibins on blood-retinal barrier permeability: diabetic milieu makes a difference." Scientific Reports, 7: 13094.	Administrative change to accurately reflect author reference.

11. REFERENCES

Arredondo Zamarripa D, et al. (2017). "Dual contribution of TRPV4 antagonism in the regulatory effect of vasoinhibins on blood-retinal barrier permeability: diabetic milieu makes a difference." Scientific Reports, 7: 13094.

Bates, DO. 2010. "Vascular endothelial growth factors and vascular permeability." Cardiovascular Research, 87, 262-271.

Blinder, KJ, et al. 2017. "Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO study report 1)." Clinical Ophthalmology, 11:393-401.

Boyer, DS, et al. 2014. "Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema." Ophthalmology, 121:1904-1914.

Dugel, PU, et al. 2015. "Dexamethasone intravitreal implant in the treatment of diabetic macular edema." Clinical Ophthalmology, 9: 1321–1335.

Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group. Photocoagulation for Diabetic Macular Edema. Early Treatment Diabetic Retinopathy Study Report 1. Arch Ophthalmology 1985: 103: 1796 – 1806.

Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group. Photocoagulation for Diabetic Macular Edema. Early Treatment Diabetic Retinopathy Study Report 4. International Ophthalmology Clinics 1987: 27(4): 256-272.

Everaerts, W, et al. 2010. "Inhibition of the cation channel TRPV4 improves bladder function in mice and rats with cyclophosphamide-induced cystitis." PNAS 107:44

Fogli, S, et al. 2016. "Pathophysiology and pharmacological targets of VEGF in diabetic macular edema." Pharmacological Research, 103:149–157.

Fragala, MS, Kaufman HW, Meigs JB, Niles JK, McPhaul MJ, "Consequences of the COVID-19 Pandemic: Reduced Hemoglobin A1c Diabetes Monitoring." *Population Health Management*, 2021; 24(1) 8-10.

Gonzalez, VH, et al. 2016. "Early and Long-Term Responses to Anti–Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data." American Journal of Ophthalmology, 172: 72-79.

GSK Document Number 2011N112198_01 Study DM2115403 A phase 2, multi-national, multi-centre, double masked, randomised, 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, 2011-Oct-11

GSK Document Number 2013N162862_07. Investigator's Brochure (IB) for GSK2798745. Version 08, 2020-June-10.

GSK Document Number 2018N386129_00. Study 207702 A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough, 2018-June-18

Haritoglou, C, et al. 2018. "Pathophysiology of diabetic macular edema – a background for current treatment modalities." Expert Review of Ophthalmology, 13(5): 273-281.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-84.

Lee, R, et al. 2015. "Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss." Eye and Vision, 2:17, DOI: 10.1186/s40662-015-0026-2, 25 pages.

Phuong, TTT, et al. 2017 "Calcium influx through TRPV4 channels modulates the adherens contacts between retinal microvascular endothelial cells." J Physiol, 595: 6869-6885.

Ryskamp, D. A. et al. 2016 "TRPV4 regulates calcium homeostasis, cytoskeletal remodeling, conventional outflow and intraocular pressure in the mammalian eye." *Sci. Rep.* 6, 30583; doi: 10.1038/srep30583

Samuels, TA, Bolen S, Yeh HC, Abuid M, Marinopoulos SS, Weiner JP, "Missed Opportunities in Diabetes Management: A Longitudinal Assessment of Factors Associated with Sub-optimal Quality." *Journal of General Internal Medicine*, 2008; 23(11)1770-1777.

Singer, MA, et al. (2016). "Diabetic macular edema: it is more than just VEGF." F1000 Research, 2015, 5(F1000 Faculty Rev):1019, DOI: 10.12688/f1000research.8265.1, 6 pages.

Wen, L, et al. (2018). "TRPV4 regulates migration and tube formation of human retinal capillary endothelial cells." BMC Ophthalmol. 18: 38.

Yau, JWY, et al. 2012. "Global Prevalence and Major Risk Factors of Diabetic Retinopathy." Diabetes Care, 35:556–564.