Statistical Analysis Plan

A Phase 1, Partially Blind, Placebo Controlled, Randomized, Combined Single Ascending Dose with a Food Effect Cohort (Part 1) and Multiple Ascending Dose Study (Part 2), and Relative Bioavailability (Part 3) Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects

Protocol Number: *TBAJ-876-CL001*

Protocol Version: *Version 8.0, dated 03 Dec 2021*

SAP Version: *Version 2.0, dated 25 July 2022*

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Previous SAP Versions

Version 1.0, dated 15 March 2021

SAP Amendments Before Database Lock

Version	Issue Date	Section	Revision / Addition
2.0	18Apr2022	Title page	Updated the protocol version, from: Version 6.0, dated 05 Feb 2021 To: Version 8.0, dated 03 Dec 2021
		1 Introduction	Added part 3 into the introduction: This document details the planned statistical analyses for Global Alliance for TB Drug Development, protocol "TBAJ-876-CL001" study titled "A Phase 1, Partially Blind, Placebo Controlled, Randomized, Combined Single Ascending Dose with a Food Effect Cohort (Part 1), ~~and~~ Multiple Ascending Dose ~~Study~~ (Part 2), **and Relative Bioavailability (Part 3)** Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects".
		1 Introduction	Changed the version of the protocol and date: The proposed analyses are based on the contents of **Version 8.0 of the protocol, dated 03 Dec 2021.**
		1 Introduction	Added part 3: This study is a **three-part**, partially blinded, placebo controlled, combined single ascending dose (SAD) with food-effect, ~~and~~ multiple ascending dose (MAD), **and a single dose relative bioavailability (BA)** study conducted in one study center in the United States.
		1 Introduction	From: Part 1 is a SAD design with 6 planned dose levels. To: Part 1 is a SAD design with 7 planned dose levels.
		1 Introduction	From: The fed group will enroll at least 10 new subjects and the fasted group will include the data from subjects who completed Cohort 4 and 3 additional subjects who will be enrolled in the fasted group. All subjects in the food-effect cohort will receive active drug of TBAJ-876, 100 mg. To: The fed group will enroll at least 10 new subjects and the fasted group will include the data from **6 subjects** who completed Cohort 4 and **at least 3 additional subjects** who will be enrolled in the fasted group. All subjects in the food-effect cohort will receive active drug of TBAJ-876, 100 mg.

		1 Introduction	From: For Part 2, MAD design, dose levels will be determined based on model predictions of multiple dose PK behavior, and safety from Part 1. In the multiple ascending dose part, each subject is expected to receive TBAJ-876 or matching placebo for up to 28 days with corresponding PK and safety measurements. Three dose cohorts are planned. After each dose cohort the Sponsor and Principal Investigator will review the PK and safety data before proceeding to the next dose level. To: For Part 2, MAD design, dose levels **of the first cohort** will be determined based on model predictions of multiple-dose PK behavior, and safety from Part 1. **The dose for the second cohort will then be informed by safety and PK results from the first cohort.** In the multiple ascending dose part, each subject is expected to receive TBAJ-876 or matching placebo for **14 days in the fed state** with corresponding PK and safety measurements. Three dose cohorts are planned. After **Cohort 1 and 2**, the Sponsor and Principal Investigator will review the PK and safety data before proceeding to the next dose level.
		1 Introduction	Added part 3 study design: Part 3 is a single-dose design study with 3 planned dose groups each consisting of 10 subjects. Subjects will be assigned to one of 3 groups and dose: • Group 1: TBAJ-876 – 100 mg (1 x 100 mg tablet) under fasted conditions. • Group 2: TBAJ-876 -100 mg (1 x 100 mg tablet) under fed conditions. • Group 3: TBAJ-876 – 100 mg (4 x 25 mg tablets) under fasted conditions. Subjects will be confined in the clinic prior to dosing (Day -1) until 7 days after dosing (Day 8). Subjects will return to the clinic to have subsequent follow up safety and PK measurements on Days 10 and 14. A follow-up phone call to collect any AEs will be conducted on Day 21. Blood samples will be obtained before each dose of study drug, and at serial time points post dose on Days 1-8 and Days 10 and 14. Plasma PK samples will be analyzed for TBAJ-876, M2 and M3 using validated analytical methods. In addition, blood and urine will be collected for clinical laboratory evaluations.

			Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure follicle stimulating hormone (FSH) levels.
		2 STUDY OBJECTIVES	Amended the primary objective of the study: • To evaluate the safety and tolerability of single and multiple ascending doses of TBAJ 876 oral suspension, **and single doses of two strengths of TBAJ-876 tablets** in healthy subjects.
		2 STUDY OBJECTIVES	Amended the secondary objectives of the study: • To determine the pharmacokinetics (PK) of TBAJ-876 and its metabolites (M2 and M3) after single and multiple doses of TBAJ-876 oral suspension, **and single doses of two strengths of TBAJ-876 tablets** in healthy adult subjects. • ***Clarified wording:*** **To evaluate the effect of food on the rate and extent of absorption of a single oral dose (100 mg) of TBAJ-876, given either as an oral suspension or a tablet.** ***Original protocol wording:*** ~~[To compare the rate and extent of absorption of a single oral dose of TBAJ-876 oral suspension and two strengths of TBAJ-876 tablets when administered after a high-calorie, high-fat meal versus when it is administered fasting in healthy adult subjects.]~~ • (no change) • ***Removed due to duplication of wording:*** ~~[To compare the rate and extent of absorption of a single oral dose of 100 mg of the TBAJ-876 oral suspension and two strengths of TBAJ-876 tablets under fed and/or fasted conditions.]~~
		3 ENDPOINTS	From: Additional samples were collected on Days 42, 56, and 70 for Cohorts 4, 5, and 6. To: Additional samples were collected on Days 42, 56, and 70 for Cohorts 4, 5, and 6. **For cohort 7, additional samples were only collected on Day 14.** Removed sampling on study day 28 for Part 2: For Part 2 (multiple ascending dose), serial blood samples will be collected pre-dose and post-dose through 24 hours on study days 1 and 14 ~~and through 1440 hours (through study day 60) on study day 28~~ to determine concentrations of TBAJ-876 and its metabolites

			(M2 and M3) in plasma. Predose trough plasma samples will be drawn daily Days 1 through **14~~28~~**. Amended parameters for Part 2 PK Analysis. Removed PK parameters for Study Day 28: For Part 2 on study day 1, noncompartmental pharmacokinetic parameters of AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, AUC_{tau}, **λz, $t_{1/2}$,** and C_{24} will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CL/F and V_z/F **may** ~~will~~ be calculated for TBAJ-876 **if reasonable** ~~only~~. For Part 2 on study day 14, noncompartmental pharmacokinetic parameters of AUC_{tau}, C_{max}, T_{max}, C_{min}, C_{trough}, C_{avg}, C_{24}~~, R_{AUC}, R_{C24}, and R_{Cmax} will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite)~~. ~~For Part 2 on study day 28, noncompartmental pharmacokinetic parameters of AUC_{tau}, C_{avg}, C_{24}, C_{max}, T_{max}, C_{min}, λz, $t_{1/2}$, AUC_{last}, AUC_{inf}, $AUC_{Extrap\%}$,~~ R_{AUC}, R_{C24}, and R_{Cmax} will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CL_{ss}/F and V_z/F will be calculated for TBAJ-876 only. **Parameters such as λ_z, and $t_{1/2}$ may be calculated as reasonable.** … For the assessment of the effect of food on TBAJ-876 and metabolites **in Part 1,** the 90% confidence intervals for geometric mean ratios, test-to-reference, of $AUC_{0\text{-}72h}$, **$AUC_{0\text{-}14}$**~~$_{d28d}$~~, and C_{max} will be determined as appropriate. Achievement of steady state concentrations during the multiple doses of TBAJ-876 **(Part 2)** will be assessed using Tukey's multiple comparison test at predose on all dosing days (Days 2-**14~~28~~**) for each dose level separately. Added PK parameters for Part 3: **For Part 3 (relative bioavailability [RBA] including assessment of food effect [FE]), serial blood samples will be collected pre-dose and post-dose through 14 days to determine concentrations of TBAJ-876 and its metabolites (M2 and M3) in plasma. Noncompartmental pharmacokinetic parameters of AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{last}, T_{last}, $AUC_{Extrap\%}$, λz, and $t_{1/2}$ will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CL/F and V_z/F will be calculated for TBAJ-876 only.**

			Added statistical analysis details for Part 3: **For Part 3, food effect will be assessed using an analysis of variance (ANOVA) model with food condition as the fixed effect. The relative bioavailability analysis for the two strengths of TBAJ-876 tablets will be assessed using an ANOVA model with the strength of tablet administered under fasting conditions as the fixed effect.**
		4 SAMPLE SIZE	Amended: For Part 1, **7**~~6~~ dose levels are planned. **For 7,**~~ enrolling 50 to 60 subjects. Each~~ dose **levels, 7 cohorts** ~~cohort will consist~~ of 8 subjects **will be used**, 6 to receive active drug and 2 to receive placebo, all under fasting conditions. The effect of food on bioavailability of TBAJ-876 will be studied in a food-effect cohort comprised of two parallel groups, one fasting and the other fed. The fed group will enroll at least 10 ~~new~~ subjects, which will yield complete data for at least 8 subjects if at most 2 fail to complete. **For the fasted group, the data from the 6**~~Six~~ subjects previously administered 100 mg TBAJ-876 in Cohort 4 (who have already completed the cohort) will be **combined with data from 3**~~considered part of the fasted group. Three~~ additional subjects **to** ~~will~~ be enrolled~~ to be dosed~~ in this fasted group. This will yield a complete data set for at least 8 subjects if at most 1 fails to complete. **Thus,** ~~Based on exposure level from the first 4 completed cohorts, the 100 mg dose was chosen for~~ the **total number of subjects planned is at least 60 to 70.** ~~food effect cohort. Therefore, all subjects in the food effect cohort will receive active drug of TBAJ-876, 100 mg.~~ For Part 2, **39**~~36~~ subjects are planned to be enrolled. There are 3 cohorts planned**. Cohort 1** with 12 subjects per cohort (9 to receive active drug and 3 to receive placebo). **Cohort 2 with 13 subjects per cohort (9 to receive active drug and 4 to receive placebo), and Cohort 3 with 14 subjects per cohort (9 to receive active drug and 5 to receive placebo). All doses in Part 2 will be under fed conditions.**
		4 SAMPLE SIZE	Added part 3: **For Part 3, 30 subjects are planned to be enrolled. There are 3 groups planned with 10 subjects per group. All subjects will receive active drug under fasted or fed conditions.**

		5 RANDOMIZATION	Amended: **In Parts 1 and 2,** each subject ~~enrolled into the Part 1 fasted cohorts~~ will receive an assigned treatment (active or placebo) based on the randomization schedule prepared by the unblinded statistician. Added: **For Part 3, all subjects will be randomly allocated to receive active drug under fasted or fed conditions.**
		6.2.11 Concentration-Time Data	Added: Part 1 (SAD): • **For Cohort 7, PK samples will be collected at predose (0), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, 168, and 336 hours (Day 14) after dosing.** Amended: ~~Part 1 (Food Effect):~~ • ~~Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing, then on Days 10, 14, 17, 21 and 28.~~ ~~Part 2 (MAD):~~ • ~~Day 1: Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 (pre-dose sample for Day 2).~~ • ~~Day 14: Predose and 0.5, 1, 2, 3, 4, 5, 8, 12, 16, 20, and 24 hours (pre-dose sample of Day 15).~~ • **For Cohort 7, PK samples will be collected at predose (0)**,~~Day 28: Predose~~ and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, **168,** and **336** ~~168~~ hours **(Day 14)** after dosing~~, then on Days 38, 42, 46, 53, and 60~~. **Part 1 (FE):** • **Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing, then on Days 10, 14, 17, 21 and 28.** **Part 2 (MAD):** • **Day 1: Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 (pre-dose sample for Day 2).** • **Day 14: 0.5, 1, 2, 3, 4, 5, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing and on Days 42, 63, 84, 105, and 126.** • **Predose trough samples will be collected daily from Days 2 through 13.**

		6.2.11 Concentration-Time Data	Added part 3 concentration time data: **Part 3 (RBA and FE):** • **Pre-dose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing, then on Days 10 (240 h) and 14 (336 h).** Added mean concentration-time profiles for Part 3: **For Part 3 (RBA, FE), mean concentration-time data will be presented for all three groups; mean concentration-time plots will be presented for Groups 1 vs. 2 (100 mg tablets under fed and fasted conditions) and for Groups 1 vs. 3 (100 mg doses in different tablet strengths under fasted conditions).**
		6.2.12 PK Analysis	From: Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.) To: Phoenix™ WinNonlin® (Version 8.3.4 or higher, Certara, L.P.) For Part 1: From: $AUC_{0\text{-}28d;}$ To: $AUC_{0\text{-}24h}$ Amended: The percentage of AUCinf based on extrapolation, calculated as: (**1 -** AUClast/AUCinf)* 100 Clarified for Part 2, Day 1: **$AUC_{0\text{-}24h}$** **(**AUCtau**)** Added λ_z (K_{el} , Lambda z), $t_{1/2}$ and removed CLss/F, and Vz/F for Part 2, Day 1. (CL/F and V_z/F may be calculated if reasonable). Added CLss/F and Vz/F for Part 2, Day 14 and removed PK parameters planned for Day 28. Parameters such as λ_z, and $t_{1/2}$ may be calculated as reasonable for Day 14. For Part 3, added PK parameters C_{max}, T_{max}, C_{last}, T_{last}, AUClast, AUC_{inf}, AUC_{Extrap}, k_{el}, $t_{1/2}$, CL/F, and Vz/F.

<table>
<tr><td></td><td></td><td>6.3 Conventions</td><td>Added Part 1 treatment label:

<table><tr><td>Placebo</td><td>TBAJ-876
(10 mg)</td><td>TBAJ-876
(25 mg)</td><td>…</td><td>TBAJ-876
(800 mg)</td></tr></table></td></tr>
<tr><td></td><td></td><td>6.3 Conventions</td><td>Changed part 2 treatment group label from:
Part 2 MAD - TBAJ-876 Oral Suspension
<table><tr><td>Placebo</td><td>TBAJ-876
(XX mg)</td><td>TBAJ-876
(XX mg)</td><td>TBAJ-876
(TBD mg)</td></tr></table>
To:
Part 2 MAD - TBAJ-876 Oral Suspension
<table><tr><td>Placebo</td><td>TBAJ-876
(25 mg)</td><td>TBAJ-876
(75 mg)</td><td>TBAJ-876
(TBD mg)</td></tr></table></td></tr>
<tr><td></td><td></td><td>6.3 Conventions</td><td>Added part 3 treatment group label:

Part 3 BA - TBAJ-876 Tablets

<table><tr><td>TBAJ-876
(1x100 mg)
Fasted</td><td>TBAJ-876
(1x100 mg)
Fed</td><td>TBAJ-876
(4x25 mg)
Fasted</td></tr></table></td></tr>
<tr><td></td><td></td><td>6.9 Exposure to Study Drug</td><td>Added part 3:
All dosing information (Parts 1 and 2, and 3) will be listed.</td></tr>
<tr><td></td><td></td><td>6.1 Statistical Analysis of Pharmacokinetic Data</td><td>Added PK summarization for Part 3:
From: PK parameters will be summarized by study part, analyte, cohort, and/or day for Part 2, using descriptive statistics. PK parameters will also be stratified by gender.
To:
PK parameters will be summarized by study part, analyte, cohort (group for Part 3), and/or day for Part 2, using descriptive statistics. PK parameters will also be stratified by gender.

Removed Day 28 from dose proportionality analysis</td></tr>
</table>

			Added food effect and relative bioavailability analysis for Part 3: **Food effect will be assessed for TBAJ-876, M2, and M3 C_{max} and AUCs using an ANOVA model for parallel study design with food condition as the fixed effect. The relative bioavailability analysis for the two strengths of TBAJ-876 tablets will be assessed for TBAJ-876, M2, and M3 C_{max} and AUCs using an ANOVA model for parallel study design with the strength of tablet administered under fasting conditions as the fixed effect.**
		6.11.1 Adverse Events	Overall summary and listing for 'Any TEAE Leading to Withdrawal of Study Drug' added. 'Any TEAE Leading to Early Discontinuation **from Study**' clarified.
		6.11.3 Vital Signs	Amended All vital sign data (including body weight at screening) will be listed.

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for Global Alliance for TB Drug Development, protocol "TBAJ-876-CL001" study titled "A Phase 1, Partially Blind, Placebo Controlled, Randomized, Combined Single Ascending Dose with a Food Effect Cohort (Part 1), Multiple Ascending Dose (Part 2), and Relative Bioavailability (Part 3) Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects".

The proposed analyses are based on the contents of Version 8.0 of the protocol, dated 03 Dec 2021.

This study is a three-part, partially blinded, placebo controlled, combined single ascending dose (SAD) with food-effect, multiple ascending dose (MAD), and a single dose relative bioavailability (BA) study conducted in one study center in the United States.

Part 1 is a SAD design with 7 planned dose levels. Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or study another dose level. Interim PK analyses and safety assessments will be performed for the dose escalation decisions and to select the dose level at which to assess the food-effect. The food-effect cohort is planned with two parallel groups, one fasting and the other fed.

Based on exposure levels from the first 4 completed cohorts, the 100 mg dose was chosen for the food effect cohort. In this food-effect cohort, there will be two parallel groups, one fasting and the other fed. The fed group will enroll at least 10 subjects and the fasted group will include the data from 6 subjects who completed Cohort 4 and at least 3 additional subjects who will be enrolled in the fasted group. All subjects in the food-effect cohort will receive active drug of TBAJ-876, 100 mg.

For Part 2, MAD design, dose levels of the first cohort will be determined based on model predictions of multiple-dose PK behavior, and safety from Part 1. The dose for the second cohort will then be informed by safety and PK results from the first cohort. In this multiple ascending dose part, each subject is expected to receive TBAJ-876 or matching placebo for 14 days in the fed state with corresponding PK and safety measurements. Three dose cohorts are planned. After Cohort 1 and 2, the Sponsor and Principal Investigator will review the PK and safety data before proceeding to the next dose level.

Part 3 is a single-dose design study with 3 planned dose groups each consisting of 10 subjects.

Subjects will be assigned to one of 3 groups and dose:

• Group 1: TBAJ-876 - 100 mg (1 x 100 mg tablet) under fasted conditions.

• Group 2: TBAJ-876 -100 mg (1 x 100 mg tablet) under fed conditions.

• Group 3: TBAJ-876 - 100 mg (4 x 25 mg tablets) under fasted conditions.

Subjects will be confined in the clinic prior to dosing (Day -1) until 7 days after dosing (Day 8). Subjects will return to the clinic to have subsequent follow up safety and PK measurements on Days 10 and 14. A follow-up phone call to collect any AEs will be conducted on Day 21.

Blood samples will be obtained before each dose of study drug, and at serial time points postdose on Days 1-8 and Days 10 and 14. Plasma PK samples will be analyzed for TBAJ-876, M2 and M3 using validated analytical methods.

In addition, blood and urine will be collected for clinical laboratory evaluations.

Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure follicle stimulating hormone (FSH) levels.

2 STUDY OBJECTIVES

The primary objective of the study is:

- To evaluate the safety and tolerability of single and multiple ascending doses of TBAJ-876 oral suspension, and single doses of two strengths of TBAJ-876 tablets in healthy subjects.

The secondary objectives of the study are:

- To determine the pharmacokinetics (PK) of TBAJ-876 and its metabolites (M2 and M3) after single and multiple doses of TBAJ-876 oral suspension, and single doses of two strengths of TBAJ-876 tablets in healthy adult subjects.
- *Clarified wording:*
  To evaluate the effect of food on the rate and extent of absorption of a single oral dose (100 mg) of TBAJ-876, given either as an oral suspension or a tablet.
  Original protocol wording:
- ~~[To compare the rate and extent of absorption of a single oral dose of TBAJ-876 oral suspension and two strengths of TBAJ-876 tablets when administered after a high-calorie, high-fat meal versus when it is administered fasting in healthy adult subjects.]~~To compare

the rate and extent of absorption of the 4 x 25 mg tablets and the 1 x 100 mg tablet under fasted conditions.

- *Removed due to duplication of wording:*
  ~~[To compare the rate and extent of absorption of a single oral dose of 100 mg of the TBAJ-876 oral suspension and two strengths of TBAJ-876 tablets under fed and/or fasted conditions.]~~

3 ENDPOINTS

3.1 Pharmacokinetic Endpoints

For Part 1 (single ascending dose including assessment of food effect), serial blood samples will be collected pre-dose and post-dose through 28 days to determine concentrations of TBAJ-876 and its metabolites (M2 and M3) in plasma. Additional samples were collected on Days 42, 56, and 70 for Cohorts 4, 5, and 6. For cohort 7, additional samples were only collected on Day 14. Noncompartmental pharmacokinetic parameters of AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{last}, T_{last}, $AUC_{Extrap\%}$, λz, and $t_{1/2}$ will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CL/F and V_z/F will be calculated for TBAJ-876 only.

For Part 2 (multiple ascending dose), serial blood samples will be collected pre-dose and post-dose through 24 hours on study days 1 and 14 to determine concentrations of TBAJ-876 and its metabolites (M2 and M3) in plasma. Predose trough plasma samples will be drawn daily Days 1 through 14.

For Part 2 on study day 1, noncompartmental pharmacokinetic parameters of AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, AUC_{tau}, λz, $t_{1/2}$, and C_{24} will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CL/F and V_z/F may be calculated for TBAJ-876 if reasonable.

For Part 2 on study day 14, noncompartmental pharmacokinetic parameters of AUC_{tau}, C_{max}, T_{max}, C_{min}, C_{trough}, C_{avg}, C_{24}, , R_{AUC}, R_{C24}, and R_{Cmax} will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CLss/F and V_z/F will be calculated for TBAJ-876 only. Parameters such as λ_z, and $t_{1/2}$ may be calculated as reasonable.

For Part 3 (relative bioavailability [RBA] including assessment of food effect [FE]), serial blood samples will be collected pre-dose and post-dose through 14 days to determine concentrations of TBAJ-876 and its metabolites (M2 and M3) in plasma. Noncompartmental pharmacokinetic

parameters of AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{last}, T_{last}, $AUC_{Extrap\%}$, λz, and $t_{1/2}$ will be calculated from plasma concentrations of TBAJ-876 (parent), M2 (metabolite), and M3 (metabolite); CL/F and V_z/F will be calculated for TBAJ-876 only.

Pharmacokinetic parameters will be summarized by cohort using descriptive statistics. Summary statistics will also be presented by gender within each cohort.

A power model approach will be used to assess of dose proportionality for Part 1 and Part 2.

For the assessment of the effect of food on TBAJ-876 and metabolites in Part 1, the 90% confidence intervals for geometric mean ratios, test-to-reference, of $AUC_{0\text{-}72h}$, $AUC_{0\text{-}14d}$, and C_{max} will be determined as appropriate.

Achievement of steady state concentrations during the multiple doses of TBAJ-876 (Part 2) will be assessed using Tukey's multiple comparison test at predose on all dosing days (Days 2-14) for each dose level separately.

For Part 3, food effect will be assessed using an analysis of variance (ANOVA) model with food condition as the fixed effect. The relative bioavailability analysis for the two strengths of TBAJ-876 tablets will be assessed using an ANOVA model with the strength of tablet administered under fasting conditions as the fixed effect.

Additional pharmacokinetic parameters may be calculated if deemed appropriate.

3.2 Safety Endpoints

Safety assessments will include physical examination (including heart murmurs), vital signs, electrocardiograms (ECGs), extensive cardiac monitoring including telemetry, adverse events (AEs), and clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis).

Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure follicle stimulating hormone (FSH) levels.

4 SAMPLE SIZE

For Part 1, 7 dose levels are planned. For 7 dose levels, 7 cohorts of 8 subjects will be used, 6 to receive active drug and 2 to receive placebo, all under fasting conditions.

The effect of food on bioavailability of TBAJ-876 will be studied in a food-effect cohort comprised of two parallel groups, one fasting and the other fed. The fed group will enroll at least 10 subjects, which will yield complete data for at least 8 subjects if at most 2 fail to complete. For the fasted group, the data from the 6 subjects previously administered 100 mg TBAJ-876 in Cohort 4 (who have already completed the cohort) will be combined with data from 3 additional subjects to be enrolled in this fasted group. This will yield a complete data set for at least 8 subjects if at most 1 fails to complete. Thus, the total number of subjects planned is at least 60 to 70.

For Part 2, 39 subjects are planned to be enrolled. There are 3 cohorts planned. Cohort 1 with 12 subjects per cohort (9 to receive active drug and 3 to receive placebo).Cohort 2 with 13 subjects per cohort (9 to receive active drug and 4 to receive placebo), and Cohort 3 with 14 subjects per cohort (9 to receive active drug and 5 to receive placebo). All doses in Part 2 will be under fed conditions.

For Part 3, 30 subjects are planned to be enrolled. There are 3 groups planned with 10 subjects per group. All subjects will receive active drug under fasted or fed conditions.

Additional cohorts may be enrolled if it is deemed appropriate by the Sponsor to repeat a dose level, to study another dose level, or to increase cohort size (subject numbers).

The number of subjects selected for the study was based on the adequate number considered to provide sufficient safety data. This study has not been formally powered.

5 RANDOMIZATION

In Parts 1 and 2, each subject will receive an assigned treatment (active or placebo) based on the randomization schedule prepared by the unblinded statistician. The unblinded pharmacy staff will ensure compliance with the randomization schedule.

All subjects entering the Part 1 food-effect cohort will receive active drug (TBAJ-876 100 mg). In this food-effect cohort, new subjects will be enrolled in two parallel groups, one fasting (3 additional subjects) and the other fed (10 subjects).

For Part 3, all subjects will be randomly allocated to receive active drug under fasted or fed conditions.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Sets

Subjects excluded from the analysis sets and the reason for their exclusion will be listed.

6.1.1 All Enrolled Subjects

Enrolled subjects include all subjects who have given informed consent to participate in the study.

6.1.2 Randomized Set

The Randomized Set includes all subjects to whom a treatment was randomly assigned.

6.1.3 Safety Analysis Set

The Safety Analysis Set includes all subjects who received any dose of study drug.

6.1.4 PK Analysis Set

The PK Analysis Set includes all subjects with sufficient data to derive PK parameters.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Age

Age at screening will be calculated in SAS as

age = floor ((intck('month',birthdate,date) - (day(date) < day(birthdate))) / 12)

6.2.2 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.3 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first (or single) dose of study drug in the relevant study part.

6.2.4 Early Withdrawal Assessments

Early withdrawal assessments will be tabulated with End of Study (EOS).

6.2.5 Study Day / Duration

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose.
- date of event – date of first dose of study drug, for events before first dose.

Duration is calculated in hours as (event end date-time – event start date-time).

6.2.6 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an AE start date or time is missing, and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken, and it will be assumed that the AE occurred after first dosing.

All dates presented in the individual subject listings will be as recorded on the Electronic Case Report Form (eCRF).

6.2.7 Exposure to Study Drug

For dosing in Part 2 MAD, exposure to study drug will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

6.2.8 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.9 Electrocardiogram Data

For ECG data recorded on continuous scales, if more than one value is recorded at a time point, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

6.2.10 Unscheduled Visits

Only scheduled post-baseline assessment values will be tabulated. Post-baseline repeat / unscheduled assessments will not be summarized, but these post-baseline assessments will be listed in the relevant appendices to the CSR.

6.2.11 Concentration-Time Data

Blood Samples for PK analysis in plasma will be collected at:

Part 1 (SAD):

- Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing, then on Days 10, 14, 17, 21 and 28.

  Additional samples will be drawn on Days 42, 56, and 70 for Cohorts 4, 5, and 6.

- For Cohort 7, PK samples will be collected at predose (0), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, 168, and 336 hours (Day 14) after dosing.

Part 1 (FE):

- Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing, then on Days 10, 14, 17, 21 and 28.

Part 2 (MAD):

- Day 1: Predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 (pre-dose sample for Day 2).

- Day 14: 0.5, 1, 2, 3, 4, 5, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing and on Days 42, 63, 84, 105, and 126.
- Additional or fewer samples may be collected at times to be determined based on the results from previous cohorts. Predose trough concentrations will be collected daily from Days 2 through 13.

Part 3 (RBA and FE):

- Pre-dose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 80, 88, 96, 120, 144, and 168 hours after dosing, then on Days 10 (240 h) and 14 (336 h).

Concentration-time data will be tabulated by part, nominal time, analyte, cohort (group for Part 3), and study day (for Part 2) using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero.

Mean and individual subject concentration-time data will be presented graphically on linear and semi-logarithmic scales.

For Part 1 (SAD), mean concentration-time data will be presented for all cohorts and for Part 1 (Food Effect), mean concentration-time data will be presented for fed vs. fasted cohorts.

For Part 2 (MAD), mean concentration-time data will be presented by day (all cohorts on Day 1 Day 14 separately), and by cohort (all days for each cohort). Mean concentration-time data will also be plotted for trough concentrations.

For Part 3 (RBA, FE), mean concentration-time data will be presented for all three groups; mean concentration-time plots will be presented for Groups 1 vs. 2 (100 mg tablets under fed and fasted conditions) and for Groups 1 vs. 3 (100 mg doses in different tablet strengths).

Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times. For all subject plots (spaghetti plots, all subjects per cohort in one plot), subjects will be identified by subject number in the legend.

6.2.12 PK Analysis

Concentration-time data for TBAJ-876, M2, and M3 will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4, Certara, L.P.).

During the pharmacokinetic analysis, concentrations below the limit of quantitation (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing".

6.2.12.1 Part 1 PK Parameters

The following PK parameters will be calculated for TBAJ-876, M2, and M3 for Part 1:

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data
T_{max}	Time of the maximum plasma concentrations
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data
T_{last}	Time of last quantifiable plasma concentration
AUC_{last}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (C_{last}), as calculated by the linear trapezoidal method
AUC_{0-24h}	Area under the plasma concentration-time curve from time-zero to 24 h postdose, as calculated by the linear trapezoidal method
AUC_{0-72h}	Area under the plasma concentration-time curve from time-zero to 72 hours postdose, as calculated by the linear trapezoidal method
AUC_{inf}	Area under the plasma concentration-time curve from the time of dosing extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda z$, where λz is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
AUC_{Extrap}	The percentage of AUC_{inf} based on extrapolation, calculated as:

Parameter	Definition
	$(1 - AUC_{last}/AUC_{inf})* 100$ (see additional criteria in Section 6.2.12.3)
λ_z (K_{el} , Lambda z)	The apparent elimination rate constant λ_z will be calculated as the negative of the slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time (see additional criteria in Section 6.2.12.3)
$t_{1/2}$	The observed terminal elimination half-life, calculated as: $t_{1/2} = \ln(2)/\lambda_z$
CL/F	The apparent total plasma clearance after an oral dose, calculated as: CL/F=Dose/AUC_{inf}, where F is the bioavailability (calculated for parent only)
Vz/F	The apparent volume of distribution after an oral dose, calculated as: Vz/F=Dose/(AUC_{inf} x λ_z), where F is the bioavailability (calculated for parent only)

6.2.12.2 Part 2 PK Parameters

6.2.12.2.1 Study Day 1 PK Parameters (Part 2)

The following PK parameters will be calculated for TBAJ-876, M2, and M3 for Part 2 (Day 1):

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data
T_{max}	Time of the maximum plasma concentrations

Parameter	Definition
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data
T_{last}	Time of last quantifiable plasma concentration
AUC_{0-24h} (AUC_{tau})	Area under the plasma concentration-time curve over the 24 hour dosing interval, calculated using the linear trapezoidal rule
C_{avg}	Average plasma concentration over 24 hours
C_{24}	Plasma concentration at 24 hours postdose
λ_z (K_{el} , Lambda z)	The apparent elimination rate constant λ_z will be calculated as the negative of the slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time (see additional criteria in Section 6.2.12.3) (may be calculated as reasonable)
$t_{1/2}$	The observed terminal elimination half-life, calculated as: $t_{1/2} = \ln(2)/\lambda_z$ (may be calculated as reasonable)
CL/F	The apparent total plasma clearance after an oral dose, calculated as: $CL/F=Dose/AUC_{inf}$, where F is the bioavailability (calculated for parent only, may be calculated as reasonable)
Vz/F	The apparent volume of distribution after an oral dose, calculated as: $Vz/F=Dose/(AUC_{inf} \times \lambda_z)$, where F is the bioavailability (calculated for parent only, may be calculated as reasonable)

6.2.12.2.2 Study Day 14 PK Parameters (Part 2)

The following PK parameters will be calculated for TBAJ-876, M2, and M3 for Part 2 (Day 14):

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data
T_{max}	Time of the maximum plasma concentrations
C_{min}	Minimum plasma concentration, determined directly from individual concentration-time data
AUC_{tau}	Area under the plasma concentration-time curve over the 24 hour dosing interval, calculated using the linear trapezoidal rule
C_{avg}	Average plasma concentration over 24 hours
C_{24}	Plasma concentration at 24 hours postdose
C_{trough}	Predose plasma concentration, (Days 2-14)
λ_z (K_{el} , Lambda z)	The apparent elimination rate constant λ_z will be calculated as the negative of the slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time (see additional criteria in Section 6.2.12.3) (may be calculated as reasonable)
$t_{1/2}$	The observed terminal elimination half-life, calculated as: $t_{1/2} = \ln(2)/\lambda_z$ (may be calculated as reasonable)
CLss/F	The apparent total plasma clearance after an oral dose at steady-state, calculated as:

Parameter	Definition
	CLss/F=Dose/AUC_{tau}, where F is the bioavailability (calculated for parent only)
Vz/F	The apparent volume of distribution after an oral dose at steady-state, calculated as: Vz/F=Dose/(AUC_{inf} x λ_z), where F is the bioavailability (calculated for parent only)
R_{AUC}	Accumulation ratio of AUC_{tau} for Day 14, calculated as: AUC_{tau} (Day 14)/AUC_{tau} (Day 1)
R_{C24}	Accumulation ratio of R_{C24} for Day 14, calculated as: C_{24} (Day 14)/ C_{24} (Day 1)
R_{Cmax}	Accumulation ratio of C_{max} for Day 14, calculated as: C_{max} (Day 14)/ C_{max} (Day 1)

6.2.12.3 Part 3 PK Parameters

The following PK parameters will be calculated for TBAJ-876, M2, and M3 for Part 3:

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data
T_{max}	Time of the maximum plasma concentrations
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data
T_{last}	Time of last quantifiable plasma concentration

Parameter	Definition
AUC_{0-24h}	Area under the plasma concentration-time curve from time-zero to 24 h postdose, as calculated by the linear trapezoidal method
AUC_{last}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (C_{last}), as calculated by the linear trapezoidal method
AUC_{inf}	Area under the plasma concentration-time curve from the time of dosing extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda z$, where λz is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
AUC_{Extrap}	The percentage of AUC_{inf} based on extrapolation, calculated as: $(1 - AUC_{last}/AUC_{inf})* 100$ (see additional criteria in Section 6.2.12.4)
λ_z (K_{el} , Lambda z)	The apparent elimination rate constant λ_z will be calculated as the negative of the slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time (see additional criteria in Section 6.2.12.4)
$t_{1/2}$	The observed terminal elimination half-life, calculated as: $t_{1/2} = \ln(2)/\lambda_z$
CL/F	The apparent total plasma clearance after an oral dose, calculated as : CL/F=Dose/AUC_{inf}, where F is the bioavailability (calculated for parent only)

Parameter	Definition
Vz/F	The apparent volume of distribution after an oral dose, calculated as: $Vz/F=Dose/(AUC_{inf} \times \lambda_z)$, where F is the bioavailability (calculated for parent only)

6.2.12.4 Lambda-z (λ_z) Acceptance and AUC_{inf} Reporting Criteria

The following criteria will be used to report lambda-z and related parameters:

- At least 3 quantifiable concentration-time points should be used in the regression
- C_{max} or data prior to C_{max} should not be included in the regression
- Adjusted R^2 should be ≥ 0.8000

If these acceptance criteria are not met, lambda-z and descriptive parameters such as the time range for the regression, adjusted R^2, etc. will be retained in a parameter listing for informational purposes. Lambda-z will be excluded from summary statistics and from subsequent PK calculations; parameters calculated using lambda-z (e.g. $t_{1/2}$, AUC_{inf}, CL/F, and V_z/F) will be reported as ND (not determinable).

If lambda-z acceptance criteria are met and AUC_{inf} is estimable, the following criteria are used to report AUC_{inf}:

- The percentage of AUC_{inf} based on extrapolation should be <20.0%.

If the percentage of AUC_{inf} based on extrapolation is 20.0% or greater, AUC_{inf} and AUC_{Extrap} will be retained in a PK parameter listing for informational purposes; these parameters will be excluded from summary statistics, subsequent PK calculations (e.g., CL/F, V_z/F), and statistical analysis (e.g. ANOVA).

6.3 Conventions

All clinical data summaries, statistical analyses and listings will be generated using SAS (Version 9.4 or higher)[1]. Data summaries and analyses will be reported within Appendix 14 and individual data listings within Appendix 16.2 of the CSR.

Subject disposition, baseline characteristics, demography and adverse event data will be presented by treatment group and overall. Other safety data will be presented by treatment group only or overall.

Treatment group labels will be displayed as follows:

Part 1 SAD - TBAJ-876 Oral Suspension

Placebo	TBAJ-876 (10 mg)	TBAJ-876 (25 mg)	TBAJ-876 (50 mg)	TBAJ-876 (100 mg) Fasted	TBAJ-876 (100 mg) Fed	TBAJ-876 (200 mg)	TBAJ-876 (400 mg)	TBAJ-876 (800 mg)

Part 2 MAD - TBAJ-876 Oral Suspension

Placebo	TBAJ-876 (25 mg)	TBAJ-876 (75 mg)	TBAJ-876 (TBD mg)

Part 3 BA - TBAJ-876 Tablets

TBAJ-876 (1x100 mg) Fasted	TBAJ-876 (1x100 mg) Fed	TBAJ-876 (4x25 mg) Fasted

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Listings will be sorted in the following order, treatment group, subject, parameter, and visit unless otherwise stated. All data will be listed, subjects who were not randomized will be displayed after the randomized treatment groups.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.3.4 or higher)[2] or SAS (Version 9.4 or higher)[1]. PK concentration data will be summarized by study part, analyte, and cohort (or group for Part 3), and study day for Part 2 at each nominal sample time. PK parameter data will be summarized by study part, analyte, and cohort (or group for Part 3), and study day for Part 2. PK data will also be stratified by gender within each cohort.

PK concentration-time data will be summarized by the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), coefficient of variation (CV%), and geometric mean. PK parameter data will be summarized by n, mean, SD, median, min, max, CV%, geometric mean, and geometric CV%. Summary statistics that are not calculable due to lack of quantifiable data will be presented as NC in the descriptive statistic tables.

6.3.1 Decimal Places

For summary statistics, n will be reported as a whole number. Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place. All data presented in the individual subject listings will be as recorded on the eCRF.

For PK data, individual concentrations and individual PK parameters will be reported 3 significant figures. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, CV%, geometric mean, and geometric CV% will be reported to the same precision as for individual data.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects who were enrolled, who were randomized and who are in each analysis set will be summarized by treatment group and overall, for the enrolled set.
- The number of early withdrawals, reasons for withdrawal and timing of withdrawal will be tabulated by treatment group and overall, for the enrolled set.

6.5 Protocol Deviations

All reported protocol deviations will be listed.

6.6 Baseline Comparability

Comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Baseline summaries will be presented by treatment group and overall, for the following variables based on the Safety Analysis Set:

Demographic Data

- Age at Informed Consent (years)
- Sex
- Ethnicity
- Race, where more than one race is selected the subject will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing.

Baseline Characteristics

- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)

Contraceptive data collected from female subjects will be listed separately.

6.7 Medical History

Prior and ongoing conditions at Screening will be listed for the Safety Analysis Set. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA) version 23.0 primary system organ class (SOC) and preferred term (PT). Any medical condition will be classed as resolved if a stop date is recorded, otherwise, the condition will be classed as ongoing.

6.8 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the Safety Analysis Set. Medications will be coded using the World Health Organization (WHO) Drug Dictionary B3 – September 2020 version. Prior medications are defined as all medications starting and stopping before the date of

first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

6.9 Exposure to Study Drug

Extent of exposure (number of doses and duration of exposure [days]) in Part 2 MAD, will be summarized by treatment group for the Safety Analysis Set. All dosing information (Parts 1 and 2, and 3) will be listed.

6.10 Statistical Analysis of Pharmacokinetic Data

PK parameters will be calculated as described in section 6.2.12.

PK parameters will be summarized by study part, analyte, cohort (group for Part 3), and/or day for Part 2, using descriptive statistics. PK parameters will also be stratified by gender.

Dose Proportionality (Parts 1 and 2):

The pharmacokinetic parameters for TBAJ-876, M2, and M3 C_{max}, AUC_{last}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}72h}$ and AUC_{inf} (Part 1); C_{max} and AUC_{tau} (Part 2, Day 1); and C_{max} and AUC_{tau}, (Part 2, Day 14) will be compared across doses to assess dose proportionality (i.e., proportionality of a change in systemic exposure with a change in dose). Statistical analyses will be done using a power model (Smith, 2000) of the following general form,

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon,$$

Where

PK is the pharmacokinetic parameter tested (e.g. C_{max} or AUC)
$\ln(\beta_0)$ is the y-intercept,
β_1 is the slope (a value of $\beta_1 \approx 1$ indicates linearity), and
ε is an error term

The estimate of β_1 with the 90% CIs will be reported along with the associated p-value and the dose range for proportionality. Dose proportionality plots will be created as well.

Food Effect (Part 1):

Statistical comparison of the PK parameters of TBAJ-876, M2, and M3 exposure (C_{max}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}72h}$ AUC_{last}, and AUC_{inf}) will be performed using an Analysis of Variance (ANOVA) model for a 2-way crossover design on the ln-transformed data with treatment as the

fixed effects and subject as a random effect. Conclusions regarding the results of the statistical analysis of PK parameters across treatments will be based on the ratio of the geometric means expressed as a percent (100×Fed/Fasted) and the 90% confidence interval about the ratio. A lack of food effect will be demonstrated if the 90% confidence intervals are fully contained within the limits of 80.00% to 125.00%.

Steady-state Assessment (Part 2):

Achievement of steady state concentrations during the multiple doses of TBAJ-876 will be assessed using Tukey's multiple comparison test at predose on all dosing days (Days 2-14) for each dose level separately.

Food Effect and Relative Bioavailability (Part 3):

Food effect will be assessed for TBAJ-876, M2, and M3 C_{max} and AUCs using an ANOVA model for parallel study design with food condition as the fixed effect. The relative bioavailability analysis for the two strengths of TBAJ-876 tablets will be assessed for TBAJ-876, M2, and M3 C_{max} and AUCs using an ANOVA model for parallel study design with the strength of tablet administered under fasting conditions as the fixed effect.

6.11 Safety Analyses

Safety analyses will be presented by the treatment received for the Safety Analysis Set.

6.11.1 Adverse Events

AEs will be collected from the date of informed consent until completion of the end-of-study visit.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug through completion of the end-of-study visit.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug through completion of the end-of-study visit.

AEs occurring prior to first dose are considered non-treatment emergent and will be listed only.

Relationship of the AE to treatment can be recorded as Not Related, Unlikely, Possible, Probable or Certain. A treatment-related AE is defined as any AE classified as possibly, probably or

certainly related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Severity of the AE will be graded using the Division of Microbiology and Infectious Disease (DMID) Toxicity Grade November 2007 version: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-Threatening). Maximum grade will be assumed for an AE with missing grade.

An overall summary of TEAEs (incidence and number of events) will be presented by treatment group and overall, for the following:

- Any TEAE
- Any Treatment-Related TEAE
- Any Serious TEAE
- Any Serious Treatment-Related TEAE
- Any TEAE Leading to Early Discontinuation from Study
- Any TEAE Leading to Withdrawal of Study Drug (MAD only)
- Any TEAE Leading to Death

Summaries of TEAEs (incidence and number of events) will be presented by system organ class and preferred term, by treatment group and overall, for the following:

- TEAEs
- Treatment-Related TEAEs
- TEAEs by Maximum Severity (incidence only)
- TEAEs by Nearest Relationship (incidence only)

The following listings of TEAEs will be presented in Appendix 14.3.2 of the CSR.

- TEAEs Leading to Early Discontinuation from Study, Listing
- TEAEs Leading to Withdrawal of Study Drug, Listing (MAD only)
- Serious TEAEs, Listing
- Deaths, Listing

In addition, a listing of all reported AEs will be provided in Appendix 16.2.7 of the CSR.

System organ class will be presented in descending order of overall frequency and then alphabetically. Preferred terms will be displayed in descending order of overall frequency and then alphabetically.

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; a non-continuous AE reported several times by the same patient will be counted as multiple events.

For summary by severity, patients reporting more than one AE per system organ class and preferred term will only be counted once for the most severe event.

6.11.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, serum chemistry, coagulation and urinalysis parameter. Change from baseline in categorical parameters will be presented in the natural order of the outcome where possible.

Each measurement (for continuous data and for categorical data where provided) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

All individual laboratory data, including serology, drug, alcohol and cotinine screening, pregnancy testing and FSH data will be listed, with a separate listing of any clinically significant laboratory measurements recorded throughout the study presented in Appendix 14.3.4 of the CSR.

6.11.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group at each visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Pulse oximetry (%)

All vital sign data (including body weight at screening) will be listed.

6.11.4 Physical Examination

Shift tables for the observed status of each of the body systems, i.e., Normal, Abnormal NCS (Not Clinically Significant), and Abnormal CS (Clinically Significant) from baseline to each follow-up visit will be tabulated by treatment group. All data, including details of clinically significant findings will be listed.

6.11.5 Heart Murmur Examination

Shift tables for the presence of heart murmur (Not Present, Present NCS, and Present CS) from baseline to each follow-up visit will be tabulated by treatment group. All data, including details of clinically significant findings will be listed.

6.11.6 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated by treatment group at each visit:

- Heart rate (bpm)
- PR duration (ms)
- QRS duration (ms)
- RR interval (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcB interval (ms) [Bazett's formula]
- QTcF interval (ms) [Fridericia's formula]

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS), from baseline to each follow-up visit will be presented. All ECG data, including details of any abnormalities, will be listed.

6.11.7 Cardiac Telemetry (Holter) Data

Data relating to the initialization and discontinuation of cardiac telemetry (Holter) will be listed.

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

No changes to the planned analyses were identified.

8 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Phoenix™ WinNonlin® (Version 8.1 or higher, Certara L.P.)

9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the electronic common technical document (eCTD). The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Subject Disposition, Analysis Sets – All Enrolled Subjects	IP	
14.1.2	**Demographics**		
14.1.2.1	Demographics, Safety Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
	Not Applicable		
14.2	**Efficacy Data**		
	Not Applicable		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Adverse Events, Overall Summary of Treatment-Emergent Adverse Events (TEAEs) – Safety Analysis Set	IP	
14.3.1.2	Adverse Events, TEAEs by Primary System Organ Class and Preferred Term – Safety Analysis Set	IP	
14.3.1.3	Adverse Events, Treatment-Related TEAEs by Primary System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.1.4	Adverse Events, TEAEs by Primary System Organ Class, Preferred Term and Maximum Grade – Safety Analysis Set	IP	
14.3.1.5	Adverse Events, TEAEs by Primary System Organ Class, Preferred Term and Nearest Relationship – Safety Analysis Set	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.2.1.1	TEAEs Leading to Early Discontinuation from Study, Listing – Safety Analysis Set	IP	
14.3.2.1.2	TEAEs Leading to Withdrawal of Study Drug, Listing – Safety Analysis Set		
14.3.2.2	Serious TEAEs, Listing – Safety Analysis Set	IP	
14.3.2.3	Deaths, Listing – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious, and ~~Certain~~ Other Significant Adverse Events**		
	Placeholder for Medical Writing		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Laboratory, Listing of Clinically Significant Values – Safety Analysis Set	IP	
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**		
14.3.5.1	Extent of Exposure – Safety Analysis Set	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1	Vital Signs, Descriptive Statistics – Safety Analysis Set	IP	
14.3.6.2	Physical Examination, Descriptive Statistics – Safety Analysis Set	IP	
14.3.6.3	Heart Murmur Examination, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7	**Other Safety**		
14.3.7.1	Hematology Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.2	Hematology Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.3	Serum Chemistry Data, Descriptive Statistics – Safety Analysis Set	IP	14.3.7.1
14.3.7.4	Serum Chemistry Data, Normal Range Shifts – Safety Analysis Set	IP	14.3.7.2
14.3.7.5	Coagulation Data, Descriptive Statistics – Safety Analysis Set	IP	14.3.7.1
14.3.7.6	Coagulation Data, Normal Range Shifts – Safety Analysis Set	IP	14.3.7.2
14.3.7.7	Urinalysis Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.8	Urinalysis Data, Normal Range Shifts – Safety Analysis Set	IP	14.3.7.2
14.3.7.9	12-Lead ECG Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.10	12-Lead ECG Data, Overall Interpretation – Safety Analysis Set	IP	
14.3.8	**Concomitant Medication**		
	Not Applicable		
14.4	**PK Tables**		
14.4.1.1	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses of 10 mg (Cohort 1), 25 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4), 200 mg (Cohort 5), 400 mg (Cohort	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	6), and 800 mg (Cohort 7) TBAJ-876 Oral Suspension Administered under Fasted Conditions (Part 1)		
14.4.1.2	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses of 10 mg (Cohort 1), 25 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4), 200 mg (Cohort 5), 400 mg (Cohort 6), and 800 mg (Cohort 7) TBAJ-876 Oral Suspension Administered under Fasted Conditions in Male and Female Subjects (Part 1)	IP	
14.4.2.1	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses 100 mg (Cohort 4) TBAJ-876 Oral Suspension Administered under Fed and Fasted Conditions (Part 1)	IP	
14.4.2.2	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses 100 mg (Cohort 4) TBAJ-876 Oral Suspension Administered under Fed and Fasted Conditions in Male and Female Subjects (Part 1)	IP	
14.4.3.1	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension on Study Day 1 (Part 2)	IP	
14.4.3.2	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension in Male and Female Subjects on Study Day 1 (Part 2)	IP	
14.4.4.1	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Multiple One-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension on Study Day 14 (Part 2)	IP	
14.4.4.2	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Multiple One-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension in Male and Female Subjects on Study Day 14 (Part 2)	IP	
14.4.5.1	Descriptive Statistics for Trough (Predose) Concentration-Time Data of TBAJ-876, M2, and M3 after Multiple One-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2)	IP	
14.4.5.2	Descriptive Statistics for Trough (Predose) Concentration-Time Data of TBAJ-876, M2, and M3 after Multiple One-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension in Male and Female Subjects (Part 2)	IP	
14.4.6.1	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses of 100 mg TBAJ-876 under Fasted	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Conditions (1 x 100 mg Tablet, Group 1), 100 mg TBAJ-876 under Fed Conditions (1 x 100 mg Tablet, Group 2), and 100 mg TBAJ-876 (4 x 25 Tablets, Group 3) (Part 3)		
14.4.6.2	Descriptive Statistics for Concentration-Time Data of TBAJ-876, M2, and M3 after Single Doses of 100 mg TBAJ-876 under Fasted Conditions (1 x 100 mg Tablet, Group 1), 100 mg TBAJ-876 under Fed Conditions (1 x 100 mg Tablet, Group 2), and 100 mg TBAJ-876 (4 x 25 Tablets, Group 3) in Male and Female Subjects (Part 3)	IP	
14.4.7.1	Plasma PK Parameters of TBAJ-876, M2, and M3 after Single Doses of 10 mg (Cohort 1), 25 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4), 100 mg (Cohort 4-Fed), 200 mg (Cohort 5), 400 mg (Cohort 6), and 800 mg (Cohort 7) TBAJ-876 Oral Suspension (Part 1)	IP	
14.4.7.2	Plasma PK Parameters of TBAJ-876, M2, and M3 after Single Doses of 10 mg (Cohort 1), 25 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4), 100 mg (Cohort 4-Fed), 200 mg (Cohort 5), 400 mg (Cohort 6), and 800 mg (Cohort 7) TBAJ-876 Oral Suspension in Male and Female Subjects (Part 1)	IP	
14.4.8.1	Plasma PK Parameters of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension on Study Day 1 (Part 2)	IP	
14.4.8.2	Plasma PK Parameters of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension in Male and Female Subjects on Study Day 1 (Part 2)	IP	
14.4.9.1	Plasma PK Parameters of TBAJ-876, M2, and M3 after Multiple One-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension on Study Day 14 (Part 2)	IP	
14.4.9.2	Plasma PK Parameters of TBAJ-876, M2, and M3 after Multiple One-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension in Male and Female Subjects on Study Day 14 (Part 2)	IP	
14.4.10.1	Plasma PK Parameters of TBAJ-876, M2, and M3 after Single Doses of 100 mg TBAJ-876 under Fasted Conditions (1 x 100 mg Tablet, Group 1), 100 mg TBAJ-876 under Fed Conditions (1 x 100 mg Tablet, Group 2), and 100 mg TBAJ-876 (4 x 25 Tablets, Group 3) (Part 3)	IP	
14.4.10.2	Plasma PK Parameters of TBAJ-876, M2, and M3 after 100 mg TBAJ-876 under Fasted Conditions (1 x 100 mg Tablet, Group 1), 100 mg TBAJ-876 under Fed Conditions (1 x 100 mg Tablet, Group 2), and 100 mg TBAJ-876 (4 x 25 Tablets, Group 3) (Part 3)	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.4.11.1	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of TBAJ-876 Comparing Single Doses of 100 mg TBAJ-876 Oral Suspension Administered under Fed (Test) and Fasted Conditions (Reference) (Part 1)	IP	
14.4.11.2	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of M2 Comparing Single Doses of 100 mg TBAJ-876 Oral Suspension Administered under Fed (Test) and Fasted Conditions (Reference) (Part 1)	IP	
14.4.11.3	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of M3 Comparing Single Doses of 100 mg TBAJ-876 Oral Suspension Administered under Fed (Test) and Fasted Conditions (Reference) (Part 1)	IP	
14.4.12.1	Assessment of Dose Proportionality of TBAJ-876 Following Single Dose Administrations of TBAJ-876 Oral Suspension (Part 1)	IP	
14.4.12.2	Assessment of Dose Proportionality of M2 Following Single Dose Administrations of TBAJ-876 Oral Suspension (Part 1)	IP	
14.4.12.3	Assessment of Dose Proportionality of M3 Following Single Dose Administrations of TBAJ-876 Oral Suspension (Part 1)	IP	
14.4.12.4	Assessment of Dose Proportionality of TBAJ-876 Following Single Dose Administrations of TBAJ-876 Oral Suspension (Part 2, Day 1)	IP	
14.4.12.5	Assessment of Dose Proportionality of M2 Following Single Dose Administrations of TBAJ-876 Oral Suspension (Part 2, Day 1)	IP	
14.4.12.6	Assessment of Dose Proportionality of M3 Following Single Dose Administrations of TBAJ-876 Oral Suspension (Part 2, Day 1)	IP	
14.4.12.7	Assessment of Dose Proportionality of TBAJ-876 Following Multiple, Once-Daily Dose Administrations of TBAJ-876 Oral Suspension (Part 2, Day 14)	IP	
14.4.12.8	Assessment of Dose Proportionality of M2 Following Multiple, Once-Daily Dose Administrations of TBAJ-876 Oral Suspension (Part 2, Day 14)	IP	
14.4.12.9	Assessment of Dose Proportionality of M3 Following Multiple, Once-Daily Dose Administrations of TBAJ-876 Oral Suspension (Part 2, Day 14)	IP	
14.4.12.10	Tukey's Multiple Comparison Test for Trough Concentrations of TBAJ-876 after Multiple, Once-Daily Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2)	IP	
14.4.13.1	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of TBAJ-876 Comparing Single Doses of 100 mg TBAJ-876 Tablets	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Administered under Fed (Test, Group 2) and Fasted Conditions (Reference, Group 1) (Part 3)		
14.4.13.2	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of M2 Comparing Single Doses of 100 mg TBAJ-876 Tablets Administered under Fed (Test, Group 2) and Fasted Conditions (Reference, Group 1) (Part 3)	IP	
14.4.13.3	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of M3 Comparing Single Doses of 100 mg TBAJ-876 Tablets Administered under Fed (Test, Group 2) and Fasted Conditions (Reference, Group 1) (Part 3)	IP	
14.4.13.4	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of TBAJ-876 Comparing Single Doses of 100 mg TBAJ-876 Tablets Administered under Fasted Conditions as 4 x 25 Tablets (Test, Group 3) and as 1 x 100 mg Tablet (Reference, Group 1) (Part 3)	IP	
14.4.13.5	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of M2 Comparing Single Doses of 100 mg TBAJ-876 Tablets Administered under Fasted Conditions as 4 x 25 Tablets (Test, Group 3) and as 1 x 100 mg Tablet (Reference, Group 1) (Part 3)	IP	
14.4.13.6	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of M3 Comparing Single Doses of 100 mg TBAJ-876 Tablets Administered under Fasted Conditions as 4 x 25 Tablets (Test, Group 3) and as 1 x 100 mg Tablet (Reference, Group 1) (Part 3)	IP	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 10 mg (Cohort 1), 25 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4-Fasted), 100 mg (Cohort 4-Fed), 200 mg (Cohort 5), 400 mg (Cohort 6), and 800 mg (Cohort 7) TBAJ-876 Oral Suspension (Part 1) on Linear and Semi-Logarithmic Scales	IP	
14.4.2	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 for Males and Females by Cohort (Part 1) on Linear and Semi-Logarithmic Scales	IP	
14.4.3	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after a Single Dose Administration of 100 mg TBAJ-876 Oral Suspension (Cohort 2) under Fasted and Fed Conditions (Part 1) on Linear and Semi-Logarithmic Scales	IP	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.4	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2, Day 1) on Linear and Semi-Logarithmic Scales	IP	
14.4.5	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2, Day 14) on Linear and Semi-Logarithmic Scales	IP	
14.4.6	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses (Day 1) and Multiple Doses (Day 14) of 25 mg (Cohort 1) TBAJ-876 Oral Suspension (Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.7	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses (Day 1) and Multiple Doses (Day 14) of 75 mg (Cohort 2) TBAJ-876 Oral Suspension (Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.8	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses (Day 1) and Multiple Doses (Day 14) of 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.9	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 for Males and Females by Cohort (Day 1, Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.10	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 for Males and Females by Cohort (Day 14, Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.11	Mean Plasma Trough Concentration-Time Profiles of TBAJ-876, M2, and M3 after Multiple Doses of TBAJ-876 Oral Suspension Administered over 14 Days (Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.12	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 100 mg Tablet under Fasted Conditions (Group 1), 100 mg Tablet under Fed Conditions (Group 2), and 100 mg Tablets (4x25 mg) under Fasted Conditions (Cohort 3) (Part 3) on Linear and Semi-Logarithmic Scales	IP	
14.4.13	Mean Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 for Males and Females by Group (Part 3) on Linear and Semi-Logarithmic Scales	IP	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.14	All Subject Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 10 mg (Cohort 1), 25 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4-Fasted), 100 mg (Cohort 4-Fed), 200 mg (Cohort 5), 400 mg (Cohort 6), and 800 mg (Cohort 7) TBAJ-876 Oral Suspension (Part 1) on Linear and Semi-Logarithmic Scales	IP	
14.4.15	All Subject Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2, Day 1) on Linear and Semi-Logarithmic Scales	IP	
14.4.16	All Subject Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2, Day 14) on Linear and Semi-Logarithmic Scales	IP	
14.4.17	All Subject Plasma Trough Concentration-Time Profiles of TBAJ-876, M2, and M3 after Multiple Doses of 25 mg (Cohort 1), 75 mg (Cohort 2), and 200 mg (Cohort 3) TBAJ-876 Oral Suspension over 14 Days on Linear and Semi-Logarithmic Scales	IP	
14.4.18	All Subject Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses of 100 mg Tablet under Fasted Conditions (Group 1), 100 mg Tablet under Fed Conditions (Group 2), and 100 mg Tablets (4x25 mg) under Fasted Conditions (Cohort 3) (Part 3) on Linear and Semi-Logarithmic Scales		
14.4.19	Individual Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after a Single 100 mg Dose of TBAJ-876 Oral Suspension under Fed and Fasted Conditions (Part 1, Cohort 4) on Linear and Semi-Logarithmic Scales	IP	
14.4.20	Individual Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses (Day 1) and Multiple Doses (Day 14) of 25 mg (Cohort 1) TBAJ-876 Oral Suspension (Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.21	Individual Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses (Day 1) and Multiple Doses (Day 14) of 75 mg (Cohort 2) TBAJ-876 Oral Suspension (Part 2) on Linear and Semi-Logarithmic Scales	IP	
14.4.22	Individual Plasma Concentration-Time Profiles of TBAJ-876, M2, and M3 after Single Doses (Day 1) and Multiple Doses (Day 14) of 200 mg (Cohort 3) TBAJ-876 Oral Suspension (Part 2) on Linear and Semi-Logarithmic Scales	IP	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.23	Concentration-Time Profiles for TBAJ-876, M2, and M3 with Linear Regression for Estimating the Terminal Elimination Rate (Part 1)	IP	
14.4.24	Concentration-Time Profiles for TBAJ-876, M2, and M3 with Linear Regression for Estimating the Terminal Elimination Rate (Part 2, Day 14)	IP	
14.4.25	Concentration-Time Profiles for TBAJ-876, M2, and M3 with Linear Regression for Estimating the Terminal Elimination Rate (Part 3)	IP	
14.4.26	Dose Proportionality Plot for TBAJ-876, M2, and M3 C_{max} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 1; Cohorts 1-7)	IP	
14.4.27	Dose Proportionality Plot for TBAJ-876, M2, and M3 AUC_{0-24h} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 1; Cohorts 1-7)	IP	
14.4.28	Dose Proportionality Plot for TBAJ-876, M2, and M3 AUC_{0-72h} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 1; Cohorts 1-7)	IP	
14.4.29	Dose Proportionality Plot for TBAJ-876, M2, and M3 C_{max} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 2; Cohorts 1-3, Day 1)	IP	
14.4.30	Dose Proportionality Plot for TBAJ-876, M2, and M3 AUC_{tau} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 2; Cohorts 1-3, Day 1)	IP	
14.4.31	Dose Proportionality Plot for TBAJ-876, M2, and M3 C_{max} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 2; Cohorts 1-3, Day 14)	IP	
14.4.32	Dose Proportionality Plot for TBAJ-876, M2, and M3 AUC_{tau} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 2; Cohorts 1-3, Day 14)	IP	
14.4.33	Dose Proportionality Plot for TBAJ-876, M2, and M3 AUC_{last} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 2; Cohorts 1-3, Day 14)	IP	
14.4.34	Dose Proportionality Plot for TBAJ-876, M2, and M3 AUC_{inf} Following Single Dose Administrations of TBAJ-876 under Fasted Conditions (Part 2; Cohorts 1-3, Day 14)	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition – All Enrolled Subjects	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Analysis Set	IP	
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Sets	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data – Safety Analysis Set	IP	
16.2.4.2	Prior and Ongoing Medical History – Safety Analysis Set	IP	
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	PK Sampling Data – Safety Analysis Set	IP	
16.2.5.2	Dosing Information – Safety Analysis Set	IP	
16.2.5.3	Prior and Concomitant Medication – Safety Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Plasma TBAJ-876, M2, and M3 Concentration Listing by Subject (Part 1)	IP	
16.2.6.2	Plasma TBAJ-876, M2, and M3 Concentration Listing by Subject (Part 2)	IP	
16.2.6.3	Plasma TBAJ-876, M2, and M3 Concentration Listing by Subject (Part 3)	IP	
16.2.6.4	Terminal Elimination Rate of TBAJ-876, M2, and M3 in Plasma for Individual Subjects after Single Dose Administrations of TBAJ-876 Oral Suspension (Part 1)	IP	
16.2.6.5	Terminal Elimination Rate of TBAJ-876, M2, and M3 in Plasma for Individual Subjects after Multiple, Once-Daily Doses of TBAJ-876 Oral Suspension (Part 2, Day 1)	IP	
16.2.6.6	Terminal Elimination Rate of TBAJ-876, M2, and M3 in Plasma for Individual Subjects after Multiple, Once-Daily Doses of TBAJ-876 Oral Suspension (Part 2, Day 14)	IP	
16.2.6.7	Terminal Elimination Rate of TBAJ-876, M2, and M3 in Plasma for Individual Subjects after Single Dose Administrations of TBAJ-876 Oral Suspension (Part 3)	IP	
16.2.6.8	PK Output Text	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.9	SAS Output Text (Dose-Proportionality Assessment): Part 1	IP	
16.2.6.10	SAS Output Text (Dose-Proportionality Assessment): Part 2, Day 1	IP	
16.2.6.11	SAS Output Text (Dose-Proportionality Assessment): Part 2, Day 14	IP	
16.2.6.12	SAS Output Text (Food Effect Assessment, Cohort 4, Part 1)	IP	
16.2.6.13	SAS Output Text (Steady-State Assessment)	IP	
16.2.6.14	SAS Output Text (Food Effect Assessment, Part 3)	IP	
16.2.6.15	SAS Output Text (Relative Bioavailability Assessment, Part 3)	IP	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Analysis Set	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Data – Safety Analysis Set	IP	
16.2.8.2	Serum Chemistry Data – Safety Analysis Set	IP	
16.2.8.3	Coagulation Data – Safety Analysis Set	IP	
16.2.8.4	Urinalysis Data – Safety Analysis Set	IP	
16.2.8.5	Vital Signs Data – Safety Analysis Set	IP	
16.2.8.6	Physical Examination Data – Safety Analysis Set	IP	
16.2.8.7	Heart Murmur Examination Data – Safety Analysis Set	IP	
16.2.8.8	12-Lead ECG Data – Safety Analysis Set	IP	
16.2.8.9	Cardiac Telemetry (Holter) Collection Data – Safety Analysis Set	IP	
16.2.8.10	Drug, Alcohol and Cotinine Screening Data – Safety Analysis Set	IP	
16.2.8.11	Serology Data – Safety Analysis Set	IP	
16.2.8.12	Pregnancy and FSH Test Data – Safety Analysis Set	IP	
16.2.8.13	Contraception Data – Safety Analysis Set	IP	