Table S6 Supplementary Material
Statistical Methods

Sample Size	Due to the exploratory nature of this study, no formal power or sample size calculations were used to determine cohort size. The number of subjects was chosen empirically, based on published data for Phase I single dose escalation studies where the cohort size is ranging from 2 to 30 subjects [1,2], and on Phase I First in Human studies in healthy volunteers conducted under a US IND at FDA, where cohort size is in the range of 4 to 24 subjects and the overall study sample size is ranging from 16 to 64 subjects (https://clinicaltrials.gov, accessed July 2016). Assuming a drop-out rate of approximately 12% (2 out of 17 subjects), a total of 17 subjects (14 subjects in active dose and 3 subjects in placebo) was assumed to ensure that there were at least 12 subjects receiving an active dose. This was also assumed to allow the assessment of the food effect in a reliable manner(i.e. with a minimum of 12 subjects completing the study, as per FDA guidelines 2002)[3].
General	All statistical tests were two-sided with a significance level of α=0.05, unless specified otherwise, and were performed using SAS® Version 9.2 or higher. Data were summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables. Plasma concentration data at each time point were summarized with number of subjects, mean, median, minimum, maximum, SD, and CV (%) for each dose level. All PK parameters were summarized with number of subjects, mean, standard deviation, median, minimum, maximum, geometric mean, CV (%), and log-transformed SD.
Safety Analyses	The safety and tolerability of ETC-206 were monitored by physical examinations, vital signs, ECGs, continuous 12-lead ECG monitoring, clinical laboratory tests, concomitant medications, and incidence of AEs. Safety was monitored throughout the study for all subjects. Baseline for all clinical laboratory evaluations and vital signs was defined as the last evaluation done before first study dose administration. Baseline for ECG was the mean of triplicate measurements. All AEs were summarized by treatment group.
Adverse Events	The verbatim terms used in the eCRF by Investigators to identify AEs were coded by system organ class and preferred terms using Medical Dictionary for Regulatory Activities (MedDRA; version 19). All reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs [TEAEs] and AEs that worsened since baseline) were included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event was summarized by treatment group.

Table S6 Supplementary Material
Statistical Methods (continued 1)

Pharmacokinetic Analysis	Individual subject plasma concentration-time data of ETC-1907206 were analysed using non-compartmental model (WinNonlin). The plasma samples for ETC-206 full PK assessments were taken just prior to dosing (pre-dose) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48 and 72 (± 6 minutes) and 144 hours (± 30 minutes) after dosing. All calculations were based on actual sampling times. The PK parameters to be calculated included, but are not limited to, $AUC0_{-inf,}$ $AUC0_{-t}$, C_{max}, kel, T_{max}, T_{lag}, CL, Vd and $T_{½}$. PK parameters and concentrations were summarized by dose levels among the PK evaluable subjects. Dose proportionality was assessed by comparing the PK parameters of ETC-206 across dose levels. The primary method of evaluation of dose proportionality was based on AUC_{0-inf} (single dose) and C_{max} using a power model that was fitted using the fasted doses. Assessment of the dose proportionality was performed on the complete dose range. The effect of concomitant food intake on ETC-206 was assessed by comparison of AUC0-inf, Cmax and other relevant PK parameters under fed and fasted conditions. The analyses were conducted on log-transformed data using a mixed ANOVA model including food condition as fixed effect and considering the subject as random effect. Estimates of differences between fed and fasted condition were estimated with their 90% CIs and back-transformed to the original scale, thus providing estimates of ratios of geometric means and their CIs.
Clinical Laboratory Tests	Laboratory data (hematology, serum chemistry, urinalysis, and AMI serum markers) were summarized by type of laboratory test. The observed values and change from baseline values for each laboratory tests/parameters were summarized using descriptive statistics at each scheduled time points.
Biomarker Analysis	The ratio of eIF4E phosphorylated on Ser209 to total eIF4E at pre-dose and the resulting percent inhibition of relative p(S209) eIF4E levels were summarized for each scheduled time point. Levels of and plasma cytokines/chemokines/growth factors were summarized for each time point.
Relative p-(Ser209) eIF4E levels	The percent inhibition of relative p(S209) eIF4E levels compared to baseline after single, ascending, oral doses of ETC- 206 was determined as follows: • Hair follicles: prior to dosing and 1, 2, 3, 6, 12, and 24 hours (± 15 minutes) post-dose on Study Day 1. • PBMCs: prior to dosing and 1, 2, 4, 6, 12, 24 and 30^ hours post-dose (± 6 minutes) on Study Day 1. • Skin: prior to dosing and 1.5 hours (± 30 minutes) post-dose on Study Day 1, only in subjects assigned to the fed period. A dose was characterized as PD active if a statistically significant inhibition of the average relative p(S209) eIF4E level was achieved at any time point post-dose, when compared to base line levels. The maximum percent inhibition observed was described additionally (irrespective of the time point). ^ Time point added during protocol amendment

Table S6 Supplementary Material
Statistical Methods (continued 2)

Plasma cytokines	The following cytokines, chemokines or growth factors in plasma were analysed and compared to baseline levels: IL-1β, IL-2, IL-4, IL-6, IL-8, IFNγ, TNFα, IL-15, IL-17A, MCP-10 and IP-10 at pre-dose and at two time points chosen from the 24 h ,48 h and 72 h (± 6 minutes) post-dose time points. The decision on which two post-dose time points was analysed was based on mean C_{max} and AUC0-inf for all dose levels and the time points chosen was the same for all subjects.
ECG, Intensive Safety monitoring, General	ECG analysis was based on the central tendency of ECG parameters changes from baseline. A categorical analysis was used for outliers. A morphological analysis was conducted for ECG waveform interpretation. The PK/PD relationship was analysed with a linear mixed effect modelling approach (Central laboratory ERT, Philadelphia, PA, USA).
ECG, Central Tendency Analysis	The ECG analysis was based on defining the central tendency of all ECG interval parameter changes (HR, PR, QRS, QT, QTcF and QTcB) as a change from baseline. For this analysis, the baseline was defined as the interval durations and heart rate measurements of the mean of the 3 sets of triplicate ECGs obtained pre-dose (-60, -45, -30 minutes) on Day 1 of each dosing period (expected 9 ECGs total). For the time point analysis, the baseline (mean of the 9 ECGs) was compared (as a change from baseline) to the mean of the triplicate (3) ECGs obtained at each of the following time points: 1, 2, 3, 4, 6, 8, 12 and 24 hours postdose on Day 1 of each dosing period. Descriptive statistics (e.g., frequency, percent, mean, standard deviation (SD), median, maximum, and minimum) were used to summarize the ECG variables and the corresponding changes from the mean baseline to each time point noted above. For QTc measurements, the QTcF measurement were considered primary and QTcB secondary.
ECG, Outlier Analysis	An outlier or categorical analysis, supplements the central tendency analysis by determining if there were subjects who had an exaggerated effect on any ECG interval that would not be revealed in a mean change from baseline central tendency analysis. Each subject was considered having an outlier value based on the most extreme value across all of the time points. The following criteria ("study endpoints") were defined for this analysis: • Heart rate: A value for a subject was considered to be an outlier at a pre-determined post-dose time point if the heart rate measurement at that follow-up time point was <50 bpm and the measure was at least a 25% decrease from the subject's baseline mean heart rate (i.e., a bradycardic event) or if the heart rate measurement at the pre-determined post-dose time point was >100 bpm and the measure was at least a 25% increase from the baseline mean heart rate (i.e., a tachycardic event). • PR interval: A value for a subject was considered to be an outlier at a pre-determined post-dose time point if the PR interval at that follow-up time point was >200 ms and it was at least a 25% increase from the subject's baseline mean PR interval. QRS interval: A value for a subject was considered to be an outlier at a pre-determined post-dose time point if the QRS interval at that follow-up time point was >100 ms and it was at least a 25% increase from the subject's baseline mean QRS interval.

Table S6 Supplementary Material
Statistical Methods (continued 3)

ECG, Outlier Analysis (continued)	• QT interval: A value for a subject was considered to be an outlier at a pre-determined post-dose time point if the QT interval at that follow-up time point was >500 ms and the subject's baseline mean QT interval was ≤500 ms. • QTcF: A value for a subject was considered to be an outlier at a pre-determined postdose time point if the QTcF interval at that follow-up time point was >500 ms and the subject's baseline mean QTcF interval was ≤500 ms. Outlier values will also be presented if the QTcF interval at a pre-determined post-dose time point was >480 ms when the subject's baseline mean QTcF interval was ≤480 ms and when a predetermined post-dose time point was >450 ms when the subject's baseline mean QTcF interval was ≤450 ms. In addition, the proportion of subjects with changes from baseline of >30-60 ms and >60 ms will be reported. • QTcB: A value for a subject was considered to be an outlier at a pre-determined postdose time point if the QTcB interval at that follow-up time point was >500 ms and the subject's baseline mean QTcB interval was ≤500 ms. Outlier values will also be presented if the QTcB interval at a pre-determined post-dose time point was >480 ms when the subject's baseline mean QTcB interval was ≤480 ms and when a predetermined post-dose time point was >450 ms when the subject's baseline mean QTcB interval was ≤450 ms. In addition, the proportion of subjects with changes from baseline of >30-60 ms and >60 ms will be reported. Data will be presented by treatment group, for each ETC-1907206 dosing period (DP) separately, and pooled for the placebo treated subjects from all DPs. The ECG timepoints collected 36 and 48 hours after dosing will be included in this analysis.
ECG, Morphological Analysis	Morphological analyses were performed with regard to the ECG waveform interpretation as defined by the central ECG laboratory's cardiologist. Changes from the baseline ECGs (looking at each of the 9 baseline ECGs individually) to any post-treatment ECG were evaluated. All findings are presented in the ECG listings. New onset (presented as percentage of subjects meeting the new criteria) for the following variables are detailed in the tables: • Atrial fibrillation • Atrial flutter • Second degree heart block • Third degree heart block • Complete right bundle branch block • Complete left bundle branch block, • ST segment elevation • St segment depression • T wave abnormalities (negative T waves only)

Table S6 Supplementary Material
Statistical Methods (continued 4)

ECG, Morphological Analysis (continued)	• Myocardial infarction pattern • New abnormal U waves "New" means not present on any baseline ECG and becoming present on at least one on- study drug ECG. Data are presented by treatment group, for each ETC-1907206 dose period separately, and for pooled placebo. The ECG timepoints collected 36 and 48 hours after dosing were included in this analysis.
(ECG) Pharmacokinetic-Pharmacodynamic (PK-PD) analysis	A pharmacokinetic-pharmacodynamic (PK-PD) analysis was performed using all subjects who had paired ECG and plasma concentrations for ETC-1907206. For this PK-PD analysis, a linear mixed effects modeling approach was used to examine the relationship between the plasma concentration of ETC-1907206 and change from baseline placebo-adjusted QTc intervals (QTcF and QTcB) and the plasma concentration of ETC-1907206 (see Equation 1 below). The model included plasma concentration, time (categorical), and treatment with random subject effects on plasma concentration and the intercept included in the model. This model was used to estimate the population slope and the standard error of the slope of the relationship between the change from baseline in QTc, PR and QRS intervals and plasma concentrations of ETC-1907206.

References

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