Official Title: A 2 Part, Randomized, Open-Label, Single Dose, Crossover Study to Assess the Relative Bioavailabilty of Phase II Tablet Formulation Compared to the Current Phase I Capsule Formulation and the Effect of Food and Taste Assessment on the Phase II Tablet Formulation in Healthy Participants

NCT Number: NCT03847987

Document Date(s): SAP Version 1: 26-April-2019

Statistical Analysis Plan

Sponsor:	F. Hoffman-La Roche Ltd
Protocol No:	BP40950
Protocol Title:	A 2 Part, Randomized, Open-Label, Single Dose, Crossover Study to Assess the Relative Bioavailability of Phase II Tablet Formulation Compared to the Current Phase I Capsule Formulation and the Effect of Food and Taste Assessment on the Phase II Tablet Formulation in Healthy Participants
PRA Project ID:	RPU532SL-186612
Version Date:	24-Apr-2019

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	[redacted] / [redacted]
Signature of Sponsor Representative / Date:	[redacted] / 26-APR-2019
Name of Author / Title:	[redacted]
Signature of Author / Date:	[redacted] 26-APR-2019

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under F. Hoffmann-La Roche Ltd Protocol BP40950.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 26-Feb-2019 (including all amendments up to this protocol date) and the final eCRF(s) dated 01-Feb-2019.

An approved and signed SAP is a requirement for database lock.

This SAP covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department as well as the pharmacokinetic (PK) results that will be processed by Roche.

PRA EDS will perform the safety and tolerability evaluations as well as bioavailability and food effect assessments.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

- To assess the relative bioavailability of Phase II tablet formulation compared to Phase I capsule formulation of RO7017773 swallowed whole under fasting conditions following single oral dose administration.
- To assess the taste masking of RO7017773 Phase II tablet formulation containing sweetener and flavor dispersed in water and the RO7017773 Phase II tablet formulation without sweetener and flavor dispersed in apple juice.

5.1.1 Primary Endpoints

- RO7017773 concentrations and RO7017773 PK parameters
- Taste questionnaire

5.2 Secondary

- To assess the PK of RO7017773 Phase II tablet formulation dispersed in water or swallowed whole.
- To assess the effect of a high-fat meal on the PK (PK) of a single oral dose of RO7017773 Phase II tablet formulation.
- To assess the taste of RO7017773 Phase II tablet formulation without sweetener and flavor dispersed in water.
- To assess the PK of RO7017773 Phase II tablet formulation containing sweetener and flavor dispersed in water and the RO7017773 Phase II tablet formulation without sweetener and flavor dispersed in apple juice.
- To evaluate the safety and tolerability of single oral doses of different RO7017773 formulations in healthy participants.

5.2.1 Secondary Endpoints

- RO7017773 concentrations and RO7017773 PK parameters
- Taste questionnaire
- Incidence and severity of AEs
- Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results during and following RO7017773 administration

5.3 Exploratory

- To screen for the presence of RO7017773-derived metabolites.
- To assess the relative abundance and PK parameters of any metabolite as appropriate

5.3.1 Exploratory Endpoints

- Concentrations of RO7017773-derived metabolites, if appropriate

6.0 Study Design

This is a single-center, randomized, single-dose, open-label, crossover study in healthy subjects consisting of two parts. Part 1 will assess the bioavailability of the Phase II tablet formulation of RO7017773 compared to the Phase I capsule formulation, the effect of food on the PK of the Phase II tablet, and the PK of the Phase II tablet dispersed in water compared to the Phase II tablet swallowed. Part 1 will also assess the taste of the Phase II tablet dispersed in water. Part 2 will assess the taste and PK of the Phase II tablet containing flavor and sweetener dispersed in water compared to the Phase II tablet without sweetener/flavor dispersed in apple juice.

All 16 subjects in part 1 will receive the following four treatments in a randomized, 4-period crossover design. Each treatment will be given as a single dose on Day 1 of each treatment period.

- Treatment A: Phase I capsule swallowed whole under fasted conditions
- Treatment B: Phase II tablet swallowed whole under fasted conditions
- Treatment C: Phase II tablet swallowed whole under fed conditions
- Treatment D: Phase II tablet dispersed in water under fasted conditions (taste assessment)

All 8 subjects in part 2 will receive the following treatments in a randomized, 2-period crossover design. Each treatment will be given as a single dose on Day 1 of each treatment period.

- Treatment A: Phase II tablet containing flavor and/or sweetener dispersed in water under fasted conditions (taste assessment)
- Treatment B: Phase II tablet without flavor and/or sweetener dispersed in apple juice under fasted conditions (taste assessment)

6.1 Sample Size Considerations

The criteria used to determine the sample size mimic common criteria to conclude bioequivalence, although they are not meant to fulfill regulatory guidance on showing bioequivalence in a strict sense.

In part 1, 16 participants will be randomized for treatment in order to obtain at least 12 evaluable participants. This sample size has been chosen to ensure that the ratios of the treatment geometric means can be estimated with sufficient precision. [redacted]

In part 2, a maximum of 8 participants is considered adequate to assess the taste masking of RO7017773 This is based on previous experience not statistical analysis.

6.2 Randomization

Computer-generated randomization schemes will be produced by a PRA statistician prior to the start of the study for part 1 and part 2.

Subjects in part 1 who meet the eligibility criteria will be randomized to one of four treatment sequences from a 4-period Williams Latin Square as defined in Table 1 prior to first dosing.

Table 1

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
ABCD	A	B	C	D
BDAC	B	D	A	C
CADB	C	A	D	B
DCBA	D	C	B	A

Subjects in part 2 who meet the eligibility criteria will be randomized to one of the two treatment sequences as defined in Table 2 prior to first dosing.

Table 2

Treatment Sequence	Period 1	Period 2
AB	A	B
BA	B	A

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

There will be no interim analyses or summaries of data provided prior to the delivery of the full set of post-lock tables, figures and listings (TFLs).

7.3 Final Analysis

Draft TFLs containing Safety, bioavailability, and food effect assessments will be provided after database lock. The sponsor will provide the PK concentration and parameter TFLs. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the first draft of the CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while

programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all summaries, the mean and median will be presented to one decimal place greater than the data, standard deviation to two greater than the data, and the minimum and maximum will be presented to the same number of decimal places as the data. Percentages will be presented with one decimal.

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics.

Additional derived data will be rounded in the derived dataset as determined by the statistician.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Daylight Savings Time Adjustments

This study is not expected to fall over Daylight Savings Time and no adjustments for time change are planned.

9.1.4 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum (min) value, median, and maximum (max) value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the CRF / Database.

9.1.5 Pooling

Summary statistics will be calculated by treatment (and timepoint, if applicable).

9.1.6 Unscheduled Measurements

Unscheduled and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping

Label	Grouping
Study Drug	Phase I RO7017773 capsule, Phase II RO7017773 tablet
Treatment	In Part 1: • A: Phase I capsule swallowed whole under fasted conditions • B: Phase II tablet swallowed whole under fasted conditions • C: Phase II tablet swallowed whole under fed conditions • D: Phase II tablet dispersed in water under fasted conditions In Part 2: • A: Phase II tablet containing flavor and/or sweetener dispersed in water under fasted conditions • B: Phase II tablet without flavor and/or sweetener dispersed in apple juice under fasted conditions
Dose Level	[redacted] mg of RO7017773

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation
Analysis Study Day (Prior to First Dose)	All	Date of Measurement minus First Dose Date
Analysis Study Day (Post First Dose)	All	Date of Measurement minus First Dose Date +1

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the general PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the key objectives of this study are to characterize the pharmacokinetics and assess safety and tolerability the datasets considered critical are subject level, pharmacokinetic, and adverse events (ADSL, ADPC, ADPP, and ADAE).

9.2.5 AdaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (AdaM) Version 2.1.

AdaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Table shells for safety and statistical analyses of PK parameters are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the PRA project statistician. Other changes to the shells may be out of scope. The TFLs will be provided as a single document in Adobe PDF format (in Letter format), and as individual files for each table, figure or listing in Rich Text Format (.rtf). Additional TLFs for PK concentrations and parameters will be provided by Roche.

10.0 Analysis Sets

Analyses	Safety Set	Pharmacokinetic Set
Disposition Summaries	✓	
Baseline Characteristics	✓	✓
Safety Assessments	✓	
PK Concentrations	✓	
PK Parameters		✓
Primary Analysis		✓

10.1 Safety Set

All subjects randomized to study treatment and who received at least one dose of the study drug, whether prematurely withdrawn from the study or not, will be included in the safety analysis. This set will be analyzed as treated.

10.2 Pharmacokinetic Set

All subjects who have received at least one dose of study drug and who have data from at least one post-dose sample will be included in the PK analysis population. Subjects will be excluded from the PK set if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. This set will be analyzed as treated.

11.0 Subject Disposition

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

12.0 Protocol Deviations

Protocol deviations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Subject demographics will be summarized overall. The summary will include the subjects' age (years), sex, race, ethnicity, weight (kg), height (cm), BMI (kg/m^2), female reproductive status, and method of contraception. Demographics will be summarized for the Safety Set and PK Set.

All demographic data as collected during the screenings visit will be listed by subject.

13.2 Medical History

Medical history will be listed by subject.

13.3 Other Baseline Characteristics

Urine drug and alcohol screen, and non-compliance with inclusion/exclusion criteria (if any) will be listed by subject.

14.0 Concomitant Medications

Concomitant medication will be listed by subject. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

15.0 Treatment Compliance and Exposure

The number of subjects receiving each dose of study drug will be summarized.

Exposure data will be listed by subject.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

The reporting of pharmacokinetic concentrations and calculation of pharmacokinetic parameters will be in accordance with Roche clinical pharmacology guiding principles for calculation and analyses of non-compartmental pharmacokinetic parameters version 4.

Individual plasma concentrations of RO7017773 and metabolites (if appropriate) will be presented together with descriptive statistics by treatment.

Individual plasma PK parameters of RO7017773 and metabolites (if appropriate) will be estimated using non-compartmental methods with WinNonlin® for each subject by treatment.

Individual values of calculated PK parameters will be presented together with their descriptive statistics by treatment. The following descriptive statistics will be used: number of subjects, mean, geometric mean, SD, CV, geoCV, median, min, and max. For tmax, only median, min and max will be presented.

16.1.1 Plasma Pharmacokinetic Parameters

The following plasma PK parameters for RO7017773 and metabolites will be estimated.

Parameter	Description
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units
AUC0-t	Area under the plasma concentration-time curve from time 0 to t hours post-dose.
AUClast	Area under the plasma concentration-time curve (time 0 to time of last quantifiable concentration).
AUCinf	Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% is required to obtain a reliable AUCinf.
T1/2	Apparent terminal half-life, calculated as ln(2)/λz
CL/F	Apparent oral clearance, calculated as Dose/AUCinf

16.1.1.1 Part 1 Bioavailability and Food Effect

The bioavailability of RO7017773 administered as a Phase I capsule compared to a Phase II tablet, the bioavailability of RO7017773 administered as a Phase II tablet dispersed in water compared to a Phase II tablet swallowed whole, and the effect of a high-fat, high calorie meal on the bioavailability of RO7017773 administered as Phase II tablet, will be assessed.

90% confidence intervals (CIs) of the geometric least-squares (LS) mean ratios of the RO7017773 plasma PK parameters Cmax and AUCinf will be calculated. If AUCinf cannot be derived, Cmax and AUClast will be used. The following linear mixed effects model will be implemented using the natural log-transformed parameters, where τ_i are fixed effects for treatment (i=1,…, 4), π_k are fixed effects for period (k=1,…,4), ω_j are fixed effects for sequence (j=1,…,4), and s_m is the random effect for subject *m*. The random subject effects and the random errors ε_{ijkm} are assumed to be independent and normally distributed with zero means and standard deviations σ_s and σ_ε, respectively.

$$Y_{ijkm} = \mu + \tau_i + \pi_k + \omega_j + s_m + \varepsilon_{ijkm}$$

Estimates on the original scale of measurement will be obtained by exponentiating point estimates on the natural log scale. Geometric LS means will be provided for each treatment. In all comparisons, treatment B will be used as the reference. No adjustments will be made for multiplicity.

The following SAS PROC MIXED pseudo-code may be used:

```
proc mixed data = adpp;
   by analyte parameter;
   class treatment period sequence subject;
   model ln(aval) = treatment period sequence/ddfm=kr;
   random subject;
   lsmeans treatment / alpha = 0.1;
   estimate "A vs B (capsule vs tablet)" treatment 1 -1 0 0 /e cl alpha=0.1;
   estimate "C vs B (fed vs fasted)" treatment 0 -1 1 0 /e cl alpha=0.1;
   estimate "D vs B (dispersed in water vs swallowed)" treatment 0 -1 0 1 /e
cl alpha=0.1;
```

```
run;
```

16.1.1.2 Part 2 Bioavailability

The bioavailability of RO7017773 administered as a Phase II tablet containing flavor and/or sweetener dispersed in water compared to a Phase II tablet without flavor and/or sweetener dispersed in apple juice will be assessed.

90% CIs of the geometric LS mean ratios of the RO7017773 plasma PK parameters Cmax and AUCinf will be calculated. If AUCinf cannot be derived, Cmax and AUClast will be used. The following linear mixed effects model with will be implemented using the natural log-transformed parameters, where τ_i are fixed effects for treatment (i=1,…, 4), π_k are fixed effects for period (k=1,2), and s_m is the random effect for subject *m*. The random subject effects and the random errors ε_{ijkm} are assumed to be independent and normally distributed with zero means and standard deviations σ_s and σ_ε, respectively.

$$Y_{ijkm} = \mu + \tau_i + \pi_k + s_m + \varepsilon_{ijkm}$$

Estimates on the original scale of measurement will be obtained by exponentiating point estimates on the natural log scale. Geometric LS means will be provided for each treatment. Treatment B will be used as the reference. No adjustments will be made for multiplicity.

The following SAS PROC MIXED pseudo-code may be used:

```
proc mixed data = adpp;
   by analyte parameter;
   class treatment period subject;
   model ln(aval) = treatment period /ddfm=kr;
   random subject;
   lsmeans treatment / alpha = 0.1;
   estimate "A vs B" treatment 1 -1 /e cl alpha=0.1;
run;
```

17.0 Safety Analyses

17.1 Safety Variables

- Adverse Events (AEs)
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis
  - Coagulation
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse rate
  - Oral body temperature
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - RR Interval
  - QTc (Frederica) Interval

- Physical Examination

17.1.1 Adverse Events

Treatment emergence will be evaluated for all AEs. Treatment-emergent adverse events (TEAE) are those which occur after the first dose of study drug.

TEAEs occurring following dosing in a specific period but before dosing in the next period will be attributed to the treatment in that period. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE but will not be attributed to a specific treatment

A summary of number and percentage of subjects reporting TEAEs, TEAEs by severity and relationship, serious AEs (SAEs), and subjects who discontinued study drug due to an AE will be provided.

A summary of the number and percentage of subjects reporting each TEAE, categorized by system organ class and preferred term coded according to the Medical Dictionary for Regulatory Activities (MedDRA), will be presented by treatment and overall. Counting will be done by subject only, not by event; subjects will only be counted once within each body system or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by relationship to study drugs (as recorded on the eCRF) and by treatment and overall. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by severity (as recorded on eCRF) and by treatment and overall. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed by subject.

A separate listing of AEs leading to study drug discontinuation will be provided.

17.1.2 Serious Adverse Events

A listing of SAEs will be provided by subject.

17.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology, and urinalysis by treatment and scheduled time will be provided.

All laboratory data will be listed by subject, including laboratory variables not listed in the protocol. A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory and will be included in the listings for reference.

17.1.4 Vital Signs

Descriptive statistics summarizing vital signs by treatment and scheduled time will be provided.

All vital signs will be listed by subject.

17.1.5 Electrocardiograms

The observed measurements for all ECG parameters and the corresponding abnormalities will be listed by subject. The means of triplicate measurements for continuous parameters at each scheduled timepoint will also be listed by subject.

Descriptive statistics summarizing mean ECG parameters by treatment and scheduled time will be provided.

17.1.6 Physical Examinations

Physical examination results will be listed by subject.

18.0 Taste Analyses

18.1.1 Taste Questionnaire

Descriptive statistics (n, median, min, and max) will be provided to summarize results of the taste questionnaire by treatment.

Taste questionnaire results will be listed by subject.

19.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A 2 PART, RANDOMIZED, OPEN-LABEL, SINGLE DOSE, CROSSOVER STUDY TO ASSESS THE RELATIVE BIOAVAILABILTY OF PHASE II TABLET FORMULATION COMPARED TO THE CURRENT PHASE I CAPSULE FORMULATION AND THE EFFECT OF FOOD AND TASTE ASSESSMENT ON THE PHASE II TABLET FORMULATION IN HEALTHY PARTICIPANTS. Version 2.0, Final, 26 Feb 2019.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
AdaM	Analysis data model
BMI	Body mass index
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CSR	Clinical study report
%CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled
SAP	Statistical analysis plan
SAE	Serious adverse event
SDTM	Study data tabulation model
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings

Appendix 2: Protocol Schedule of Assessments

Day	Screening	Study Days in Each Period																		Follow Up Visit[k]
		Day -1	Day 1													Day 2		Day 3	Day 4	Day 5	
Scheduled Time (h)	Up to -28 days																				
Informed Consent	X																				
Demography	X																				
Medical History	X																				
Inclusion/exclusion criteria review	X	X																			
Physical Examination [a]	X	X																X			X
In-house Period		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Ambulatory visit																			X	X	
Discharge from unit																		X			
Vital Signs [b]	X	X	X													X		X			X
ECG-12 lead [c]	X	X	X			X		X			X	X	X			X		X	X	X	X
Serology	X																				
Pregnancy Test [d]	X	X																			X
Hormone Panel [e]	X																				
Alcohol Breath Test	X	X																			
Urine Cotinine Test	X	X																			
Urine Drugs of abuse	X	X																			
Urinalysis	X	X																X			X
Blood Chemistry	X	X																X			X
Hematology	X	X																X			X
Coagulation	X																				
Randomization [f]			X																		
Administration of Study Medication [g]				X																	
Standard Meal [h]			X[i]							X				X		X		X			

[redacted]

Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) Physical examination will include body weight at screening and follow-up, and height at screening when BMI will be derived.
b) Vital signs will include blood pressure, pulse rate and body temperature. Temperature will be recorded at screening, Day 1 predose and follow-up. All measurements will be taken after the subject has rested in a supine position for at least 5 min.
c) Triplicate 12-lead ECGs will be collected after the subject has rested in a supine position for at least 10 min.
d) Pregnancy test for females. Serum test at screening, urine test at Day -1.
e) Hormonal panel for postmenopausal women only.
f) Randomization only in Period 1 of each Part
g) [redacted]
h) [redacted]
i) [redacted]
k) The follow up visit is 7 to 14 days after the last dosing.

Appendix 3: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	**Title**	**Analysis Set**
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Subject Disposition	All Subjects
Table 14.1.2.1	Summary of Demographics – Part 1	Safety
Table 14.1.2.2	Summary of Demographics – Part 2	Safety
Table 14.1.3.1	Summary of Study Drug Administration – Part 1	Safety
Table 14.1.3.2	Summary of Study Drug Administration – Part 2	Safety
Section 14.2 – Pharmacokinetic Data		
Table 14.2.1	Statistical Analysis to Assess the Relative Bioavailability and Food Effect for RO7017773	PK
Table 14.2.2	Statistical Analysis to Compare RO7017773 with Flavor/Sweetener Dispersed in Water to RO7017773 without Flavor/Sweetener Dispersed in Apple Juice	PK
Section 14.3 – Safety Data		
Table 14.3.1.1.1	Summary of Adverse Events – Part 1	Safety
Table 14.3.1.1.2	Summary of Adverse Events – Part 2	Safety
Table 14.3.1.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 1	Safety
Table 14.3.1.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 2	Safety
Table 14.3.1.3.1	Summary of Treatment Emergent Adverse Events by Relationship to Study Drugs – Part 1	Safety
Table 14.3.1.3.2	Summary of Treatment Emergent Adverse Events by Relationship to Study Drugs – Part 2	Safety
Table 14.3.1.4.1	Summary of Treatment Emergent Adverse Events by Severity – Part 1	Safety
Table 14.3.1.4.2	Summary of Treatment Emergent Adverse Events by Severity – Part 2	Safety
Table 14.3.2.1	Listing of Serious Adverse Events - Part 1	All Subjects
Table 14.3.2.2	Listing of Serious Adverse Events - Part 2	All Subjects
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR	
Table 14.3.4.1	Listing of Abnormal Laboratory Values – Part 1	All Subjects
Table 14.3.4.2	Listing of Abnormal Laboratory Values – Part 2	All Subjects
Table 14.3.5.1	Summary of Laboratory Results – Part 1	Safety
Table 14.3.5.2	Summary of Laboratory Results – Part 2	Safety

Table 14.3.6.1	Summary of Vital Signs – Part 1	Safety
Table 14.3.6.2	Summary of Vital Signs – Part 2	Safety
Table 14.3.7.1	Summary of Mean 12-Lead Electrocardiogram Results – Part 1	Safety
Table 14.3.7.2	Summary of Mean 12-Lead Electrocardiogram Results – Part 2	Safety
Table 14.2.8.1	Summary of Taste Panel Questionnaire Results – Part 1	Safety
Table 14.2.8.2	Summary of Taste Panel Questionnaire Results – Part 2	Safety

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1.1	Subject Disposition – Part 1
Listing 16.2.1.2	Subject Disposition – Part 2
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Other Appendix Outputs:	
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Appendix 16.1.9.2.1	Statistical Appendices – Part 1
Appendix 16.1.9.2.2	Statistical Appendices – Part 2

Appendix 4: Shells for Post-Text Tables, Figures and Listings

Shells are provided in a separate document.

20.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
03-Apr-2019	[redacted]	Created from template EDSREP 009 T 01 G
22-Apr-2019	[redacted]	Added additional details to PK analyses section
24-Apr-2019	[redacted]	Updated sections 16.1.1.1 and 16.1.1.2 to indicate that only AUCinf and Cmax will be analyzed if AUCinf can be derived.

Effective Date	Version	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)