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

Study No: HMD114728
Title : A Multicenter, Randomized, Parallel Group, Placebo Controlled Study to Evaluate the Safety and Efficacy of GSK256073 Administered Once or Twice Daily for 12 Weeks in Subjects with Type 2 Diabetes Mellitus who are being treated with Metformin
Rationale: GlaxoSmithKline (GSK) is investigating GSK256073 based on the current understanding of the mechanism of action of acipimox. In addition to its effects on lipids, acipimox has shown a reduction in glucose area under concentration-time curve (AUC) following an oral glucose tolerance test when administered in patients with Type 2 diabetes mellitus (T2DM). GSK256073 binds to HM74a receptors in the adipocyte and this ultimately results in inhibition of lipolysis, with an associated decrease in circulating free fatty acids. This is thought to result in restoration of insulin action in the liver and skeletal muscle. The results from previous GSK studies indicate that an HM74A agonist may have a potential benefit for glucose control in the treatment of T2DM.
Phase: II
Study Period: 13 July 2011 – 17 September 2012
Study Design: This was a multi-center, randomized, single-blinded (subjects and the site medical staff were blinded; while some sponsor staff and site pharmacy staff were unblinded to treatment), placebo-controlled, dose ranging study in subjects with T2DM. Screening: To determine the eligibility for the enrolment into the study, screening procedures were performed within 50 days of the first dose of study drug, Two-week Placebo Run-in Period: Subjects continued their current metformin monotherapy and took 2 placebo capsules once per day in the morning during this 2-week placebo run-in period. Subjects monitored fasting blood glucose levels daily using a glucometer and recorded their daily glucose levels in a diary. Twelve-week Treatment Period: At the end of the placebo run-in period and prior to randomization at the baseline visit, investigators confirmed the average of the last 3 subject-recorded glucometer readings as reported on the subject glucometer log. The average was to be less than 240 mg/dL (13.3 mmol/L) to qualify for participation. Subjects were admitted to the research facility on Day -1 for baseline evaluations and procedures. On the morning of Day 1, after successfully completing all baseline assessments, subjects received placebo along with standardized meals. Serial pharmacokinetic (PK) and pharmacodynamic (PD) samples were taken and these served as baseline profiles. On Day 2, subjects were planned to be randomized in a 2:2:2:2:1:1 ratio to receive doses of GSK256073 5 mg twice a day (BID), 10 mg once a day (QD), 25 mg BID, 50 mg QD; placebo BID or QD. Subjects continued on their current treatment with metformin throughout the study. Subjects could either take 2 capsules in the morning (QD arms) or 1 capsule in the morning and 1 in the evening (BID arms). All doses were taken in a fed state. Serial PK and PD samples were taken and after the last assessment was completed on Day 2, subjects were discharged from the research facility. Subjects visited the clinic every 3 weeks (Weeks 3, 6, 9, and 12) after the start of dosing. Subjects recorded the results of daily glucometer assessments in a diary and reported results to clinic staff during the scheduled study visits. At Week 6 (on Day 41), subjects were again admitted to the research facility and received the randomized study treatments on Day 42, and a 12-hour PK/PD samples were taken. After the last assessment was completed, subjects were discharged from the research facility. Follow-up Period: Subjects returned to the clinic for a follow-up visit 5-10 days after completing the treatment period. During the 2-week follow-up period, subjects continued to check their fasting blood glucose values at home as instructed at screening visit. A subject's total participation in the study was approximately 20 weeks.
Centers: 14 centers in 4 countries (France [4], Spain [3], United Kingdom [4], Unites States [3])
Indication: Type 2 Diabetes Mellitus

Treatment: Subjects were assigned to 1 of 6 possible treatment regimens in a 2:2:2:2:1:1 ratio and were stratified based on subjects' triglyceride (TG) level (≥150 mg/dL or <150 mg/dL) in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software (i.e., RandAll).

Regimen	Description
A	GSK256073 5 mg BID
B	GSK256073 10 mg QD
C	GSK256073 25 mg BID
D	GSK256073 50 mg QD
P1	GSK256073 matched placebo BID
P2	GSK256073-matched placebo QD

Note: Placebo results (Treatment regimen P1 and P2) were pooled in results tables.

Objectives:

Primary:

- To investigate the safety and efficacy of 12 weeks of daily dosing with GSK256073 in subjects with Type 2 diabetes mellitus (T2DM) who are on metformin monotherapy

Secondary

- To evaluate the sustainability of effects, and to examine the correlation between Week 6 non-esterified fatty acids (NEFA) inhibition and glucose lowering
- To characterize the exposure-response pharmacokinetic/pharmacodynamic (PK/PD) relationship for change from baseline in Week 12 glycated hemoglobin (HbA1c)
- To assess the effects of 12 weeks daily dosing with GSK256073 on fasting plasma glucose
- To assess the effects of 12 weeks daily dosing with GSK 256073 on insulin sensitivity relative to placebo
- To assess the effects of 6 weeks and 12 weeks daily dosing with GSK256073 on fructosamine
- To determine number of subjects achieving HbA1c treatment targets for diabetes management
- To characterize the exposure response PK/PD relationship with selected secondary endpoints, if feasible*
  *No positive exposure/response relationships were observed between drug exposure and pharmacodynamic endpoints so formal PK/PD analyses were not performed.

Statistical Methods: A sample size of 14 subjects completing the study in each treatment arm was calculated based on observations from previous studies.

No formal statistical analyses were planned for safety data. Safety data were listed and summarized by treatment. All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability (safety population).

Change from baseline HbA1c data was analyzed for the PD population (all subjects who provided PD data) using a mixed effect model with regimen, week, regimen by week interaction and as fixed effects, and a repeated measure statement using unstructured variance/covariance matrix for subject, baseline HbA1c and TG level (continuous variable) as covariate.

Plasma GSK256073 concentration-time data were analyzed for the PK Population (all subjects from whom a PK sample was obtained and analyzed) by non-compartmental methods with the most current version of WinNonlin.

Study Population: Male and female subjects with a diagnosis of T2DM with onset at least 6 months prior to Screening were eligible to participate in this study. Subjects were required to have HbA1c levels ≥7.0% and ≤9.5% and fasting plasma glucose level <13.3 mmol/L (240 mg/dL) at Screening. Subjects on a stable dose of metformin (monotherapy) for 2 months were eligible.

Subjects were to be overweight with a body mass index (BMI) ≥25 kg/m2 for non-Asian Indians and ≥24 kg/m2 for Asian-Indian, and <40 kg/m2. Subjects in France were eligible only if they were affiliated to or had a beneficiary of a social security category.

Subjects requiring insulin therapy or use of combination oral antidiabetic medications or use of monotherapy other than metformin within the 3 months prior to screening were not eligible to participate in the study.

Number of Subjects:	**Placebo (pooled) (N=20)**	**GSK256073 5 mg BID (N=18)**	**GSK256073 10 mg QD (N=19)**	**GSK256073 25 mg BID (N=19)**	**GSK256073 50 mg QD (N=18)**	**Total**
Planned N	18	18	18	18	18	90
Dosed N	20	18	19	19	18	94
Completed n (%)	18 (90%)	17 (94%)	16 (84%)	14 (74%)	17 (94%)	82 (87%)
Total Number Subjects Withdrawn N (%)	2 (10%)	1 (6%)	3 (16%)	5 (26%)	1 (6%)	12 (13%)
Withdrawn due to Adverse Events n (%)	1 (5%)	0	0	2 (11%)	0	3 (3%)
Withdrawn for Other Reasons n (%)	1 (5%)	1 (6%)	3 (16%)	3 (16%)	1 (6%)	9 (11%)
Demographics	**PBO**	**A**	**B**	**C**	**D**	**Total**
N (Safety Population)	20	18	19	19	18	94
Females: Males	4: 16	7: 11	10: 9	5: 14	1: 17	27: 67
Mean Age in Years (SD)	57.0 (7.01)	60.0 (6.24)	59.6 (8.07)	60.2 (6.21)	57.1 (7.30)	58.8 (7.01)
Mean Weight in Kg (SD)	88.81 (14.896)	84.94 (13.434)	83.80 (19.575)	89.85 (13.130)	92.16 (14.931)	87.91 (15.369)
Race, n (%)						
White – White/ Caucasian/ European Heritage	16 (80)	18 (100)	19 (100)	16 (84)	18 (100)	87 (93)
African American/African Heritage	3 (15)	0	0	2 (11)	0	5 (5)
Asian – South East Asian Heritage	1 (5)	0	0	0	0	1 (1)
Mixed race	0	0	0	1 (5)	0	1 (1)

Pharmacodynamics (PD) Endpoints:

Change from Baseline in HbA1c (% TL HB) by Visit and Treatment in HMD1114728

	Treatment				
	Placebo (pooled) (N=20)	**GSK256073 5 mg BID (N=18)**	**GSK256073 10 mg QD (N=19)**	**GSK256073 25 mg BID (N=19)**	**GSK256073 50 mg QD (N=18)**
Day 41, n	19	17	17	17	18
Mean	-0.34	-0.18	-0.37	-0.42	-0.44
90% CI	-0.62, -0.06	-0.41, 0.06	-0.56, -0.18	-0.60, -0.24	-0.60, -0.29
SD	0.709	0.555	0.443	0.423	0.370
Median (Min., Max)	-0.50 (-1.8, 1.2)	0.00 (-1.2, 0.8)	-0.40 (-1.3, 0.4)	-0.40 (-1.3, 0.2)	-0.40 (-1.2, 0.6)
Week 9, n	18	17	16	16	17
Mean	-0.44	-0.24	-0.48	-0.56	-0.59
(90% CI)	-0.77 -0.11	-0.50, 0.02	-0.70, -0.25	-0.78, -0.33	-0.78, -0.39
SD	0.808	0.608	0.503	0.512	0.464
Median (Min., Max)	-0.60 (-1.8 1.4)	-0.10 (-1.4, 0.8)	-0.35 (-1.6, 0.4)	-0.60 (-1.5 0.6)	-0.50 (-1.4, 0.5)
Week 12, n	18	17	16	15	17
Mean	-0.36	-0.14	-0.46	-0.56	-0.64
(90% CI)	-0.65 -0.07	-0.47, 0.19	-0.68, -0.24	-0.82, -0.30	-0.91, -0.37
SD	0.698	0.778	0.507	0.562	0.630
Median (Min., Max)	-0.45 (-1.6, 0.8)	-0.10 (-1.3, 1.9)	-0.30 (-1.2, 0.5)	-0.60 (-1.4, 0.4)	-0.60 (-1.7, 0.8)

Note: Baseline is defined as Day -1 visit

Point Estimates and 90% Confidence Intervals for Comparisons of Change from Baseline HbA1c Between Treatment Groups and Between BID and QD Treatments at Week 12 in HMD114728						
Comparison Test vs. Ref.	LS Mean				Treatment Difference	90% CI of the Difference
	n	Test	n	Ref.		
Comparisons of Change from Baseline HbA1c between Treatment Groups						
A-P	17	-0.16	18	-0.40	0.24	-0.13, 0.60
B-P	16	-0.41	18	-0.40	-0.01	-0.37, 0.35
C-P	15	-0.53	18	-0.40	-0.13	-0.49, 0.23
D-P	17	-0.70	18	-0.40	-0.30	-0.66, 0.06
Comparisons of Change from Baseline HbA1c between BID and QD Treatments						
10mg BID-QD	17	-0.13	16	-0.41	0.28	-0.07, 0.63
50mg BID-QD	15	-0.52	17	-0.68	0.16	-0.19, 0.51
P=Placebo (Pooled); A=GSK256073 5mg BID; B=GSK256073 10mg QD, C=GSK256073 25mg BID; D=GSK256073 50mg QD Note: Baseline is defined as Day -1 visit						

Summary of Percentage of Subjects with HbA1c (% TL HB) <7.0% and <6.5% and Subjects Achieving HbA1c (% TL HB) Treatment Target at Week 12 in HMD114728					
	Treatment				
	Placebo (pooled) (N=20)	GSK256073 5 mg BID (N=18)	GSK256073 10 mg QD (N=19)	GSK256073 25 mg BID (N=19)	GSK256073 50 mg QD (N=18)
HbA1c (% TL HB) <7.0% and <6.5%					
n	18	17	16	15	17
< 7.0%	4 (22%)	3 (18%)	2 (13%)	3 (20%)	11 (65%)
< 6.5%	2 (11%)	0	0	1 (7%)	4 (24%)
HbA1c (% TL HB) Treatment Target					
n	18	17	16	15	17
≤ -0.7%	6 (33%)	4 (24%)	6 (38%)	7 (47%)	7 (41%)
≤ -0.5%	9 (50%)	5 (29%)	7 (44%)	8 (53%)	9 (53%)
Note: Baseline is defined as Day -1 visit					

Change from Baseline Predose Fasting Glucose, Insulin and Homeostasis Assessment Index (HOMA) Concentration in HMD1114728					
	Treatment				
	Placebo (pooled) (N=20)	GSK256073 5 mg BID (N=18)	GSK256073 10 mg QD (N=19)	GSK256073 25 mg BID (N=19)	GSK256073 50 mg QD (N=18)
Glucose (mmol/L)					
Week 12, n	18	17	16	15	17
Mean	-0.64	-0.85	-0.71	-0.44	-0.83
(95% CI)	(-1.36, 0.07)	(-2.16, 0.45)	(-1.40, -0.02)	(-0.94, 0.07)	(-1.60, -0.06)
SD	1.439	2.547	1.290	0.913	1.497
Median (Min, Max)	-0.73 (-3.0, 3.4)	-0.73 (-6.1, 3.6)	-0.55 (-3.7, 0.8)	-0.20 (-1.9, 0.7)	-0.93 (-3.4, 1.9)
Insulin (pmol/L)					
Week 12, n	14	14	15	13	15
Mean	27.3	14.7	-2.0	33.4	4.7
(95% CI)	(-53.1, 107.7)	(-7.6, 37.0)	(-16.3, 12.3)	(-15.5, 82.3)	(-19.3, 28.8)
SD	139.30	38.66	25.80	80.94	43.42
Median (Min, Max)	4.0 (-58, 498)	17.0 (-58, 78)	0.0 (-40, 56)	6.0 (-90, 198)	-6.0 (-48, 96)
HOMA					
Week 12, n	14	14	15	13	15
Mean	-0.0	0.0	-0.3	1.5	-0.1
(95% CI)	(-2.1, 2.0)	(-1.4, 1.4)	(-1.5, 0.8)	(-1.1, 4.0)	(-2.0, 1.8)
SD	3.57	2.47	2.08	4.17	3.44
Median (Min, Max)	0.1 (-5, 9)	-1.1 (-3, 5)	-0.8 (-3, 5)	0.1 (-6, 9)	-0.4 (-4, 8)
Note: Baseline is defined as Day -1 visit					

Change from Baseline in Glucose, Insulin, and NEFA 0 to 12 hour Weighted Mean Concentrations by Visit and Treatment in HMD1114728					
	Treatment				
	Placebo (pooled) (N=20)	GSK256073 5 mg BID (N=18)	GSK256073 10 mg QD (N=19)	GSK256073 25 mg BID (N=19)	GSK256073 50 mg QD (N=18)
Glucose (mmol/L)					
Day 2, n	20	17	18	18	18
Mean	0.462	-0.502	0.036	-0.517	-0.076
95% CI	-0.031, 0.954	-1.579, 0.575	-0.485, 0.556	-0.944, -0.091	-0.561, 0.408
SD	1.0525	2.0948	1.0464	0.8577	0.9745
Median	0.440	-0.520	-0.090	-0.625	-0.115
Min., Max	-1.66, 2.77	-7.00, 2.47	-1.87, 2.82	(-2.22, 1.01)	-1.94 1.54
Week 6, n	19	17	17	16	18
Mean	0.009	-0.786	-0.502	-0.647	-0.544
95% CI	-0.863, 0.882	-2.385, 0.813	-1.170, 0.166	-1.182, -0.112	-1.210, 0.123
SD	1.8099	3.1101	1.2995	1.0043	1.3403
Median	0.110	-0.400	-0.250	-0.505	-0.515
Min., Max	-4.63, 3.02	-8.09, 4.76	-3.20, 1.22	-3.12, 1.12	-3.71, 1.68
Insulin (pmol/L)					
Day 2, n	20	17	18	18	18
Mean	25.30	-2.15	0.69	-15.78	-2.08
95% CI	3.19, 47.41	-42.61, 38.30	-19.99, 21.38	-37.85, 6.29	-39.91, 35.75
SD	47.247	78.689	41.595	44.381	76.069
Median	15.85	1.30	2.10	-13.25	4.00
Min., Max	-95.6, 112.5	-145.6, 187.6	-112.9, 112.1	-119.9, 71.0	-234.8, 146.4
Week 6, n	19	17	17	16	18
Mean	12.49	-18.45	19.06	-32.78	-22.82
95% CI	-13.71, 38.70	-51.74, 14.83	-0.50, 38.63	-72.45, 6.90	-54.31, 8.67
SD	54.373	64.739	38.059	74.460	63.326
Median	4.40	1.60	10.50	-15.85	-11.10
Min., Max	-80.4, 140.5	-144.4, 85.6	-41.3, 96.6	-224.1, 42.6	-193.7, 78.0
NEFAs (mmol/L)					
Day 2, n	20	17	18	18	18
Mean	-0.0152	-0.1307	-0.1326	-0.1926	-0.1503
95% CI	-0.0530, 0.0226	-0.1771, -0.0844	-0.1944, -0.0707	-0.2613, -0.1238	-0.1986, -0.1019
SD	0.08082	0.09016	0.12437	0.13820	0.09720
Median	-0.0050	-0.0970	-0.1440	-0.1540	-0.1270
Min., Max	-0.240, 0.132	-0.303, -0.018	-0.367, 0.261	-0.672, -0.056	-0.416, 0.011
Week 6, n	19	17	17	16	18
Mean	-0.0457	-0.0342	-0.0423	-0.0293	-0.1032
95% CI	-0.0802, -0.0113	-0.1235, 0.0550	–0.0856, 0.0011	-0.1504, 0.0919	-0.1613, -0.0452
SD	0.07154	0.17352	0.08431	0.22736	0.11673
Median	-0.0400	-0.0400	-0.0630	-0.0120	-0.1150
Min., Max	-0.258, 0.071	-0.452, 0.262	-0.172, 0.182	-0.673, 0.444	-0.333, 0.153
Note: Baseline is defined as Day -1 visit					

Change from Baseline Pre-dose (fasting) Glucose, and Insulin between Treatment Groups on Day 84 (Week 12) in HMD114728						
Comparison Test vs. Ref.	LS Mean				Treatment Difference	95% CI of the Difference
	n	Test	n	Ref.		
Glucose (mmol/L)						
A-P	17	-0.608	19	-0.057	-0.551	-1.645, 0.543
B-P	17	-0.439	19	-0.057	-0.382	-1.472, 0.708
C-P	16	-0.647	19	-0.057	-0.590	-1.696, 0.516
D-P	18	-0.651	19	-0.057	-0.595	-1.669, 0.480
Insulin (pmol/L)						
A-P	17	-16.027	19	16.475	-32.502	-69.712, 4.707
B-P	17	13.629	19	16.475	-2.846	-40.355, 34.662
C-P	16	-34.904	19	16.475	-51.379	-89.307, -13.450
D-P	18	-23.046	19	16.475	-39.521	-76.230, -2.811
NEFAs (mmol/L)						
A-P	17	-0.010	19	-0.045	0.036	-0.042, 0.113
B-P	17	-0.041	19	-0.045	0.004	-0.073, 0.081
C-P	16	-0.025	19	-0.045	0.021	-0.058, 0.099
D-P	18	-0.129	19	-0.045	-0.083	-0.160, -0.007
P=Placebo (Pooled); A=GSK256073 5mg BID; B=GSK256073 10mg QD, C=GSK256073 25mg BID; D=GSK256073 50mg QD Note: Baseline is defined as Day -1 visit						

Change from Baseline in 0 to 12 hour Weighted Mean AUC for Glucose and Insulin at Week 12 in HMD114728						
Comparison Test vs. Ref.	LS Mean				Treatment Difference	95% CI of the Difference
	n	Test	n	Ref.		
Glucose (mmol/L)						
A-P	17	-0.50	18	-0.57	0.07	-0.79, 0.94
B-P	16	-0.61	18	-0.57	-0.04	-0.90, 0.82
C-P	15	-0.60	18	-0.57	-0.02	-0.90, 0.85
D-P	17	-1.00	18	-0.57	-0.42	-1.27, 0.42
Insulin (pmol/L)						
A-P	14	12.14	14	9.87	2.27	-48.62, 53.16
B-P	15	2.20	14	9.87	-7.67	-58.04, 42.70
C-P	13	33.96	14	9.87	24.08	-27.75, 75.92
D-P	15	7.78	14	9.87	-2.09	-52.72, 48.53
P=Placebo (Pooled); A=GSK256073 5mg BID; B=GSK256073 10mg QD, C=GSK256073 25mg BID; D=GSK256073 50mg QD Note: Baseline is defined as Day -1 visit						

Point Estimates and 95% Confidence Intervals for Comparisons of Change from Baseline Fructosamine (umol/L) at Week 12						
Comparison Test vs. Ref.	LS Mean				Treatment Difference	95% CI of the Difference
	n	Test	n	Ref.		
A-P	17	-18.10	18	-16.52	-1.58	-19.36, 16.20
B-P	15	-31.61	18	-16.52	-15.10	-33.00, 2.81
C-P	14	-30.61	18	-16.52	-14.09	-32.41, 4.23
D-P	17	-35.63	18	-16.52	-19.12	-36.55, -1.68
P=Placebo (Pooled); A=GSK256073 5mg BID; B=GSK256073 10mg QD, C=GSK256073 25mg BID; D=GSK256073 50mg QD Note: Baseline is defined as Day -1 visit						

Point Estimates and 95% Confidence Intervals for Comparisons of Change from Baseline in Total Cholesterol HDL-Cholesterol, and Triglycerides at Week 12 in HMD114728						
Comparison Test vs. Ref.	LS Mean				Treatment Difference	95% CI of the Difference
	n	Test	n	Ref.		
Cholesterol (mmol/L)						
A-P	16	-0.056	18	0.345	-0.401	-0.814, 0.012
B-P	16	-0.307	18	0.345	-0.653	-1.056, -0.250
C-P	15	-0.337	18	0.345	-0.682	-1.089, -0.275
D-P	17	-0.283	18	0.345	-0.628	-1.035, -0.222
HDL Cholesterol, direct (mmol/L)						
A-P	16	-0.057	18	-0.053	-0.004	-0.112, 0.105
B-P	16	-0.086	18	-0.053	-0.032	-0.140, 0.076
C-P	15	-0.080	18	-0.053	-0.026	-0.133, 0.081
D-P	17	0.013	18	-0.053	0.066	-0.039, 0.172
Triglycerides (mmol/L)						
A-P	16	-0.15	18	0.15	-0.20	-0.63, 0.27
B-P	16	-0.15	18	0.15	-0.33	-0.86, 0.13
C-P	15	-0.28	18	0.15	-0.43	-0.99, 0.02
D-P	17	-0.68	18	0.15	-0.77	-1.29, -0.25

P=Placebo (Pooled); A=GSK256073 5mg BID; B=GSK256073 10mg QD, C=GSK256073 25mg BID; D=GSK256073 50mg QD

Note: Baseline is defined as Day -1 visit

Pharmacokinetics (PK) Endpoints:

Summary of Plasma GSK256073 Pharmacokinetic Parameters[1]

Treatment	N	Visit	n	AUC(0-t) (µg·h/mL)	Cmax (µg/mL)	tmax (h)[2]
GSK256073 5mg BID	17	Study Day 2[3]	16	4170 (24.3)	518 (18.4)	6.00 (0.50 - 7.00)
		Week 6	17	12114 (75.1)	1359 (58.8)	2.00 (0.50 - 7.00)
GSK256073 10mg QD	18	Study Day 2	18	7865 (36.9)	942 (33.4)	4.00 (0.50 - 6.50)
		Week 6	17	16370 (56.1)	1863 (40.8)	4.00 (0.50 - 7.00)
GSK256073 25mg BID	18	Study Day 2	18	21450 (42.5)	2553 (38.5)	4.97 (0.50 - 6.67)
		Week 6	16	58581 (129)	6223 (107.1)	1.55 (0.50 - 8.00)
GSK256073 50mg QD	18	Study Day 2	18	26099 (52.3)	3352 (46.0)	4.00 (1.00 - 7.00)
		Week 6	18	53673 (61.7)	6538 (47.9)	4.00 (0.50 - 6.52)

1. Geometric Mean (CVb%).
2. Median (range).
3. Study Day 2 = First Day Dosing, Data were collected over a 12 hour period.

AUC(0-t)=Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments, Cmax=Maximum observed concentration, tmax=Time of occurrence of Cmax

Safety results: Adverse events (AEs) and serious adverse events (SAEs) were collected from the start of investigational product (IP) and until the final follow-up visit. However, any SAEs assessed as related to study participation (e.g. IP, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication was recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

No deaths or pregnancies occurred during the study.

Summary of All Adverse Events Occurring in 2 or More Subjects in Any Treatment Group of Study HMD114728

Adverse Events:	**Placebo (pooled) (N=20)**	**GSK256073 5 mg BID (N=18)**	**GSK256073 10 mg QD (N=19)**	**GSK256073 25 mg BID (N=19)**	**GSK256073 50 mg QD (N=18)**
N (Safety Population)	20	18	19	19	18
No. subjects with AEs, n (%)	11 (55%)	12 (67%)	12 (63%)	11 (58%)	10 (56%)
Nasopharyngitis	3 (15%)	0	1 (5%)	2 (11%)	3 (17%)
Headache	1 (5%)	1 (6%)	1 (5%)	2 (11%)	2 (11%)
Arthralgia	1 (5%)	2 (11%)	1 (5%)	0	1 (6%)
Diarrhea	1 (5%)	0	1 (5%)	0	1 (6%)
Oropharyngeal pain	0	0	1 (5%)	0	3 (17%)
Pain in extremity	1 (5%)	1 (6%)	1 (5%)	0	2 (11%)
Back pain	0	2 (11%)	1 (5%)	0	1 (6%)
Dizziness	1 (5%)	0	0	1 (5%)	2 (11%)
Nausea	0	0	2 (11%)	1 (5%)	0
Asthenia	2 (10%)	1 (6%)	0	0	0
Enterocolitis	2 (10%)	0	0	0	0
Abdominal pain upper	0	0	2 (11%)	0	0
Vomiting	0	0	0	2 (11%)	0

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

Preferred Term	**Placebo (pooled) (N=20)**	**GSK256073 5 mg BID (N=18)**	**GSK256073 10 mg QD (N=19)**	**GSK256073 25 mg BID (N=19)**	**GSK256073 50 mg QD (N=18)**
Subjects with any SAE	1 (5%) [0]	0	0	2 (11%) [0]	0
Atrial fibrillation*	0	0	0	1 (5%) [1]	0
Joint dislocation	0	0	0	1 (5%) [0]	0
Nephrotic syndrome*	1 (5%) [0]	0	0	0	0

*These subjects were withdrawn due to these SAEs. An additional subject was withdrawn due to the AEs of cold sweat, headache, and intermittent nausea, vomiting, and dizziness.

Conclusions:

- GSK256073 was administered for 12 weeks at doses of 5 mg BID, 10 mg QD, 25 mg BID, and 50 mg QD compared to placebo in this study. No deaths occurred during the study. The proportion of subjects experiencing AEs was similar comparing the combined GSK256073 arms (45/74, 61%) to placebo (11/20, 55%).
- The most commonly occurring AEs were nasopharyngitis and headache. Three subjects experienced SAEs during treatment (2/74 (3%) GSK256073; 1/20 (5%) on placebo). Three subjects were withdrawn due to AEs (2/74 (3%) GSK256073; 1/20 (5%) on placebo).
- Decreases from baseline in HbA1c were observed in all treatment groups including placebo, with the largest decreases from baseline over time observed in the GSK256073 50 mg QD group. When compared with the placebo group, no significant HbA1c changes from baseline were observed among the GSK256073 treatment groups.
- Following single doses on Day 2 (first day of dosing), GSK256073 showed a dose proportional increase in mean Cmax and AUC(0-t) values with the increase from 5 to 25 mg and less than dose proportional increases from 25 to 50 mg.
- At Week 6, mean AUC(0-t) values for GSK256073 at the 10 mg QD and the 5 mg BID (10 mg total) dose level and at the 50 mg QD and 25 mg BID (50 mg total) dose level of GSK256073 were generally similar.
- Accumulation of GSK256073 was observed after multiple dosing for all treatment groups.
- No positive exposure/response relationships were observed between drug exposure and pharmacodynamic endpoints so formal PK/PD analyses were not performed.