Table S2 Supplementary Material
Study Procedures Overview

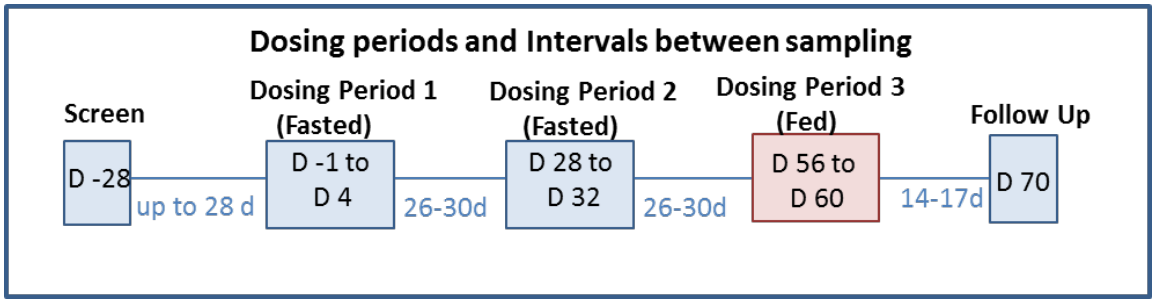
Outline	Each subject was expected to participate in 2 study dosing periods for fasted analyses followed by 1 study dosing period for fed analyses. The procedures indicated below were e repeated for each dosing period (fasted and fed). Each dosing period was separated by a washout period of at least 26 days between dosing periods for individual subjects (see schematic below). 
Screening (Day -28 to -2)	The following activities were the subject screening process: • Informed consent obtained before any study-related procedures were initiated. • Study inclusion/exclusion criteria were checked. • Medical history recording was done. • Physical examination, including height, weight, and ophthalmic fundus were performed. • Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature, were recorded. Heart rate and systolic and diastolic blood pressure were measured as triplicate assessments, after 3 minutes in the supine position and at least 2 minutes apart. The average value of the 3 assessments was used as a reference. • Alcohol breath test, urine cotinine, and urine drug screen were performed

Table S2 Supplementary Material
Study Procedures Overview (continued 1)

Screening (Day -28 to -2) [continued]	• Blood sampling for safety laboratory tests (haematology, serum chemistry) and virology (human immunodeficiency [HIV] antibodies, hepatitis B surface antigen [HBsAg], hepatitis C [HCAb] antibodies) were performed. • Urine dipstick analysis was performed. • Acute myocardial infarction (AMI) serum marker sample were collected. • Standard 12-lead ECG were performed. • Serum pregnancy test, human chorionic gonadotropin (hCG) for pre-menopausal women who had documented evidence of sterilisation and follicle-stimulating hormone (FSH) levels for post-menopausal subjects with at least 6 months, but less than 12 months of spontaneous amenorrhea were measured. • Concomitant medications the subject was taking at study entry were reviewed and recorded. • AEs reported after subject provided informed consent were recorded. • Subject was randomised to study dosing sequence.
Study Day -1: Prior to Study Dosing Period	The following procedures were performed on the day before the subject was dosed in each of the 2 fasting dosing periods and the fed dosing period (unless otherwise specified): • The subject checked-in and start housing at the investigational medical unit (IMU). • Study inclusion/exclusion criteria were checked. • Continuous 12-lead ECG recording was performed (only for the first dosing period). • Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature, were recorded. Heart rate and systolic and diastolic blood pressure were measured as triplicate assessments, after 3 minutes in the supine position and at least 2 minutes apart. The average value of the 3 assessments was used as a reference. • Physical examination, including weight, and ophthalmic fundus were performed.

Table S2 Supplementary Material
Study Procedures Overview (continued 2)

Study Day -1: Prior to Study Dosing Period [continued]	• Alcohol breath test, urine cotinine test, and urine drug screen were performed. • Blood sampling for safety laboratory tests (haematology and serum chemistry) were performed. • Urine dipstick analysis was performed. • AMI serum marker sample was collected. • A laboratory test could be repeated if deemed necessary to assess a subject's safety to remain in the study. • Skin punch biopsy was performed **only in subjects assigned to the fed period.** • Concomitant medications were recorded. • AE experienced since last visit were recorded.
Two Study Dosing Periods for Fasted Analyses and One Dosing Period for Fed Analyses	The following procedures were performed for each dosing period (unless otherwise specified): • AEs were monitored continuously Days 1 – 7. • Concomitant medications (i.e., for treatment of AEs) were recorded throughout Days 1 – 7. <u>Study Days 1-3</u> • Subjects continued to be housed at the IMU. • Study drug was administered on Day 1 (single dose; per randomisation schedule during fasted periods and staggered day assignment during fed period). • Vital signs were measured as follows: pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours (±15 minutes) after dosing on Day 1; at 24 and 36 hours (±15 minutes) after dosing on Day 2; and at 48 hours (±15 minutes) after dosing on Day 3. Heart rate and systolic and diastolic blood pressure were measured as triplicate assessments, after 3 minutes in the supine position and at least 2 minutes apart. The average value from 3 assessments were used as a reference. • Continuous 12-lead ECG recording were performed from Day 1 (pre-dose) through 48-hours post-dose (until Day 3).

Table S2 Supplementary Material
Study Procedures Overview (continued 3)

Two Study Dosing Periods for Fasted Analyses and One Dosing Period for Fed Analyses [continued]	• Triplicate 12-lead ECG were extracted from continuous 12-lead ECG recording at the following time points: pre-dose and at 1, 2, 3, 4, 6, 8, and 12 hours after dosing on Day 1; at 24 and 36 hours after dosing, on Day 2; and at 48 hours after dosing on Day 3. Extraction had to be done at each time point (as described in the dedicated section of the protocol). • Standard 12-lead ECG were performed at pre-dose 1, 2, 4, 8 and 24 hours post dosing. • Hair follicle sampling were performed pre-dose and at 1, 2, 3, 6, 12, and 24 hours (±15 minutes) after dosing. • PBMC sampling were performed pre-dose and at 1, 2, 4, 6, 12, 24 and 30 hours (±6 minutes) after dosing. • Plasma sampling for cytokine/chemokine growth factor assessment (PD plasma) were performed pre-dose on Day 1, at 24 hours after dosing on Day 2, and at 48 hours (±6 minutes) after dosing on Day 3. • PK blood sampling was performed pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing on Day 1; at 24, 30 and 36 hours after dosing on Day 2; and at 48 hours (±6 minutes) after dosing on Day 3. • AMI serum marker samples (troponin I [TPN I] and troponin T [TPN T] only) were collected at 12 hours (±6 minutes) after dosing on Day 1 and at 24 hours (±6 minutes) after dosing on Day 2. • Skin punch biopsy was performed at 1.5 hour after dosing (± 30 minutes) only in subjects **assigned to the fed period.** <u>Study Day 3 only</u> • Physical examination including ophthalmic fundus (± 1 day) was performed. • Blood sampling for safety laboratory tests (haematology and serum chemistry) was performed. • Urine dipstick analysis was performed. • AMI serum marker sample was collected at 48 hours (±6 minutes) after dosing.

Table S2 Supplementary Material
Study Procedures Overview (continued 4)

Two Study Dosing Periods for Fasted Analyses and One Dosing Period for Fed Analyses [continued]	<u>Study Day 4 only</u> • PK blood sampling 72 hours (±6 minutes) after dosing. • Plasma sampling for cytokine/chemokine growth factor assessment (PD plasma) 72 hours (±6 minutes) after dosing. • Subjects were discharged from the IMU after at least 2 hours from completion of all requested study procedures. The Investigator could decide to postpone discharge, if deemed necessary for subject safety. <u>Study Day 7 only</u> • Subjects l returned to the IMU for AEs and concomitant medication check. • PK blood sampling 144 hours (±30 minutes) after dosing was done. • Blood sampling for safety laboratory tests (haematology and serum chemistry) was performed Urine dipstick analysis was performed. <u>Fed Dosing Period</u> The 10 mg dose administered in the trial was also given under fed conditions. The 10 mg dose was administered during a third dosing period to all subjects that had received the same dose under fasting conditions (without matching placebo). Subjects treated at the dose of 10 mg (fasted) that, for non-safety reasons, were not be available to be dosed at 20 mg were replaced. The replaced subjects who participated in dosing period 2 and dosing period 3, were required to complete dosing period 1 thereafter.
Washout Period between Dosing Periods	Each dosing period was followed by a washout period of at least 26 days before the next dosing period could begin.

Table S2 Supplementary Material
Study Procedures Overview (continued 5)

Study Follow-up Visit: 14 (± 3) Days After Last Dose of Study Drug	The following activities were included in the study follow-up visit, which will occur 14 (± 3) days after the subject had received the last dose of study drug: • Physical examination, including weight, and ophthalmic fundus was performed. • Vital signs, including HR, systolic and diastolic blood pressure, respiratory rate, and body temperature, were recorded. Heart rate and systolic and diastolic blood pressure were measured as triplicate assessments, after 3 minutes in the supine position and at least 2 minutes apart. • Standard 12-lead ECG was performed. • Blood sampling for safety laboratory tests (haematology and serum chemistry) was performed. • Urine dipstick analysis was performed. • Serum pregnancy test, human chorionic gonadotropin (hCG), for pre-menopausal women who had documented evidence of sterilisation and FSH levels for post-menopausal female subjects with at least 6 months, but less than 12 months of spontaneous amenorrhoea were measured. • Concomitant medications were recorded. • AEs experienced since last visit were recorded.
Randomisation and Blinding	The Investigator followed the study's randomisation procedures and ensured that the code was broken only in accordance with the protocol. The Investigator was expected to promptly document and explain to the Sponsor any premature unblinding of the investigational product (e.g., accidental unblinding, unblinding due to a serious adverse event [SAE]) (instruction for unblinding of individual subjects in cases of emergency were given in a dedicated section of the study protocol). Staff in charge of the interim PK evaluations was unblinded and provided anonymisation of subject results when passing data to the staff in charge of clinical decisions.