CLINICAL STUDY PROTOCOL

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

PROTOCOL NUMBER

TBAJ-876-CL001

VERSION 8.0 DATE

03 Dec 2021

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PROTOCOL APPROVAL PAGE

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

Protocol Number:	TBAJ-876-CL001
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SUMMARY OF CHANGES

The main purpose for this amendment is to add an additional study part (Part 3) to evaluate the relative bioavailability of two strengths of TBAJ-876 tablets. The formulation of the two strengths of tablets is identical and dose proportional.

Part 3: TBAJ-876 Tablets

Part 3 is a single dose, open-label, parallel design study to investigate the safety, tolerability, and relative bioavailability of two strengths of TBAJ-876 tablets: 25 mg and 100 mg. Three groups of ten subjects per group are planned.

- Group 1: Single dose 100 mg TBAJ-876 as 1 x 100 mg Tablet fasting
- Group 2: Single dose 100 mg TBAJ-876 as 1 x 100 mg Tablet fed
- Group 3 Single dose 100 mg TBAJ-876 as 4 x 25 mg Tablets fasting

Subjects will check-in on Day -1 following a 21-day screening period, remain in the clinic for 7 days and be discharged on Day 8. They will then return to the clinic for a follow-up visit on Day 10 and Day 14 for PK and safety. A follow-up phone call will occur on Day 21 to check for AEs.

The amendment also includes the updates from two previous protocol clarification letters:

- The first dated 02 Sep 2021 for the multiple ascending dose (MAD) (Part 2) of the study which added an additional electrocardiogram (ECG) extraction on Day 1 and Day 14 at the 16 hour time point for Cohort 2 and 3, and updated the number of subjects from a total of 36 subjects to 39.
- The second letter dated 06 Oct 2021 added an additional cohort (Cohort 7) to the single ascending dose (SAD) (Part 1) of the study and clarified the ECGs timings and procedures for Cohort 3 in Part 2 of the study.

In addition, based on the review of the Cohort 1 (MAD) PK and safety, the dose for Cohort 2 (MAD) was changed (as allowed by the protocol) to 75 mg versus the original planned dose of 50 mg.

The sections of protocol version 7.0 dated 17 May 2021 affected by these changes are indicated below.

Section Number (s)	Section Title(s)	Description of Change (s)
Title page, protocol approval page,	Study Title	*Update the title of the study, from:* A Phase 1, Partially Blind, Placebo Controlled, Randomized, Combined Single Ascending Dose with a Food Effect Cohort (Part 1), Multiple Ascending Dose Study (Part 2) Study to Evaluate the

Section Number (s)	Section Title(s)	Description of Change (s)
		Safety, Tolerability, Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects *To:* 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, Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects
Synopsis	Title of study	*Update the title of the study, from:* A Phase 1, Partially Blind, Placebo Controlled, Randomized, Combined Single Ascending Dose with a Food Effect Cohort (Part 1), Multiple Ascending Dose Study (Part 2) to Evaluate the Safety, Tolerability, Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects *To:* 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, Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects
Synopsis	Study Period	*Add the following after Part 2:* **Part 3: Single dose, open-label parallel relative bioavailability (BA) design: approximately 45 days, from Screening to study exit.**
Synopsis	Duration of treatment	*Add the following after Part 2:* **Part 3: One single dose of 100 mg TBAJ-876 as 1 x 100 mg tablet (either fasted or fed) or 4 x 25 mg tablets (fasted).**
Synopsis	Number of subjects	*Add the following after Part 1 Paragraph 2:* **<u>Additional cohort, Cohort 7</u>: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. Subjects will receive 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 oral suspension.**

Section Number (s)	Section Title(s)	Description of Change (s)
		Part 2 paragraph 1, from: Planned to enroll 36 subjects in 3 MAD cohorts of 12 subjects each (9 to receive active drug and 3 to receive placebo). All cohorts will receive the assigned dose under fed conditions. *To:* Planned to enroll **39** subjects in 3 MAD cohorts. **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 cohorts will receive the assigned dose under fed conditions. *Add the following after Part 2:* **Part 3:** **Planned to enroll 30 subjects in 3 groups of 10 subjects each. All groups to receive active drug under fasted or fed conditions.** • **Group 1: Single dose 1 x 100 mg tablet fasted** • **Group 2: Single dose 1 x 100 mg tablet fed** • **Group 3: Single dose 4 x 25 mg tablets fasted**
Synopsis	Objectives	*From:* The primary objective of the study is: • To evaluate the safety and tolerability of single and multiple ascending doses of TBAJ-876 oral suspension 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 in healthy adult subjects. • To compare the rate and extent of absorption of a single oral dose of TBAJ-876 when administered after a high-calorie, high fat meal versus when its administered fasting in health adult subjects. *To:*

Section Number (s)	Section Title(s)	Description of Change (s)
		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. • 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.** • **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.**
Synopsis	Study design overview	*Paragraph 1, from:* This study is a two-part, partially blinded, placebo controlled, combined single ascending dose with food-effect and multiple ascending dose study conducted in one study center in the United States. *To:* This study is a **three-part**, partially blinded, placebo controlled, combined single ascending dose with food-effect, a multiple ascending dose study**, and a single dose relative bioavailability study** conducted at one study center in the United States. *Add the following after Part 1 Paragraph 4:*

Section Number (s)	Section Title(s)	Description of Change (s)
		<u>Additional cohort, Cohort 7</u>: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. **Dose = 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 Oral Suspension** **Subjects will follow the procedures in Table 15, Schedule of Assessments and Procedures, Part 1 SAD with the following clarifications:** **Subjects will check-in to the clinic on Day -1 and be confined through Day 8. Subjects will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21. Subjects will complete the procedures specified for those study days only. All ECGs performed in Cohort 7 will be triplicate ECGs at each time point.** **In addition, subjects will have triplicate ECGs at 16 hours postdose.** *Part 2 Paragraph 1, from:* Three cohorts of 12 subjects per cohort are planned to receive TBAJ-876 or matching placebo for 14 days, under fed conditions. *To:* Three cohorts are 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)** to receive TBAJ-876 or matching placebo for 14 days, **all** under fed conditions. **For Cohorts 2 and 3, an additional ECG extraction will occur at 16 hours postdose on Day 1 and Day 14. For Cohort 3, all ECGs performed will be triplicate ECGs at each time point listed in the Schedule of Assessments.** *Add the following after Part 2:* **Part 3:** **Three groups each consisting of 10 subjects are planned.**

<table>
<tr><th>Section Number (s)</th><th>Section Title(s)</th><th>Description of Change (s)</th></tr>
<tr><td>Synopsis</td><td>Test product, dosage, and mode of administration</td><td>Add the following dose level for Part 1:
Dose Level 7: 800 mg TBAJ-876
Update Dose levels 2 and 3 for Part 2, from:
Dose Level 2: 50 mg TBAJ-876
Dose Level 3: 100 mg TBAJ-876
To:
Dose Level 2: 75 mg TBAJ-876
Dose Level 3: TBD mg TBAJ-876
Add the following after Part 2:
Part 3:
TBAJ-876 Tablets, orally administered
Group 1: 100 mg TBAJ-876 (1 x 100 mg tablet) under fasted conditions
Group 2: 100 mg TBAJ-876 (1 x 100 mg tablet) under fed conditions
Group 3: 100 mg TBAJ-876 (4 x 25 mg tablets) under fasted conditions</td></tr>
<tr><td>Synopsis</td><td>Criteria for evaluation</td><td>Pharmacokinetics, add the following Part clarifications to the PK parameters table:
<table>
<tr><td>AUC_{Extrap} (%)</td><td>The percentage of extrapolated AUC (area under the [plasma concentration vs. time] curve) to AUC_{inf} based on extrapolation (Parts 1 and 3)</td></tr>
<tr><td>AUC_{inf}</td><td>Area under the concentration-time curve from time-zero extrapolated to infinity; calculated for Parts 1 and 3 as:
$AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$</td></tr>
<tr><td>AUC_{last}</td><td>Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule (Parts 1 and 3)</td></tr>
</table></td></tr>
</table>

		AUC_{tau} — Area under the concentration-time curve during the dosing interval; calculated using the linear trapezoidal rule **(Part 2)**
		C_{avg} — Average concentration during the dosing interval **(Part 2)**
		C_{last} — The last quantifiable concentration determined directly from individual concentration-time data **(Parts 1, 2, and 3)**
		CL/F — Apparent total clearance after single administration **(Parts 1 and 3)**
		CLss/F — Apparent total clearance after multiple administration **(Part 2)**
		C_{max} — Maximum concentration, determined directly from individual concentration-time data **(Parts 1, 2, and 3)**
		R_{AUC} — Accumulation factor during multiple dosing, based on AUC_{tau} **(Part 2)**
		R_{Cmax} — Accumulation factor during multiple dosing, based on C_{max} **(Part 2)**
		T_{last} — Time of the last quantifiable concentration **(Parts 1, 2, and 3)**
		T_{max} — Time of the maximum concentration **(Parts 1, 2, and 3)**
		$T_{1/2}$ — The observed terminal half-life, calculated for **Parts 1 and 3** as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
		Vz/F — Apparent volume of distribution in the terminal phase **(Parts 1, 2, and 3)**
		λ_z — The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile **(Parts 1, 2, and 3)**
		Update Day 1 and Day 14 parameters for Part 2, from: • Day 1: AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{max}, and C_{avg}. • Day 14: AUC_{tau}, C_{max}, C_{min}, T_{max}, C_{trough}, C_{avg}, R_{AUC}, and R_{Cmax}. Parameters such as λz, and $t_{1/2}$ may be calculated as reasonable.

Section Number (s)	Section Title(s)	Description of Change (s)
		To: • Day 1: AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{max}, and C_{avg} **(λz, $t_{1/2}$, CLss/F, and Vz/F may be calculated as reasonable).** • Day 14: AUC_{tau}, C_{max}, C_{min}, T_{max}, C_{trough}, C_{avg}, **CLss/F, Vz,/F,** R_{AUC}, and R_{Cmax}. Parameters such as λz, and $t_{1/2}$ may be calculated as reasonable. *Add the following at the end of section:* **For Part 3, the following PK parameters will be calculated for Group 1 (1 x 100 mg tablet, fasted), Group 2 (1 x 100 mg tablet, fed), and Group 3 (4 x 25 mg tablets, fasted):** **C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{Extrap}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, and Vz/F.** **PK parameters will be summarized by group using descriptive statistics. Food effect (Group 2, fed, 1 x 100 mg tablet vs. Group 1, fasted, 1 x 100 mg tablet) and relative bioavailability of the two fasted groups (Group 3, 4 x 25 mg tablets vs. Group 1, 1 x 100 mg tablet) will be assessed using an analysis of variance (ANOVA) approach.**
1.2	Tuberculosis and Rationale for New Medications	*Add the following at end of section:* **In addition, a Part 3 will be included that is an open-label study to determine the relative bioavailability (BA) of two strengths of TBAJ-876 tablets.**
1.6	Potential Adverse Effects in Human Subjects	*Paragraph 9, Number 4, from:* 4) Treatment with TBAJ-876 at single doses between 10 mg and 400 mg was not associated with evidence of QT prolongation or myocardial damage. One subject in the 400 mg had an episode of non-sustained ventricular tachycardia observed in the Holter extraction on Study Day 1, approximately 5 hours after dosing. Upon questioning, the subject reported a few seconds of "more prominent heartbeat" at the same time. There were no symptoms of chest pain, syncope, or palpitations, and her physical examination and vital signs were normal. No QT prolongation was observed on the Holter or in subsequent ECGs. This event was reported as "possibly related". One subject in Cohort 6 had a mildly elevated troponin I on Day 21, with a value of 0.038 ng/mL, confirmed at 0.034 ng/mL (ULN 0.028 ng/mL). The subject was completely asymptomatic, and her physical examination, vital signs, and ECG were normal. On the same day of the troponin I elevation, her CPK

Section Number (s)	Section Title(s)	Description of Change (s)
		and CPK-Mb were also normal. The subject returned to the clinic on Study Day 23, and her troponin I levels were within the normal range. The finding of elevated troponin I on Study Day 21 was deemed to be "spurious". *To:* 4) Treatment with TBAJ-876 at single doses between 10 mg and 400 mg was not associated with evidence of QT prolongation or myocardial damage. One subject in **Cohort 6 (400 mg)** had an episode of non-sustained ventricular tachycardia observed in the Holter extraction on Study Day 1, approximately 5 hours after dosing. Upon questioning, the subject reported a few seconds of "more prominent heartbeat" at the same time. There were no symptoms of chest pain, syncope, or palpitations, and her physical examination and vital signs were normal. No QT prolongation was observed on the Holter or in subsequent ECGs. This event was reported as "possibly related". **Another** subject in Cohort 6 had a mildly elevated troponin I on Day 21, with a value of 0.038 ng/mL, confirmed at 0.034 ng/mL (ULN 0.028 ng/mL). The subject was completely asymptomatic, and her physical examination, vital signs, and ECG were normal. On the same day of the troponin I elevation, her CPK and CPK-Mb were also normal. The subject returned to the clinic on Study Day 23, and her troponin I levels were within the normal range. The finding of elevated troponin I on Study Day 21 was deemed **by the primary investigator** to be "spurious".
1.7	Rationale for Dose selection (MAD)	*Delete the last sentence from the paragraph:* The choice of the doses for subsequent cohorts will be reconsidered after observing the exposures and safety in the first cohort. *Add the following paragraph to end of section:* **Upon review of the MAD Cohort 1 (25 mg) PK and safety, the 50 mg dose planned for Cohort 2 was changed to 75 mg. This decision was made based on the safety of the 25 mg dose which was shown to be safe and well tolerated without evidence of cardiac, muscle skeletal, gastrointestinal, hepatic, or hematological toxicity, and because the total exposure of TBAJ-876 plus M3 at the dose of 75 mg was predicted to still remain below thresholds determined by the corresponding sum in the three-month toxicity study in dogs.**

Section Number (s)	Section Title(s)	Description of Change (s)
2	Objective	*From:* The primary objective of the study is: • To evaluate the safety and tolerability of single and multiple ascending doses of TBAJ-876 oral suspension 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 in healthy adult subjects. • To compare the rate and extent of absorption of a single oral dose of TBAJ-876 when administered after a high-calorie, high fat meal versus when its administered fasting in health adult subjects. *To:* 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. • 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.** • **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.**

Section Number (s)	Section Title(s)	Description of Change (s)
3	Study design summary	*Paragraph 1, from:* This study is a two-part, partially blinded, placebo controlled, combined single ascending dose (SAD) with food-effect and multiple ascending dose (MAD) study conducted in one study center in the United States. *To:* This study is a **three-part**, partially blinded, placebo controlled, combined single ascending dose with food-effect, a multiple ascending dose study**, and a single dose relative bioavailability study** conducted in one study center in the United States. *Add the following after Part 1 Paragraph 9:* **Additional cohort, Cohort 7: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. Subjects will receive 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 Oral Suspension.** **Subjects will follow the procedures in the Schedule of Assessments (Table 15) with the following clarifications:** **Subjects will check-in to the clinic on Day -1 and be confined through Day 8. Subjects will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21. Subjects will complete the procedures specified for those study days only. All ECGs performed in Cohort 7 will be triplicate ECGs at each time point.** **In addition, subjects will have triplicate ECGs at 16 hours postdose.** *Update sentence before Table 6, from:* Table 6 presents the planned dose cohorts for Part 1 of the study. *To:* Table 6 presents the planned **6** dose cohorts **and the additional Cohort 7** for Part 1 of the study. *Add the following to Table 6, Single Ascending Dose Cohorts, Part 1:*

7	Single dose of 800 mg TBAJ-876 (n=6)	Placebo (n=2)

Update Part 2, Paragraph 2 and 3, from:

For Part 2, MAD design, dose level will be determined based on model predictions of multiple-dose PK behavior, and safety from Part 1.

In this multiple ascending dose part, each subject is expected to receive TBAJ-876 or matching placebo for 14 days with corresponding PK and safety measurements.

To:

For Part 2, MAD design, **the** dose level **of the first cohorts** 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 (see Section 1.7). At the time of this writing, it is expected that the dose of the third cohort will be informed by the results from the first two.**

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.

Add the following after Part 2 Paragraph 7:

For Cohorts 2 and 3, an additional ECG extraction will occur at 16 hours postdose on Day 1 and Day 14. For Cohort 3, all ECGs performed will be triplicate ECGs at each time point listed in Table 16, including the additional 16 hour postdose time point.

Add the following after Part 2:

Part 3:

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.**

<table>
<tr><th>Section Number (s)</th><th>Section Title(s)</th><th>Description of Change (s)</th></tr>
<tr><td></td><td></td><td>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. Refer to the schedule of assessments in Table 17.

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.</td></tr>
<tr><td>4</td><td>Identity of Investigational Product</td><td>Update, from:

The Investigational Medicinal Product (IMP) will be supplied as TBAJ-876 Oral Suspension, 5 mg/mL formulation or matching placebo.
Refer to Appendix 2 for details regarding the description and composition of TBAJ 876 oral suspension.
To:

The Investigational Medicinal Product (IMP) will be supplied as TBAJ-876 Oral Suspension, 5 mg/mL formulation or matching placebo, TBAJ-876 tablets 25 mg, and TBAJ-876 tablets 100 mg.

Refer to Appendix 2 for details regarding the description and composition of TBAJ 876 oral suspension, TBAJ-876 tablets 25 mg, and TBAJ-876 tablets 100 mg.

Update Table 7, Identity of Investigational Products, from:

<table><tr><td>Test Product:</td><td>TBAJ-876 Oral Suspension 5 mg/mL
Manufactured for Global Alliance for TB Drug Development</td></tr></table>To:
<table><tr><td>Test Products:</td><td>TBAJ-876 Oral Suspension 5 mg/mL</td></tr></table></td></tr>
</table>

Section Number (s)	Section Title(s)	Description of Change (s)
		Manufactured for Global Alliance for TB Drug Development **TBAJ-876 Tablets 25 mg** **Manufactured by Piramal Pharma Limited for Global Alliance for TB Drug Development** **TBAJ-876 Tablets 100 mg** **Manufactured by Piramal Pharma Limited for Global Alliance for TB Drug Development**
5.2	Exclusion Criteria	*Update exclusion # 25, from:* 25. If assigned to the fasted/fed cohort, is lactose intolerant. *To:* 25. Is lactose intolerant.
6.1	Subject assignment	*Add the following after Paragraph 4:* **<u>Additional cohort, Cohort 7</u>: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. Subjects will receive 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 Oral Suspension.** *Update Paragraph 6, from:* For Part 2, 36 subjects are planned to be enrolled. There are 3 cohorts planned with 12 subjects per cohort (9 to receive active drug and 3 to receive placebo). All doses in Part 2 will be under fed conditions. To: 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. *Add the following to end of section:*

Section Number (s)	Section Title(s)	Description of Change (s)
		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.
6.2	Blinding	*Update the section title, from:* Blinding *To:* Blinding **(Parts 1 and 2)** *Add the following to end of section:* **Part 3 is open-label.**
6.4	Confinement	*Add the following after Paragraph 1:* **<u>Additional cohort, Cohort 7</u>: Subjects will check-in to the clinic on Day -1 and be confined through Day 8. Subjects will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21.** *Add the following to end of section:* **For Part 3, subjects will be admitted to the research center on the evening of Day -1 and remain in the research center until completion of the procedures on Day 8. Subjects will return for subsequent follow-up visits on Days 10 and 14 and will receive a follow-up phone call on Day 21.**
6.5.1	Fasting/Meals	*Add the following after Part 2:* **Part 3, BA** **An optional meal or snack will be served the evening of check-in.** **Subjects in Group 1 and Group 3 will be required to fast for at least 10 hours before dosing. The subjects will fast for 4 hours after dosing.** **Subjects in Group 2 will fast for at least 10 hours before consuming the required FDA standard high-fat, high calorie breakfast as described above in the food effect cohort in Part 1.**

Section Number (s)	Section Title(s)	Description of Change (s)
		Standard meals will be provided at appropriate times after dosing for all groups.
6.5.2	Beverages	*Add the following at end of section:* **Part 3, BA** **Each dose of TBAJ-876 Tablet(s) will be administered orally with approximately 240 mL of room temperature water.** **Except for the room temperature water provided with the study treatment, no water may be consumed for 1 hour prior to each dose through 1 hour after each dose.** **At other times, subjects will be encouraged to drink water ad libitum.**
6.6	Drug Administration	*Update the section title of 6.6.1, from:* Administration of Oral Care Strips *To:* Administration of Oral Care Strips **(Parts 1 and 2)** *Add the following section:* **6.6.3 Administration of TBAJ-876 Tablet** **Each dose of TBAJ-876 Tablet will be administered orally with approximately 240 mL of room temperature water. A mouth check will be performed immediately after dose to ensure that the medication has been appropriately swallowed.** **Subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after dosing, subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary. Subjects will not be allowed to lie down, except as directed by clinical staff secondary to AEs, for the first 4 hours after dosing.**
6.7.1	Part 1	*Paragraph 1, Sentence 1 from:* A total of 140 mL (35 x 4 mL samples) will be collected from each subject for PK analysis.

<table>
<tr><th>Section Number (s)</th><th>Section Title(s)</th><th>Description of Change (s)</th></tr>
<tr><td></td><td></td><td>To:

For Cohorts 1-6, a total of 140 mL (35 x 4 mL samples) will be collected from each subject for PK analysis.

Add the following footnote to Table 8, Total Volume of Blood to be Collected for Testing: Part 1:

a. Subjects in Cohort 7 will not have collections after Day 14.

Update Paragraph 2, Last sentence from:

The total volume of blood collected from each subject in Part 1 will not exceed approximately 320.5 mL.

To:

The total volume of blood collected from each subject in Part 1 Cohorts 1-6 will not exceed approximately 320.5 mL.

Add the following after Paragraph 2:

For Cohort 7, a total of 124 mL (31 x 4 mL samples) will be collected from each subject for PK analysis. Approximately 78.5 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing. The total volume of blood collected from each subject in Part 1 Cohort 7 will not exceed approximately 203 mL.</td></tr>
<tr><td>6.7</td><td>Blood sampling, Processing and Shipment</td><td>Add the following section and table:

6.7.3 Part 3

A total of 128 mL (32 x 4ml samples) will be collected for PK Analysis. Approximately 91 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing.
Table 10 Total Volume of Blood to be Collected for Testing: Part 3
<table>
<tr><th>Reason for Collection</th><th>Number of Samples</th><th>Volume per Sample (mL)</th><th>Total Volume (mL)</th></tr>
<tr><td>Clinical labs at screening</td><td>1</td><td>12.5</td><td>12.5</td></tr>
<tr><td>Clinical labs during study (check-in, 6 and 48 hours and Days 5, 7, 10, and 14 (end-of-study).</td><td>7</td><td>8.5</td><td>59.5</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Section Number (s)</th><th>Section Title(s)</th><th>Description of Change (s)</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Coagulation</td><td>7</td><td>2.7</td><td>18.9</td></tr>
<tr><td>Pharmacokinetic analysis</td><td>32</td><td>4.0</td><td>128.0</td></tr>
<tr><td colspan="3">Total</td><td>218.9</td></tr>
</table>
The Principal Investigator, in conjunction with the Sponsor, may collect additional blood if necessary, for repeat laboratory or safety evaluations including AE follow-up.
</td></tr>
<tr><td>6.7.3</td><td>Pharmacokinetic Sampling Time Windows</td><td>Change section numbering, from,
6.7.3
To:
6.7.4
Update Table 10, from:
Table 10 Acceptable Pharmacokinetic Sampling Time Windows, Part 1
To:
Table 11 Acceptable Pharmacokinetic Sampling Time Windows, Part 1, and Part 3</td></tr>
<tr><td>6.8</td><td>End of Study Procedures</td><td>Update ECG bullet, from:
ECG
To:
Triplicate ECG</td></tr>
<tr><td>6.9.4</td><td>Vital Signs</td><td>Add the following:
For Part 3, vital signs (blood pressure, pulse rate, temperature, respiration rate, and pulse oximetry) will be measured at the times noted on the appropriate events schedule (Table 17).</td></tr>
<tr><td>6.9.5</td><td>Electrocardiograms</td><td>Add the following after Paragraph 2:
For Cohort 7, all ECGs will be triplicate at each time point. In addition, subjects in will have triplicate ECGs at 16 hours postdose.
Add the following after Paragraph 4:
For Cohorts 2 and 3, an additional ECG extraction will occur at 16 hours postdose on Day 1 and Day 14. For Cohort 3, all</td></tr>
</table>

<table>
<tr><th>Section Number (s)</th><th>Section Title(s)</th><th>Description of Change (s)</th></tr>
<tr><td></td><td></td><td>ECGs performed will be triplicate ECGs at each time point listed in Table 16.
Add the following:
For Part 3, triplicate ECGs will be completed with 15 minutes at all timepoints on Table 17.</td></tr>
<tr><td>6.9.6</td><td>Cardiac Holter Monitoring and Cardiodynamic Assessment</td><td>Add the following:
For Part 3, continuous 12-lead ECGs (Holter) will be recorded for 1 hour prior to dose and continue for at least 24 hours post dose.</td></tr>
<tr><td>7.2</td><td>Attribution/Causality</td><td>Bullet point 6, Sentence 2, from:
However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
To:
However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor/designee.</td></tr>
<tr><td>7.7</td><td>Clinical Laboratory Adverse Events</td><td>Update the last sentence, from:
If this laboratory value is determined by the Investigator to be a clinically significant change from baseline for that participant, it is considered to be an AE.
To:
All laboratory changes greater than or equal to Grade 2 must be reported as an AE regardless of clinical significance.</td></tr>
<tr><td>9.2</td><td>Pharmacokinetic Analysis</td><td>Pharmacokinetics, add the following Part clarifications to the PK parameters table:
<table>
<tr><td>AUC_{Extrap} (%)</td><td>The percentage of extrapolated AUC (area under the [plasma concentration vs. time] curve) to AUC_{inf} based on extrapolation (Parts 1 and 3)</td></tr>
<tr><td>AUC_{inf}</td><td>Area under the concentration-time curve from time-zero extrapolated to infinity; calculated for Parts 1 and 3 as:
$AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$</td></tr>
</table></td></tr>
</table>

		AUC_{last} — Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule **(Parts 1 and 3)**
		AUC_{tau} — Area under the concentration-time curve during the dosing interval; calculated using the linear trapezoidal rule **(Part 2)**
		C_{avg} — Average concentration during the dosing interval **(Part 2)**
		C_{last} — The last quantifiable concentration determined directly from individual concentration-time data **(Parts 1, 2, and 3)**
		CL/F — Apparent total clearance after single administration **(Parts 1 and 3)**
		CLss/F — Apparent total clearance after multiple administration **(Part 2)**
		C_{max} — Maximum concentration, determined directly from individual concentration-time data **(Parts 1, 2, and 3)**
		R_{AUC} — Accumulation factor during multiple dosing, based on AUC_{tau} **(Part 2)**
		R_{Cmax} — Accumulation factor during multiple dosing, based on C_{max} **(Part 2)**
		T_{last} — Time of the last quantifiable concentration **(Parts 1, 2, and 3)**
		T_{max} — Time of the maximum concentration **(Parts 1, 2, and 3)**
		$T_{1/2}$ — The observed terminal half-life, calculated for **Parts 1 and 3** as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
		Vz/F — Apparent volume of distribution in the terminal phase **(Parts 1, 2, and 3)**
		λ_z — The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile **(Parts 1, 2, and 3)**
		Update Day 1 and Day 14 parameters for Part 2, from:

Section Number (s)	Section Title(s)	Description of Change (s)
		• Day 1: AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{max}, and C_{avg}. • Day 14: AUC_{tau}, C_{max}, C_{min}, T_{max}, C_{trough}, C_{avg}, R_{AUC}, and R_{Cmax}. Parameters such as λz, and $t_{1/2}$ may be calculated as reasonable. *To:* • Day 1: AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{max}, and C_{avg} **(λz, $t_{1/2}$, CLss/F, and Vz/F may be calculated as reasonable).** • Day 14: AUC_{tau}, C_{max}, C_{min}, T_{max}, C_{trough}, C_{avg}, **CLss/F, Vz,/F,** R_{AUC}, and R_{Cmax}. Parameters such as λz, and $t_{1/2}$ may be calculated as reasonable. *Add the following at the end of section:* **For Part 3, the following PK parameters will be calculated for Group 1 (1 x 100 mg tablet, fasted), Group 2 (1 x 100 mg tablet, fed), and Group 3 (4 x 25 mg tablets, fasted): C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{Extrap}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, and Vz/F.** **PK parameters will be summarized by group using descriptive statistics. Food effect (Group 2, fed, 1 x 100 mg tablet vs. Group 1, fasted, 1 x 100 mg tablet) and relative bioavailability of the two fasted groups (Group 3, 4 x 25 mg tablets vs. Group 1, 1 x 100 mg tablet) will be assessed using an analysis of variance (ANOVA) approach.**
9.3	Statistical Analysis	*Update the section, from:* Final statistical analyses will be performed using appropriate software, e.g. 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 or higher, Certara, L.P.]) and SAS® (Version 9.4 or higher, SAS Institute Inc.). PK parameters will be summarized by cohort using descriptive statistics. Summary statistics will also be presented by gender within each cohort. Dose proportionality for exposure parameters (C_{max}, AUCs) will be assessed using a power model approach. Food effect: The effect of food will be assessed comparing PK parameters (C_{max}, AUCs) under fed versus fasting conditions using an analysis of variance (ANOVA) approach.[5] *To:*

Section Number (s)	Section Title(s)	Description of Change (s)
		Final statistical analyses will be performed using appropriate software, e.g. 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 or higher, Certara, L.P.]) and SAS® (Version 9.4 or higher, SAS Institute Inc.). **For Parts 1, 2, and 3, PK parameters will be summarized by cohort using descriptive statistics. Summary statistics will also be presented by gender within each cohort.** **For Part 1, dose proportionality for exposure parameters (C_{max}, AUCs) will be assessed using a power model approach. Food effect will be assessed using an analysis of variance (ANOVA) with food condition as the fixed effect.** **For Part 2, dose proportionality for exposure parameters (C_{max}, AUCs) will be assessed using a power model approach. Steady state for each dose level will be assessed using an appropriate statistical methodology.** **For Part 3, Food effect will be assessed using an 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 details will be provided in the SAP.**
10	Facilities	*Update the email for analytical lab, from:* nauman@alliancepharmaco.com *To:* **rguan@alliancepharmaco.com**
11	Drug Supplies	*Update Paragraph 1, from:* Global Alliance for TB Drug Development will supply sufficient a quantity of the study drug, TBAJ-876 for preparation of TBAJ-876 Oral Suspension. Study drug will be shipped to Worldwide Clinical Trials Early Phase Services, LLC pursuant to site SOPs. Upon receipt of the study drug, the study drug will be inventoried and stored in an environmentally controlled and secure, limited access area. The suspending vehicle (also used as Placebo) and other

Section Number (s)	Section Title(s)	Description of Change (s)
		supplies will be procured, inventoried, and stored appropriately by Worldwide Clinical Trials Early Phase Services, LLC pursuant to site SOPs. *To:* Global Alliance for TB Drug Development will supply sufficient a quantity of the study drug, TBAJ-876 for preparation of TBAJ-876 Oral Suspension, **TBAJ-876 tablets 25 mg, and TBAJ-876 tablets 100 mg**. Study drug will be shipped to Worldwide Clinical Trials Early Phase Services, LLC pursuant to site SOPs. Upon receipt of the study drug, the study drug will be inventoried and stored in an environmentally controlled and secure, limited access area. **For oral suspension, the** suspending vehicle (also used as Placebo) and other supplies will be procured, inventoried, and stored appropriately by Worldwide Clinical Trials Early Phase Services, LLC pursuant to site SOPs.
13	Events schedule	*Update numbering for Table 14 Schedule of Assessments and Procedures, Part 1 SAD to* **Table 15** Table 15 Schedule of Assessments and Procedures, Part 1 SAD: *Add "**" to "Study Day" and "Event" rows.* *Add "**X**[d]" to "12-lead safety ECG" row on "16[a]" column.* *Add the following footnote:* **** Subjects in Cohort 7 will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21. Subjects will complete the procedures specified for those study days only.** *Add the following to the end of footnote d:* **All ECGs in Cohort 7 will be triplicate at each time point. In addition, subjects in Cohort 7 will have triplicate ECGs at 16 hours postdose.** *Update numbering for Table 15 Schedule of Assessments and Procedures, Part 2 MAD to* **Table 16** Table 16 Schedule of Assessments and Procedures, Part 2 MAD: *Add the following to the end of footnote j:*

Section Number (s)	Section Title(s)	Description of Change (s)
		All ECGs in Cohort 3 will be triplicate at each time point. In addition, subjects in Cohort 3 will have triplicate ECGs at 16 hours postdose on Day 1 and Day 14. *Add the following to the end of footnote n:* **For Cohorts 2 and 3, an additional extraction will be done at the 16 hour time point on Days 1 and 14.** *Add the following Table:* **Table 17 Schedule of Assessments and Procedures, Part 3 BA**
Appendix 1	Shipment	*Update the contact Email, from:* Contact e-mail: samples@alliancepharmaco.com *To:* Contact E-mail: **rguan@alliancepharmaco.com** samples@alliancepharmaco.com
Appendix 2	Description and composition of test product	*Update and add the following to the description of the dosage form, last paragraph, from:* The required doses of the drug product are dispensed using commercially available oral syringes of suitable capacity. *To:* The required doses of the **suspension** drug product are dispensed using commercially available oral syringes of suitable capacity. **TBAJ-876 Tablets 25 mg are white to off white, round uncoated tablets, plain on both sides.** **TBAJ-876 Tablets 100 mg are white to off white, capsule-shaped uncoated tablets, plain on both sides.** *Add the following to beginning of Composition of the Drug Product:* **TBAJ-876 Oral Suspension** *Add the following to the end of Composition of the Drug Product:* **TBAJ-876 Tablets** **Each 25 mg tablet contains 25 mg of TBAJ-876 equivalent to 30.7 mg of TBAJ-876 tartrate. Each 100 mg tablet contains 100 mg of TBAJ-876 equivalent to 122.8 mg of TBAJ-876**

Section Number (s)	Section Title(s)	Description of Change (s)
		tartrate. The composition of the tablets is as follows: lactose monohydrate, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. The formulation of the two strengths of tablets is identical and dose proportional. *Add the following to the end of Container and Closure System:* **TBAJ-876 Tablets 25 mg are packaged as 30-count in 30 cc round high-density polyethylene (HDPE) bottles induction sealed and with 28 mm polypropylene (PP) child resistant closures (CRC). TBAJ-876 Tablets 100 mg are packaged as 30-count in 40 cc round HDPE bottles induction sealed and with 33 mm PP CRC. The tables are stored at 15-30 °C (59-86 °F).**

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Global Alliance for TB Drug Development</td></tr>
<tr><td colspan="2">Name of test product: TBAJ-876</td></tr>
<tr><td colspan="2">Name of active ingredient: TBAJ-876 Tartrate</td></tr>
<tr><td colspan="2">Title of study: 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, Pharmacokinetics of TBAJ-876 in Healthy Adult Subjects</td></tr>
<tr><td colspan="2">Principal Investigator: Ingela Danielsson, MD</td></tr>
<tr><td colspan="2">Study Center
Worldwide Clinical Trials Early Phase Services, LLC
2455 NE Loop 410, Suite 150
San Antonio, Texas 78217</td></tr>
<tr><td>Study period:

Part 1: Single ascending dose (SAD) cohorts which includes a Food-effect Cohort: approximately 56 days, from Day -1 to study exit.

Part 2: Multiple ascending dose (MAD) cohorts: approximately 133 days, from Day -1 through completion of clinical procedures on Day 126 followed by a phone call on Day 133.

Part 3: Single dose, open-label parallel relative bioavailability (BA) design: approximately 45 days, from Screening to study exit.

The maximum duration of the study will depend upon the final number and timing of each cohort and the observed terminal half-life ($T_{1/2}$).</td><td>Phase of development: 1</td></tr>
<tr><td>Duration of treatment:

Part 1: One single dose of TBAJ-876 Oral Suspension or placebo for TBAJ-876 Oral Suspension

Food-effect Cohort: One single dose of TBAJ-876 Oral Suspension. Subjects will receive TBAJ-876 Oral Suspension in fasted or fed conditions.

Part 2: Multiple doses (14 doses per cohort) of TBAJ-876 Oral Suspension or placebo for TBAJ-876 Oral Suspension</td><td>Number of sites enrolling subjects: 1</td></tr>
</table>

Part 3: One single dose of 100 mg TBAJ-876 as 1 x 100 mg tablet (either fasted or fed) or 4 x 25 mg tablets (fasted).	

Number of subjects (planned)**:**

Part 1:

Plan to enroll 50 to 60 subjects in 6 SAD cohorts. Each cohort will consist of 8 subjects, 6 to receive active drug and 2 to receive placebo, all under fasting conditions.

In addition, 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. Six subjects previously administered 100 mg TBAJ-876 in Cohort 4 (who have already completed the cohort) will be considered part of the fasted group. At least three additional subjects will be enrolled to be dosed in the fasted group. This will yield a complete data set for at least 8 subjects if 1 fails to complete. Based on exposure levels from the first 4 completed cohorts, the 100 mg dose was chosen for the food-effect cohort. Therefore, all subjects in the food-effect cohort will receive active drug of TBAJ-876, 100 mg.

Additional cohort, Cohort 7: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. Subjects will receive 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 oral suspension.

Part 2:

Planned to enroll 39 subjects in 3 MAD cohorts. 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 cohorts will receive the assigned dose under fed conditions.

Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level or to increase number of subjects based on PK and safety information learned from initial cohorts. These decisions on additional cohorts will not take place until the Sponsor, in conjunction with the Principal Investigator, has determined that adequate safety, tolerability, and pharmacokinetics from the previous cohorts have been demonstrated. The Institutional Review Board (IRB) should be immediately notified of this revised approach.

Part 3:

Planned to enroll 30 subjects in 3 groups of 10 subjects each. All groups to receive active drug under fasted or fed conditions.

- Group 1: Single dose 1 x 100 mg tablet - fasted
- Group 2: Single dose 1 x 100 mg tablet - fed
- Group 3: Single dose 4 x 25 mg tablets - fasted

Diagnosis and main criteria for inclusion:

Volunteers will be healthy adults, male or female, ages 19 to 50 years (inclusive) at screening, with a body mass index (BMI) ≥18.5 and ≤32.0 kg/m^2 and body weight of no less than 50.0 kg, who do not use tobacco or nicotine-containing products. Females must be of non-childbearing potential or must use an allowable method of birth control.

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.
- 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.
- 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.

Study design overview:

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

Safety will be assessed throughout the study for all subjects.

Blood will be collected for PK analysis. Plasma samples will be analyzed for TBAJ-876 and its metabolites (M2 and M3).

Part 1:

Six dose levels are planned. Based on interim PK data obtained during the dose escalation, a dose level will be selected at which to study the effect on PK of a high-calorie, high-fat meal.

The first cohort will be separated into 2 groups. A sentinel group of 3 subjects (2 active and 1 placebo) will be dosed at least 24 hours before the remaining 5 subjects (4 active and 1 placebo). The remaining cohorts will not be so separated.

Food-effect: 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 new subjects and the fasted group will include 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.

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

Additional cohort, Cohort 7: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions.

Dose = 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 Oral Suspension

Subjects will follow the procedures in Table 15, Schedule of Assessments and Procedures, Part 1 SAD with the following clarifications:

> Subjects will check-in to the clinic on Day -1 and be confined through Day 8. Subjects will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21. Subjects will complete the procedures specified for those study days only. All ECGs performed in Cohort 7 will be triplicate ECGs at each time point.
>
> In addition, subjects will have triplicate ECGs at 16 hours postdose.

Dose escalation to the next cohort (i.e., dose level) or any changes of PK sampling and safety assessment timepoints will not take place until the Sponsor, in conjunction with the Principal Investigator and Dose Escalation Committee, has determined that adequate safety, tolerability and PK from the previous cohort have been demonstrated to permit proceeding to the next cohort.

The decision for the study to progress to the planned MAD cohorts (Part 2) will not take place until the Sponsor, in conjunction with the Principal Investigator and the Dose Escalation Committee, has determined that adequate safety, tolerability, and PKs from the previous cohorts (Part 1) have been demonstrated to permit proceeding.

Part 2:

Three cohorts are 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) to receive TBAJ-876 or matching placebo for 14 days, all under fed conditions.

For Cohorts 2 and 3, an additional ECG extraction will occur at 16 hours postdose on Day 1 and Day 14. For Cohort 3, all ECGs performed will be triplicate ECGs at each time point listed in the Schedule of Assessments.

Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level.

Part 3:

Three groups each consisting of 10 subjects are planned.

Test product, dosage, and mode of administration: **Part 1:** TBAJ-876 Oral Suspension, orally administered Dose Level 1: 10 mg TBAJ-876 Dose Level 2: 25 mg TBAJ-876 Dose Level 3: 50 mg TBAJ-876 Dose Level 4 and food-effect cohort: 100 mg TBAJ-876 Dose Level 5: 200 mg TBAJ-876 Dose Level 6: 400 mg TBAJ-876 Dose Level 7: 800 mg TBAJ-876 Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level. **Part 2:** TBAJ-876 Oral Suspension, orally administered Dose Level 1: 25 mg TBAJ-876 Dose Level 2: 75 mg TBAJ-876 Dose Level 3: TBD mg TBAJ-876 Doses may change based on what is learned from previous cohorts. Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level. **Part 3:** TBAJ-876 Tablets, orally administered Group 1: 100 mg TBAJ-876 (1 x 100 mg tablet) under fasted conditions Group 2: 100 mg TBAJ-876 (1 x 100 mg tablet) under fed conditions Group 3: 100 mg TBAJ-876 (4 x 25 mg tablets) under fasted conditions
Control product, dosage, and mode of administration: Placebo for TBAJ-876 Oral Suspension; orally administered All levels (except Part 1 food-effect cohort and Part 3) = Matching dose of placebo for TBAJ-876 Oral Suspension
Criteria for evaluation: *Safety*: 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.

Pharmacokinetics:

Final PK calculations will be performed using appropriate software, e.g. 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 or higher, or comparable product, Certara, L.P.]) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.). PK parameters will be calculated using non-compartmental analysis. The following PK parameters will be determined as appropriate for each study part and analyte.

AUC_{Extrap} (%)	The percentage of extrapolated AUC (area under the [plasma concentration vs. time] curve) to AUC_{inf} based on extrapolation (Parts 1 and 3)
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated for Parts 1 and 3 as: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule (Parts 1 and 3)
AUC_{tau}	Area under the concentration-time curve during the dosing interval; calculated using the linear trapezoidal rule (Part 2)
C_{avg}	Average concentration during the dosing interval (Part 2)
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data (Parts 1, 2, and 3)
CL/F	Apparent total clearance after single administration (Parts 1 and 3)
CLss/F	Apparent total clearance after multiple administration (Part 2)
C_{max}	Maximum concentration, determined directly from individual concentration-time data (Parts 1, 2, and 3)
R_{AUC}	Accumulation factor during multiple dosing, based on AUC_{tau} (Part 2)
R_{Cmax}	Accumulation factor during multiple dosing, based on C_{max} (Part 2)
T_{last}	Time of the last quantifiable concentration (Parts 1, 2, and 3)
T_{max}	Time of the maximum concentration (Parts 1, 2, and 3)

$T_{1/2}$	The observed terminal half-life, calculated for Parts 1 and 3 as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
Vz/F	Apparent volume of distribution in the terminal phase (Parts 1, 2, and 3)
λ_z	The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile (Parts 1, 2, and 3)

Additional PK analysis and modeling with multiple compartment model may be performed and will be reported separately, if conducted.

Food-effect: The effect of food will be assessed comparing PK parameters under fed versus fasting conditions using an analysis of variance (ANOVA) approach.

For Part 2, the following PK parameters will be calculated from plasma concentrations of TBAJ-876 following doses on Days 1 and 14:

- Day 1: AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{max}, and C_{avg} (λz, $t_{1/2}$, CLss/F, and Vz/F may be calculated as reasonable).
- Day 14: AUC_{tau}, C_{max}, C_{min}, T_{max}, C_{trough}, C_{avg}, CLss/F, Vz,/F, R_{AUC}, and R_{Cmax}. Parameters such as λz, and $t_{1/2}$ may be calculated as reasonable.

For Parts 1 and 2, PK parameters will be summarized by cohort using descriptive statistics. Dose proportionality will be assessed using the power model approach.

For Part 3, the following PK parameters will be calculated for Group 1 (1 x 100 mg tablet, fasted), Group 2 (1 x 100 mg tablet, fed), and Group 3 (4 x 25 mg tablets, fasted):

C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{Extrap}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, and Vz/F.

PK parameters will be summarized by group using descriptive statistics. Food effect (Group 2, fed, 1 x 100 mg tablet vs. Group 1, fasted, 1 x 100 mg tablet) and relative bioavailability of the two fasted groups (Group 3, 4 x 25 mg tablets vs. Group 1, 1 x 100 mg tablet) will be assessed using an analysis of variance (ANOVA) approach.

Efficacy: No efficacy evaluations will be performed in this study.

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LIST OF ABBREVIATIONS

ADL	activity of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the (plasma concentration vs. time) curve
AUC_{last}	area under the curve from time 0 hours to last quantifiable concentration
AUC_{inf}	area under the curve from time 0 hours to infinity
BDQ	bedaquiline
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
bpm	beats per minute
Ca	calcium
CFR	Code of Federal Regulations
CI	confidence interval
Cl^-	chloride
C_{last}	last quantifiable drug concentration
CLIA	Clinical Laboratory Improvement Amendments
cm	centimeter(s)
C_{max}	maximum concentration
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DARQ	diarylquinoline
dL	deciliter
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FIH	first-in-human
fl	fluid
FOB	functional observational battery
FSH	follicle-stimulating hormone
g	gram(s)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IP	Investigational Product
IRB	institutional review board
ISF	Investigator Site File
IUD	intrauterine device
IV	intravenous
K^+	potassium
kg	kilogram(s)
L	liter(s)
lbs	pounds
LDH	lactate dehydrogenase
LOQ	limit of quantitation
m	meter(s)
MAD	multiple ascending dose
MAOI	monoamine oxidase inhibitor
max.	maximum
MDR TB	multidrug-resistant tuberculosis
mg	milligram(s)
MIC	minimal inhibitory concentrations
min.	minute(s)
mIU	milli international units
mL	milliliter(s)
mmHg	millimeter of mercury
msec	millisecond
Mtb	*Mycobacterium tuberculosis*
n or N	number of occurrences
Na^+	sodium
NOAEL	no observed adverse event level
ng	nanogram(s)
OTC	over-the-counter
oz	ounce(s)
rbc	red blood cell
rpm	revolutions per minute
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
TB	tuberculosis

$T_{½}$ or $t_{½}$	terminal elimination half-life
T_{lag}	time prior to the first measurable (non-zero) concentration
T_{last}	time of the last measurable concentration
T_{max}	time to reach C_{max}
UDS	urine drug screen
Worldwide	Worldwide Clinical Trials Early Phase Services, LLC Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, LLC
β-hCG	beta-human chorionic gonadotropin
λ_z or Lambda-z	apparent elimination rate constant in terminal phase
°C	degrees Celsius/Centigrade

1 INTRODUCTION

1.1 Background Information

This study will be conducted in accordance with the protocol, International Good Clinical Practice (GCP) Guidelines, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

A brief overview of available confidential information regarding TBAJ-876 is summarized below from the Investigator's Brochure.[1] Unless noted otherwise, the information in this introduction was provided by TB Alliance.

1.2 Tuberculosis and Rationale for New Medication

Current tuberculosis (TB) treatment regimens are lengthy in duration and involve multi-drug therapy. High rates of noncompliance are common, which often result in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and treatment conditions demonstrate the clear need for new TB drugs and drug regimens for patients with drug-sensitive or drug-resistant TB that are safe and well tolerated and will shorten the overall treatment duration required for cure. In addition, new TB drugs and regimens should be affordable, easy to adopt and implement, suitable for pediatric use and for co-administration with antiretroviral therapy in individuals co-infected with *Mycobacterium tuberculosis* (Mtb) and human immunodeficiency virus (HIV).

Bedaquiline is a first-in-class diarylquinoline TB drug approved by the U.S. Food and Drug Administration (FDA) for use as part of a combination therapy in adults with pulmonary multidrug-resistant tuberculosis (MDR TB) when an effective treatment regimen cannot otherwise be provided. TBAJ-876 is a preclinical drug candidate from the TB Alliance's efforts to develop a safer diarylquinoline (DARQ) with the potential to safely deliver superior efficacy to bedaquiline (BDQ), as part of novel TB treatment regimens. Current data suggest that TBAJ-876 could contribute to a new TB regimen with utility for both drug-sensitive and drug-resistant TB and could have significant advantages over BDQ. In particular, TBAJ-876 demonstrates a low risk of corrected QT (QTc) prolongation (whereas QTc prolongation is observed with BDQ), a higher predicted clearance than BDQ (greater suitability for daily dosing), and lower minimal inhibitory concentrations (MICs) against Mtb. In preclinical models of TB, TBAJ-876 demonstrates superior efficacy as monotherapy and within regimens compared to BDQ given at the same dose. Taken together, these attributes may allow TBAJ-876 to safely deliver superior efficacy compared to BDQ.

At this stage, only the early clinical studies have been designed in detail. However, the overall goal during early clinical development of TBAJ-876 will be to demonstrate that

TBAJ-876 is well tolerated and effective as a part of a treatment for TB. TBAJ-876 will be studied in a standard Phase 1 safety, tolerability and pharmacokinetic (PK) studies. This first-in-human (FIH) study is planned to be a randomized, combined single ascending dose (SAD) study with a food-effect cohort (Part 1) and multiple ascending dose (MAD) study (Part 2). In addition, a Part 3 will be included that is an open-label study to determine the relative bioavailability (BA) of two strengths of TBAJ-876tablets.

1.3 Preclinical Studies and Toxicity Studies

In primary pharmacology studies, TBAJ-876 had clear and potent anti-mycobacterial activity in vitro and in animal models; therefore, it is a good candidate for clinical investigation.

Secondary and safety pharmacology studies suggest that, at the dose levels proposed for evaluation in human subjects, TBAJ-876 is unlikely to produce adverse effects due to off target pharmacologic activity or to adversely affect the function of important organ systems.

Repeat-dose toxicity studies have identified safe TBAJ-876 dose levels, as well as systemic exposures for TBAJ-876 and several of its metabolites, that are safe. This information was used to select a safe starting dose for the first clinical trial. The repeat-dose toxicity studies also have characterized the toxicity profile of TBAJ-876 in rats and dogs. This information has been used to identify potential adverse effects in human subjects and inform the dose-escalation schedule and clinical safety monitoring plan.

In rats dosed for 13 weeks, the dose-limiting toxicities were diarrhea and skeletal muscle damage. Microscopically, skeletal muscle fiber degeneration/necrosis was present in multiple muscles of about 1/3rd of the rats after 13 weeks at 25 mg/kg/day or after up to 16 days at 60 mg/kg/day but in no rat after 13 weeks at 10 mg/kg/day. Muscle damage was accompanied by changes in several clinical chemistry biomarkers; e.g., by very high serum CK, AST, and ALT activities and high serum potassium and phosphorus concentrations. Muscle damage was reversible, as it was absent after a 10- or 13-week recovery period.

In dogs dosed for 13 weeks, no dose-limiting toxicity was seen, but cardiac muscle damage was present microscopically (as cardiac muscle fiber necrosis/infiltrate) in all but one dog at 15 mg/kg/day but in no dogs at ≤7.5 mg/kg/day. While this can be an incidental background finding in dogs, the high incidence of this finding at 15 mg/kg/day was considered to be related to TBAJ-876, in part because the finding was accompanied by an increase in serum troponin I concentration. Cardiac muscle damage was reversible, as it was absent after a 13-week recovery period.

Various other TBAJ-876-related findings were seen in one of both species. These included:

- Microscopic findings in the glandular mucosa of the stomach in both species,
- Effects on intestinal function (diarrhea) in both species,
- Effects on the liver in both species,
- Decreased hematopoiesis in dogs,
- Effects on the incisors in rats,
- Effects on the lacrimal glands in rats,
- Increased serum amylase concentration in dogs.

In the glandular stomach, hyperplasia was seen in several rats after 13 weeks at 25 mg/kg/day or after two weeks at 60 mg/kg/day. This finding was reversible, as it was absent after a 10- or 13-week recovery period. Degeneration/necrosis was seen in two rats after 13 weeks at 25 mg/kg/day and several rats after two weeks at 60 mg/kg/day. At the end of the recovery period, degeneration/necrosis also was present in two rats that had been given TBAJ-876 for 13 weeks at 25 mg/kg/day. Finally, erosion of the pyloric mucosa in one rat after 13 weeks at 25 mg/kg/day.

In dogs, minimal to moderate degeneration/atrophy of the fundic glands in the stomach was seen in a pilot study after 2 weeks at 15 or 45 mg/kg/day. This was characterized by loss of chief cells with overall atrophy of glands, dilated glands with attenuated epithelium, and occasional glands with luminal cell debris. When minimal, the primary alteration was individual cell necrosis of chief cells with infrequent, minimally dilated glands. The grade of fundic gland degeneration/atrophy increased with dose level. Stomach findings were not seen in 8 dogs given daily oral doses of TBAJ-876 for 13 weeks at 15 mg/kg (the highest dose level tested). One possible explanation is that the 2-week study used TBAJ-876 free base, while the 13-week study used TBAJ-876 tartrate. It may be that the presence of the tartrate di-anion protected the fundic mucosa against damage. In any event, the clinical drug product will be made with TBAJ-876 tartrate, which produced no stomach findings in dogs dosed daily for 13 weeks.

Diarrhea was seen in rats given two doses of TBAJ-876, approximately 24 hours apart, at ≥ 500 mg/kg in a micronucleus study and also during the second week of dosing at 60 mg/kg/day in the 13-week study. At 60 mg/kg/day, diarrhea was accompanied by anogenital staining and dehydration, and contributed to the decision to stop dosing early at this dose level. Diarrhea resolved when dosing stopped. In dogs in the 13-week study, the frequency of discolored, mucoid or with mucous, watery, and/or soft feces was greater at 15 mg/kg/day than in the control group, but this difference was not clearly related to TBAJ-876.

Effects on the liver in rats were limited to single-cell vacuolar degeneration or necrosis of hepatocytes and/or vacuolation of periportal hepatocytes in a few females after

16 days at 60 mg/kg/day. This finding resolved when dosing stopped, although at the end of the recovery phase, single cell necrosis was present in one male that had been given TBAJ-876 for 16 days at 60 mg/kg/day. In dogs dosed for 13 weeks, hepatocellular vacuolation with greater mean liver weight and lower mean serum triglycerides concentration was present at all dose levels. At the lowest dose level (25 mg/kg/day), these findings were not considered adverse because they were not associated with clinical pathologic or microscopic evidence of hepatocellular degeneration or necrosis. At ≥7.5 mg/kg/day, mean serum ALT activity was increased after 4 and 13 weeks of dosing, but there still was no microscopic evidence of hepatocellular injury.

Evidence of decreased hematopoiesis was seen in dogs dosed for 13 weeks, where the incidence and average grade of decreased cellularity in sternal bone marrow was greater at 15 mg/kg/day. This microscopic finding was not associated with any changes in peripheral blood cell counts and was absent after a 13-week recovery period.

In female dogs, mean serum amylase concentration was slightly greater after 4 and 13 weeks of dosing at 15 mg/kg/day, without associated microscopic findings in the pancreas.

Two findings related to TBAJ-876 were seen only in rats and are of questionable relevance for humans:

- Degeneration/necrosis of ameloblasts was present in the incisors of rats dosed for 13 weeks. At 25 mg/kg/day, four rats also had acute inflammation in the nasal cavity (near tooth root), one rat also had pulp cavity necrosis, another had moderate periodontal inflammation, and a third had mild acute gingivitis. These dental findings were reversible, as they were absent at the end of the 13-week recovery period. While the effects on incisors were clearly adverse in rats, it is unclear if these findings are relevant for human subjects, because the incisors of rats grow continuously throughout life, unlike human teeth. The teeth were not examined microscopically in dogs dosed for 13 weeks; however, there was no clinical evidence of an effect on teeth, nor were there any findings involving the teeth or oral cavity at necropsy.
- In the lacrimal glands of rats dosed for 13 weeks, the average grade of acinar cell alteration (characterized by histologic characteristics of Harderian gland) was greater at all dose levels. After 13 weeks at 25 mg/kg/day, a few rats also had lacrimal gland atrophy. The differences in grade showed evidence of reversing when dosing stopped. Acinar cell alteration is a rodent-specific finding, and so it is unclear if an increase in this finding implies a risk for human subjects. There were no effects on lacrimal glands in dogs dosed for 13 weeks.

1.4 Safety Pharmacology

Cardiovascular Function

In surgically instrumented dogs given repeated doses of TBAJ-876 for 12 days at escalating dose levels up to 30 mg/kg/day, there was no effect on blood pressure, heart rate, PR or QT interval duration, QRS complex duration, or qualitative aspects of the electrocardiogram (ECG). There were slight decreases in QTc interval duration at 30 mg/kg/day, but these appeared to be driven by slight increases in body temperature and were not large enough to be considered adverse; therefore, the no observed adverse event level (NOAEL) for effects on cardiovascular function was 30 mg/kg/day. Plasma exposure to TBAJ-876 and its M2 and M3 metabolites after the third dose at the NOAEL are summarized in Table 1.

Table 1 Plasma Exposure to TBAJ-876 and Metabolites after the Third Dose at the NOAEL (30 mg/kg/day) and Comparison to Predicted Clinical Exposures

Analyte	Cmax (µg/mL)	Fold over clinical	AUC0-23.5h (hr*µg/mL)	Fold over clinical
TBAJ-876	**2.32**	**21*/3****	**26.9**	**13*/3***
TBAJ-876-M2	**0.16**	**ND**	**3.4**	**ND**
TBAJ-876-M3	**1.64**	**27*/16****	**33.5**	**26*/16****

*Predicted clinical exposures following daily dosing at 25 mg, estimated to be similar efficacy compared to BDQ: steady state C_{max} (Day 28) for TBAJ-876 and TBAJ-876-M3 of 0.11 and 0.06 µg/mL, respectively; and $AUC_{0\text{-}24h}$ = 2.1 and 1.3 µg.hr/mL, respectively.
**Predicted clinical exposures of the highest proposed single clinical dose of 400 mg: C_{max} (Day 1) for TBAJ-876 and TBAJ-876-M3 of 0.688 and 0.104 µg/mL, respectively; and $AUC_{0\text{-}24h}$ = 10.4 and 2.08 µg.hr/mL, respectively.

In a 13-week general toxicology study in dogs, oral administration of TBAJ-876 tartrate at doses of 2.5, 7.5, and 15 mg/kg/day did not have any adverse effects on ECG rhythm, morphology, or quantitative measurements; therefore, the 13-week NOAEL for effects on cardiovascular function was 30 mg/kg/day. Plasma exposure to TBAJ-876 and its M2 and M3 metabolites after the last dose at the cardiovascular NOAEL are summarized in Table 2.

Table 2 Plasma Exposure to TBAJ-876 and Metabolites after the Last Dose at the Cardiovascular NOAEL (15 mg/kg/day) and Comparison to Predicted Clinical Exposures

Analyte	C_{max} (µg/mL)	Fold over clinical	AUC_{0-24hr} (hr*µg/mL)	Fold over clinical
TBAJ-876	1.7	15*/2.5**	25.0	12*/2*
TBAJ-876-M2	0.7	ND	15.2	ND
TBAJ-876-M3	4.7	84*/45**	102.5	79*/149**

*Predicted clinical exposures following daily dosing at 25mg, estimated to be similar efficacy compared to BDQ: steady state C_{max} (Day 28) for TBAJ-876 and TBAJ-876-M3 of 0.11 and 0.06 µg/mL, respectively; and AUC_{0-24h} = 2.1 and 1.3 µg.hr/mL, respectively.
**Predicted clinical exposures of the highest proposed single clinical dose of 400 mg: C_{max} (Day 1) for TBAJ-876 and TBAJ-876-M3 of 0.688 and 0.104 µg/mL, respectively; and AUC_{0-24h} = 10.4 and 2.08 µg.hr/mL, respectively.

Nervous System Function

As part of the 13-week general toxicology study in which rats were given daily oral doses of TBAJ-876, functional observational battery (FOB) testing was conducted on 10 rats/sex at approximately 8 hours after the 13th dose. Rats tolerated daily oral doses of TBAJ-876 for 13 weeks at 10 or 25 mg/kg but not at 60 mg/kg, where dosing was stopped after 16 days due to toxicity. There were no differences between control and treated rats in FOB test results; therefore, 2-week NOAEL for effects on nervous system function was 60 mg/kg/day. Plasma exposure to TBAJ-876 and its M2 and M3 metabolites after the last dose at the nervous system NOAEL are summarized in Table 3.

Table 3 Plasma Exposure to TBAJ-876 and Metabolites after the 16th and Last Dose at the Nervous System NOAEL (60 mg/kg/day)

Analyte	C_{max} (µg/mL)	Fold over clinical	AUC_{0-24hr} (hr*µg/mL)	Fold over clinical
TBAJ-876	4.1	37*/6**	64.6	31*/6*
TBAJ-876-M2	0.4	ND	6.3	ND
TBAJ-876-M3	2.2	39*/21**	47.5	37*/23**

*Predicted clinical exposures following daily dosing at 25mg, estimated to be similar efficacy compared to BDQ: steady state C_{max} (Day 28) for TBAJ-876 and TBAJ-876-M3 of 0.11 and 0.06 µg/mL, respectively; and AUC_{0-24h} = 2.1 and 1.3 µg.hr/mL, respectively.
**Predicted clinical exposures of the highest proposed single clinical dose of 400 mg: C_{max} (Day 1) for TBAJ-876 and TBAJ-876-M3 of 0.688 and 0.104 µg/mL, respectively; and AUC_{0-24h} = 10.4 and 2.08 µg.hr/mL, respectively.

Respiratory Function

In rats given daily oral doses of TBAJ-876 for 7 days at 10, 30, or 75 mg/kg and evaluated by plethysmography, there was no effect on respiratory function at ≤30 mg/kg/day. At 75 mg/kg/day, TBAJ-876 resulted in slight, recoverable, increases in respiratory rate and tidal volume (and therefore in minute volume), which were smaller after the 7th dose than after the first dose and had resolved completely within 4 days after the last dose. These effects on respiratory function were too slight to be considered adverse; therefore, the 7-day NOAEL for effects on respiratory function was 75 mg/kg/day. Plasma exposure to TBAJ-876 and its M2 and M3 metabolites after the 8th and last dose at the respiratory NOAEL are summarized in Table 4.

Table 4 Plasma Exposure to TBAJ-876 and Metabolites after the 8th and Last Dose at the NOAEL (75 mg/kg/day)

Analyte	C_{max} (µg/mL)	Fold over clinical	$AUC_{0\text{-}24hr}$ (hr*µg/mL)	Fold over clinical	$AUC_{0\text{-}96hr}$ (hr*µg/mL)
TBAJ-876	6.16	56*/9**	92.10	44*/9**	123.00
TBAJ-876-M2	0.04	ND	0.69	ND	0.91
TBAJ-876-M3	0.87	16*/8**	16.20	13*/8**	24.90

*Predicted clinical exposures following daily dosing at 25mg, estimated to be similar efficacy compared to BDQ: steady state C_{max} (Day 28) for TBAJ-876 and TBAJ-876-M3 of 0.11 and 0.06 µg/mL, respectively; and $AUC_{0\text{-}24h}$ = 2.1 and 1.3 µg.hr/mL, respectively.
**Predicted clinical exposures of the highest proposed single clinical dose of 400 mg: C_{max} (Day 1) for TBAJ-876 and TBAJ-876-M3 of 0.688 and 0.104 µg/mL, respectively; and $AUC_{0\text{-}24h}$ = 10.4 and 2.08 µg.hr/mL, respectively.

1.5 Pharmacokinetics and Product Metabolism in Animals

Absorption

Following intravenous (IV) administration, TBAJ-876 exhibited low clearance and a large volume of distribution (≥9.45 L/kg). The plasma disposition of TBAJ-876 in nonclinical species was multiexponential and due to differences in PK sampling schedule, estimates of terminal half-life ($t_{1/2}$) of TBAJ-876 varied widely, ranging from 5 to 12 hr (sampling out to 24 hr postdose) to 26 to 77 hr (sampling out to 96 hr postdose).

TBAJ-876 free base had good oral bioavailability ranging from 36% to 44% in rodents, 28% to 80% in dogs, and 19% to 24% in monkeys, despite low permeability in the Caco-2 cell monolayer. Based on the efflux ratio of 0.2 in Caco-2 cells, TBAJ-876 was not a substrate of efflux pumps.

When TBAJ-876 was orally administered as tartrate salt to nonclinical species in the fasted state, C_{max} increased 40% to 70% and AUC_{0-t} increased 39% to 59% in rats and dogs, whereas in monkeys C_{max} and AUC_{0-t} decreased 43% and 49%, respectively.

The in vivo exposure to two active metabolites, TBAJ-876-M2 and TBAJ-876-M3, was quantified in the PK and toxicokinetic (TK) studies. At the NOAELs in the 13-week toxicology studies in the rat and dog, the steady state AUC of TBAJ-876-M3 was 0.6x and 1.8x of parent AUC, respectively, while TBAJ-876-M2 was present at lower concentrations with AUC representing 0.2 x of parent AUC in both species. There was no marked sex-related difference in the systemic exposure to TBAJ-876, TBAJ-876-M3, or TBAJ-876-M2 in rats and dogs.

In mice following the last dose of 4-week dosing at 3.125 mg/kg, steady state plasma exposure to TBAJ-876 and metabolites was approximately 0.4x of that of BDQ and metabolite at 25 mg/kg. After 6 weeks dosing in a mouse model of chronic TB, 3.125 mg/kg TBAJ-876 showed superior efficacy to 25 mg/kg BDQ indicative of TBAJ-876 being more potent than BDQ (Table 5). TBAJ-876-M3, TBAJ-876-M2, and BDQ-M2 AUC_{0-24} was 5x of parent AUC_{0-24h}.

Table 5 Plasma Exposure to TBAJ-876 and Metabolites vs. BDQ and BDQ-M2 Following 4-week Repeated Oral Administration to Mice

Dose Analyte	C_{max} (µg/mL)	AUC_{0-24h} (hr*µg/mL)
3.125 mg/kg/day TBAJ-876		
TBAJ-876	0.47	4.1
TBAJ-876-M2	0.93	20.2
TBAJ-876-M3	1.0	22.1
25 mg/kg/day BDQ		
BDQ	1.9	10.6
BDQ-M2	2.8	57.2

Distribution

TBAJ-876 and its metabolite TBAJ-876-M3 were not significantly distributed to red blood cells. TBAJ-876 and TBAJ-876-M3 were highly protein-bound in mouse, rat, dog, monkey, and human plasma (≥99.8%) and exhibited a species-independent protein binding. At steady state, high concentrations of TBAJ-876 and TBAJ-876-M3 were observed in the mouse lung at 2 hr and 24 hr postdose with the lung to plasma

concentration ratio for TBAJ-876 and TBAJ-876-M3 in the range of 5 to 7 and 12 to 20, respectively.

Metabolism

TBAJ-876 and TBAJ-876-M3 were relatively stable metabolically with TBAJ-876 showing a half-life of >240 min in rat, dog, and human liver microsomes and a half-life of 114 and 31 min in monkey and mouse liver microsomes, respectively, and TBAJ-876-M3 showing a half-life of >240 min in mouse, rat, dog, monkey, and human liver microsomes. The in vitro metabolic stability result is consistent with low in vivo clearance observed. TBAJ-876 was mainly metabolized by recombinant human CYP3A4 followed by CYP2A6, while both CYP3A4 and CYP2A6 play an equal role in the metabolism of TBAJ-876-M3.

In vitro metabolic profile in liver microsomes from nonclinical species and human concluded that TBAJ-876-M3 was the major metabolite and there were no human unique metabolites.

TBAJ-876 showed no or limited inhibition to CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 activities in human liver microsomes with IC_{50} >50 μM. TBAJ-876-M3 at 30 μM (i.e., nearly 90x the projected TBAJ-876-M3 $C_{max,ss}$ in humans at the potentially supra-therapeutic TBAJ-876 dose of 100 mg) caused a maximum 78% inhibition of CYP2C19 activity in human liver microsomes. Therefore, it can be concluded that the risk for TBAJ-876 and TBAJ-9876-M3 to cause PK drug interactions in humans by inhibition of the major drug metabolizing enzymes is low.

The major metabolite TBAJ-876-M3 did not active AhR, CAR, or PXR nuclear receptors in vitro. However, TBAJ-876 at 1 μM (i.e., 6 x the projected TBAJ-876 $C_{max,ss}$ in humans at the potentially therapeutic dose of 25 mg) induced CYP3A4 mRNA in one of three lots of human hepatocytes tested. The relevance of this finding to the potential for induction in humans will be addressed during an initial clinical development for TBAJ-876.

In vitro transporter inhibition studies showed that TBAJ-876 at 1 μM did not cause notable inhibition of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. The IC_{50} for BCRP cannot be determined due to insufficient inhibition over a concentration range of 0.5 to 30 μM. The IC_{50} for P-gp was determined to be 5.08 μM based on nominal concentrations, equivalent to approximately 2.30 μM after taking into account the non-specific binding. Cautions will be exercised in subjects who are enrolled in the clinical programs for TBAJ-876 and requiring concomitant medication with digoxin.

1.6 Potential Adverse Effects in Human Subjects

Based on the nonclinical safety studies, human subjects should be monitored for the following potential effects:

- Myocardial damage (seen in dogs) by way of clinical chemistry biomarkers
- Skeletal muscle myopathy (seen in rats) by way of clinical chemistry biomarkers and clinical signs of muscle pain or weakness
- Damage to the stomach mucosa (seen in both species) by way of clinical signs of nausea, vomiting, or dyspepsia
- Diarrhea (seen in both species)
- Liver injury, both hepatocellular and biliary (seen in both species) by way of clinical chemistry biomarkers
- Effects on hematopoiesis (seen in dogs) by way of hematology analyses
- Effects on the pancreas (seen in dogs) by way of clinical chemistry biomarkers

In animals, all of these effects were reversible when dosing stopped, and they are expected to be so in humans, too, if they occur.

No studies have been done to evaluate the potential effects of TBAJ-876 reproductive function in male animals. The following side effects were noted in adult subjects/patients in studies of a similar drug in this class (bedaquiline - marketed as Sirturo™): nausea, tiredness, headache, vomiting, dizziness, diarrhea, liver injury, heart problems; prolongation of QTc interval, and pancreas injury. [2]

Clinical Safety Evaluation (Single Ascending Dose)

In the SAD part of TBAJ-876 CL-001, 47 healthy volunteers aged 20 to 50 years were dosed with a single dose of TBAJ-876 or placebo and followed up to Week 4 (Cohorts 1 through 3) or up to Week 10 (Cohorts 4 through 6) after dosing . Each cohort enrolled 8 subjects (6 randomized to active treatment and 2 to placebo), except for Cohort 4, which enrolled only 7 subjects. Review of the blinded safety data showed that TBAJ-876 was generally safe and well tolerated at doses between 10 mg and 400 mg. There were no serious or severe AEs. Most of the AEs were mild and all resolved.

AEs of interest, based on preclinical findings, included myocardial damage, skeletal muscle injury, gastrointestinal irritation, elevated pancreatic enzymes, elevated liver enzymes, and cytopenia.

1) There were 3 subjects with elevated lipase (1 in the 10 mg cohort, and 2 in the 50 mg cohort) and 1 with elevated amylase (50 mg), who also had an elevated lipase. These laboratory abnormalities were not associated with any symptoms and resolved completely.

2) Two subjects with elevated liver enzymes (10 mg). These laboratory abnormalities were not associated with any symptoms and resolved completely.
3) One subject in the 25 mg cohort experienced rhabdomyolysis 9 days after dosing, deemed related to physical exertion and not to study drug.
4) Treatment with TBAJ-876 at single doses between 10 mg and 400 mg was not associated with evidence of QT prolongation or myocardial damage. One subject in Cohort 6 (400 mg) had an episode of non-sustained ventricular tachycardia observed in the Holter extraction on Study Day 1, approximately 5 hours after dosing. Upon questioning, the subject reported a few seconds of "more prominent heartbeat" at the same time. There were no symptoms of chest pain, syncope, or palpitations, and her physical examination and vital signs were normal. No QT prolongation was observed on the Holter or in subsequent ECGs. This event was reported as "possibly related". Another subject in Cohort 6 had a mildly elevated troponin I on Day 21, with a value of 0.038 ng/mL, confirmed at 0.034 ng/mL (ULN 0.028 ng/mL). The subject was completely asymptomatic, and her physical examination, vital signs, and ECG were normal. On the same day of the troponin I elevation, her CPK and CPK-Mb were also normal. The subject returned to the clinic on Study Day 23, and her troponin I levels were within the normal range. The finding of elevated troponin I on Study Day 21 was deemed by the primary investigator to be "spurious".

Based on a review of the blinded data from the SAD part of the study, there was no evidence of myocardial, skeletal muscle, gastrointestinal, hepatic, or hematological toxicity associated with single doses of TBAJ-876 between 10 mg and 400 mg. There were no clinically significant changes from baseline in vital signs and ECG's including no prolongation of QTc's.

While there were a few subjects with mild to moderate elevations in amylase and/or lipase, these abnormalities did not appear to be dose-dependent, were not associated with any symptomatology, and resolved rapidly without therapeutic interventions. The potential adverse effects of TBAJ-876 in human subjects will be further investigated in the MAD part of the study, where subjects will receive treatment with multiple ascending doses of the drug for 14 consecutive days.

1.7 Rationale for Dose Selection (MAD)

A mathematical model for the PK of TBAJ-876 and its M3 metabolite was developed using data from the single-ascending-dose component of the study under fasting conditions. The food-effect component of the study was used to estimate the relationship between dosing under fed and fasted conditions. These two inputs were used to predict the time course of the daily 24-hour AUCs of TBAJ-876 and M3 with dosing under fed conditions for 14 days. These AUCs were predicted to increase

through 14 days of dosing. The maximum predicted values on the 14th day were compared with safety thresholds determined from the three-month toxicity study in dogs where cardiotoxicity was observed. Exposure for the planned dose of 25 mg for the first cohort was predicted to remain below those thresholds.

Upon review of the MAD Cohort 1 (25 mg) PK and safety, the 50 mg dose planned for Cohort 2 was changed to 75 mg. This decision was made based on the safety of the 25 mg dose which was shown to be safe and well tolerated without evidence of cardiac, muscle skeletal, gastrointestinal, hepatic, or hematological toxicity, and because the total exposure of TBAJ-876 plus M3 at the dose of 75 mg was predicted to still remain below thresholds determined by the corresponding sum in the three-month toxicity study in dogs.

2 OBJECTIVE

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.
- 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.
  - 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 STUDY DESIGN SUMMARY

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

Safety will be assessed throughout the study for all subjects. Safety assessments will include physical examinations, vital signs, serial ECGs, cardiac monitoring, adverse events (AEs), and clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis).

Part 1:

Part 1 is a SAD design with 6 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.

Current duration and scheduling of safety and PK sampling assumes that the terminal half-life ($T_{1/2}$) will be approximately 7 days. The number and timing of PK sampling and safety assessments may be further revised based on evolving PK and safety information.

Subjects will be housed in the clinic from at least 24 hours prior (from Day -1), until 7 days after dosing (Day 8).

Subjects from Dose Level 1 will return to the clinic to have subsequent follow up safety (collection of AEs) and PK assessments on Days 10, 14, 17, 21, and 28.

Food-Effect: 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 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.

Note: PK sampling for making a decision on escalating to the next dose will be through the morning trough sample of Day 8, and a dose escalation meeting will take place around Day 15 when interim PK data is available from the bioanalytical lab. Therefore, the dose escalation meeting and decision will be based on PK through the morning of Day 8 and approximately 14 days of safety data, depending on the turnaround time of the bioanalysis. Subjects will continue to be monitored for PK and safety up to 10 weeks or longer after the dose. The duration of the follow-up period will be based on the analysis of interim PK data. Available subjects from Cohorts 4 and 5, and all subjects in Cohort 6 will be asked to return bi-weekly (+/- 2 days) up to 10 weeks or longer postdose. Subjects will complete the same procedures as required for Day 28 at each visit.

Interim PK analyses and safety assessments will be performed for the dose escalation decisions and to select the dose for the food-effect assessment, and to reconsider, if needed, the PK sampling time points as the study progresses. All samples will be sent for analysis on active treatment, and only the bioanalytical lab will be unblinded and will only run the analysis on active treatment subjects. Data from the analysis used for the escalation meetings will only include active treatment subjects and will be blinded by subject.

Dose escalation to the next cohort (i.e., dose level) or any changes to PK sampling and safety assessment timepoints will not take place until the Sponsor, in conjunction with the Principal Investigator and Dose Escalation Committee, has determined that adequate safety, tolerability and PK from the previous cohort have been demonstrated to permit proceeding to the next cohort.

Additional cohort, Cohort 7: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. Subjects will receive 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 Oral Suspension.

Subjects will follow the procedures in the Schedule of Assessments (Table 15) with the following clarifications:

> Subjects will check-in to the clinic on Day -1 and be confined through Day 8. Subjects will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21. Subjects will complete the procedures specified for those study days only. All ECGs performed in Cohort 7 will be triplicate ECGs at each time point.
>
> In addition, subjects will have triplicate ECGs at 16 hours postdose.

Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level, to study another dose level, or to increase cohort size (subject numbers). The number and timing of PK sampling and safety assessments may be further revised based on what is learned based on evolving data PK information.

These decisions concerning additional cohorts will not take place until the Sponsor, in conjunction with the Principal Investigator, has determined that adequate safety, tolerability, and PK from the previous cohorts have been demonstrated. The Institutional Review Board (IRB) should be immediately notified of this revised approach.

During each cohort, blood samples will be obtained before each dose of study drug, and at serial timepoints postdose on Days 1-8, 10, 14, 17, 21, and 28. Plasma PK samples will be analyzed for TBAJ-876, M2, and M3 using validated analytical methods. Appropriate PK parameters will be calculated using non-compartmental 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.

Table 6 presents the planned 6 dose cohorts and the additional Cohort 7 for Part 1 of the study.

Table 6 Single Ascending Dose Cohorts, Part 1

Cohort (Dose Level)[a]	Dose[c]	
1 (sentinel group)[b]	Single dose of 10 mg TBAJ-876 (n=2)	Placebo (n=1)
1 (remainder of cohort)[b]	Single dose of 10 mg TBAJ-876 (n=4)	Placebo (n=1)
2	Single dose of 25 mg TBAJ-876 (n=6)	Placebo (n=2)
3	Single dose of 50 mg TBAJ-876 (n=6)	Placebo (n=2)
4	Single dose of 100 mg TBAJ-876 (n=6)	Placebo (n=2)
5	Single dose of 200 mg TBAJ-876 (n=6)	Placebo (n=2)
6	Single dose of 400 mg TBAJ-876) (n=6)	Placebo (n=2)
7	Single dose of 800 mg TBAJ-876 (n=6)	Placebo (n=2)

mg = milligram; n = number of subjects.

a. Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level or another dosage formulation.
b. Dosing between sentinel cohort and remainder to occur at least 24 hours apart.
c. Subjects will be dosed at all dose levels under fasted conditions except for the fed group of the food-effect cohort. Based upon the exposure levels and PK results, the dose level of Cohort 4 (100 mg) will be used in the 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 data from 6 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.

At the end of Part 1, PK and safety data along with reasons for choosing the doses for the next part (Part 2) will be sent to the appropriate regulatory authorities and the IRB for review and approval. The study will not proceed to Part 2 until the above parties have provided approval.

Part 2:

The decisions for the study to progress to the planned MAD cohorts (Part 2) will take place when the Sponsor, in conjunction with the Principal Investigator and the Dose Escalation Committee, has determined that adequate safety, tolerability, and PK from the previous cohorts (Part 1) have been demonstrated to permit proceeding.

For Part 2, MAD design, the dose level 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 (see Section 1.7). At the time of this writing, it is expected that the dose of the third cohort will be informed by the results from the first two.

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.

Note: PK sampling for deciding to escalate to the next dose will be through the morning of Day 15, i.e., will include the profile on Day 14, and the dose escalation meeting will take place around Day 28 when interim PK data is available from the bioanalysis lab. Therefore, the dose escalation meeting and decision will be based on PK through the morning of Day 15 and approximately 28 days of safety data, depending on the turnaround time of the bioanalysis.

Subjects will continue to be dosed up to 14 days and be monitored for safety at timepoints indicated in the schedule of assessments (Table 16). After the last dose, subjects will remain in the clinic for 7 additional days and will then enter an additional follow-up period of 15 weeks or longer, if indicated by interim PK analyses.

During each cohort, blood samples will be obtained before each dose of study drug, and at serial timepoints postdose on Days 1 and 14. Samples will be taken according to the schedule provided in Table 16, with the last sample being obtained on Day 126, or possibly later if a decision is made to extend monitoring. Plasma PK samples will be analyzed for TBAJ-876, M2, and M3 using validated analytical methods. Appropriate PK parameters will be calculated using non-compartmental methods. In addition, blood and urine will be collected for clinical laboratory evaluations.

For Cohorts 2 and 3, an additional ECG extraction will occur at 16 hours postdose on Day 1 and Day 14. For Cohort 3, all ECGs performed will be triplicate ECGs at each time point listed in Table 15, including the additional 16 hour postdose time point. The sampling and safety assessment schedule may be revised based on what is learned about PK from Part 1 of the study and it may be further revised based on evolving data in Part 2.

Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure FSH levels.

Subjects who withdraw from the study will not be replaced.

Part 3:

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. Refer to the schedule of assessments in Table 17.

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.

3.1 Dose Escalation

The first cohort of the SAD will start with a sentinel group. The decision to continue dosing the remainder of Cohort 1 will occur after a minimum of 24 hours following sentinel group dosing and after the Sponsor, in conjunction with the Principal Investigator, has determined that adequate safety and tolerability have been demonstrated. It is not possible to stop dosing during an individual cohort of the SAD, except for the first cohort of SAD where dosing may be stopped following the sentinel cohort if any safety signal/concern arises, or, if the food effect is assessed by crossing over a single cohort, after the dosing of that cohort in the fasting state.

Dose Escalation Review

A review period will take place after the dosing of all subjects in each cohort in order evaluate and interpret all PK and safety data collected. The review of all pertinent blinded safety/tolerability data will include physical examinations, ECGs, vital signs, clinical laboratory tests, cardiac monitoring, and AEs or serious adverse events (SAEs) through approximately Day 14 (SAD) and Day 21 (MAD). Also, data from the current dose cohort and all previous cohorts will be considered.

The Sponsor and Investigator will determine if there are sufficient data available to make a dose escalation decision. Any AEs of Grade ≥2 toxicities (per Division of Microbiology and Infectious Disease [DMID] toxicity table; Appendix 3) must be considered in the decision to escalate to the next dose level. PK analysis will be completed on the active treatment subjects and will be blinded by subject.

As data from each cohort is informative for dose escalation decisions in subsequent cohorts, review of unblinded data will be conducted after completion of each cohort by 2 experienced individuals not directly involved in the study, one of whom must be a physician. Per protocol, the dose escalation meeting and decision require PK data through the morning of Day 8 and approximately 14 days of safety data, depending on

the turnaround time of the bioanalysis. Upon completion of the review, they will communicate to the study team modifications, if any, that should be implemented for subsequent cohorts. See unblinding procedures (Section 6.2.6).

Note: Although safety data for deciding on escalating to the next dose or cohort will be through approximately 14 days (SAD, Part 1) or 28 days (MAD, Part 2), subjects will continue to be monitored for safety up to 10 weeks or longer after the last dose. The duration of the follow-up period will be based on the analysis of interim PK data. For Part 1, available subjects from Cohorts 4 and 5, and all subjects in Cohort 6 will be asked to return bi-weekly (+/- 2 days) up to 10 weeks or longer postdose. Subjects will complete the same procedures as required for Day 28 at each visit. For Part 2, subjects will be discharged 1 week after the last dose and will be asked to return every 3 weeks for an additional follow-up period of 15 weeks or longer for safety and PK evaluation. Subjects will complete the same procedures as required for Day 21 at each visit.

Upon review of relevant data, the Sponsor, in conjunction with the Investigator, may decide to:

1. Escalate the dose as planned.
2. Evaluate an intermediate dose level prior to proceeding to the next planned dose level if concerns arise from PK and safety that do not warrant ceasing escalation.
3. Repeat a given dose level in a new cohort of subjects.
4. Increase the dose of the next cohort if the PK is lower than expected in the previous cohort.
5. Add a cohort if the PK is lower than expected after a cohort and there are no safety concerns.
6. Halt the study.

During the dose-escalation phase of this first clinical trial, escalation will be guided by emerging safety and PK data.

Dose escalation to the next cohort (i.e., dose level) will not take place until the Sponsor, in conjunction with the Principal Investigator and Dose Escalation Committee, has determined that adequate safety, tolerability and PK from the previous cohort has been demonstrated. The IRB will be notified, and the next cohort will start once IRB approval is received.

3.2 Stopping Rules for Cohorts for Participants Receiving Active Drug

If any of the cohort stopping rules are met, cohort dosing must be stopped to allow review of the data by the Sponsor and the Investigator. As with dose escalation review, the review of data here is also blinded except for review by the 2 experienced

individuals not directly involved in the study (see unblinding procedures; Section 6.2.6).

Rules for stopping dosing of a cohort include the following:

a. One subject experiences one or more drug-related SAEs.

b. Two or more subjects experience Grade 3 or 4 (per DMID) myalgia in combination with increase of CPK (at least 3 times the upper limit of the normal range [ULN] confirmed at 48 hours).

c. Two or more subjects have a QTcF ≥ 500 ms with an increase from baseline > 60 ms.

d. Two or more subjects experience confirmed Grade 3 or 4 AEs (per DMID) in any one of the following laboratory parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), amylase, or lipase.

4 IDENTITY OF INVESTIGATIONAL PRODUCT

The Investigational Medicinal Product (IMP) will be supplied as TBAJ-876 Oral Suspension, 5 mg/mL formulation or matching placebo, TBAJ-876 tablets 25 mg, and TBAJ-876 tablets 100 mg.

Refer to Appendix 2 for details regarding the description and composition of TBAJ-876 oral suspension, TBAJ-876 tablets 25 mg, and TBAJ-876 tablets 100 mg.

Table 7 Identity of Investigational Products

Test Products:	TBAJ-876 Oral Suspension 5 mg/mL
	Manufactured for Global Alliance for TB Drug Development
	TBAJ-876 Tablets 25 mg
	Manufactured by Piramal Pharma Limited for Global Alliance for TB Drug Development
	TBAJ-876 Tablets 100 mg
	Manufactured by Piramal Pharma Limited for Global Alliance for TB Drug Development

Control Product:	Placebo for TBAJ-876 Oral Suspension
	Manufactured for Global Alliance for TB Drug Development

5 SUBJECT SELECTION

5.1 Inclusion Criteria

All volunteers must satisfy the following criteria to be considered for study participation:

1. Understands study procedures and voluntarily provides written informed consent prior to the start of any study-specific procedures.
2. Is a healthy adult male or female, 19 to 50 years of age (inclusive) at the time of screening.
3. Has a body mass index (BMI) ≥18.5 and ≤32.0 (kg/m^2) and a body weight of no less than 50.0 kg at the time of screening and check-in.
4. Is medically healthy with no clinically significant screening results (e.g., laboratory profiles normal or up to Grade 1 per DMID Toxicity Tables), as deemed by the Investigator. Note: Lab results within the testing facility's normal range will not be considered AEs when referenced to the DMID assessment/grading scale. If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.
5. Has not used tobacco- or nicotine-containing products (including smoking cessation products), for a minimum of 6 months before dosing.
6. If female of non-childbearing potential, she has undergone one of the following sterilization procedures at least 6 months before dosing:
   - Hysteroscopic sterilization;
   - Bilateral tubal ligation or bilateral salpingectomy;
   - Hysterectomy; or
   - Bilateral oophorectomy;
   - Or is postmenopausal with amenorrhea for at least 1 year before the first dose with serum FSH levels consistent with postmenopausal status (i.e., greater than 40 mIU/mL) at screening.
7. If female of childbearing potential, must be using effective birth control methods, as defined below and is willing to continue practicing birth control methods and not planning to conceive throughout treatment until after the last follow-up visit (or until at least 12 weeks [male participants] or 6 weeks [female participants] after the date of early withdrawal). The following are allowed birth control methods for this study:

- Double barrier method (e.g., diaphragm with spermicide; condoms with spermicide);
- Intrauterine device (IUD);
- Abstinence (and must agree to use a double barrier method if they become sexually active during the study);
- Vasectomized partner (at least 6 months before dosing);
- Non-surgical permanent sterilization (e.g., Essure® procedure) at least 3 months before dosing;
- Implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months before study dosing; and/or

8. If a non-vasectomized male (or male vasectomized less than 120 days prior to study start) he must agree to the following during study participation and for 90 days after the last follow-up visit (or until at least 90 days after the date of early withdrawal):
   - Use a condom with spermicide while engaging in sexual activity or be sexually abstinent; and
   - Not donate sperm during this time.

   In the event the sexual partner is surgically sterile or postmenopausal, use of a condom with spermicide is not necessary. None of the birth control restrictions listed above are required for vasectomized males whose procedure was performed more than 120 days before study start.
9. Is willing to answer inclusion and exclusion criteria questionnaire at check-in.
10. Is able to comply with the protocol and the assessments therein, including all restrictions.
11. Is willing and able to remain in the study unit for the entire duration of the assigned confinement period and return for outpatient visits.
12. If assigned to receive study drug under fed conditions, is willing and able to consume the entire high-calorie, high-fat breakfast meal in the timeframe required.

5.2 Exclusion Criteria

Volunteers will be excluded from study participation for any of the following:

1. History or presence of clinically significant cardiovascular (heart murmur), pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychiatric disease, or any other condition that, in the

opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.

2. Any presence of musculoskeletal toxicity (severe tenderness with marked impairment of activity, or frank necrosis).
3. Surgery within the past 90 days prior to dosing as determined by the Investigator to be clinically relevant.
4. History or presence of alcoholism or drug abuse within the past 2 years as determined by the Investigator to be clinically relevant.
5. Participation in another clinical trial within 30 days prior to dosing.
6. Female subjects who are pregnant or lactating.
7. Positive result on a urine drug/alcohol screen at screening or check-in.
8. Positive result on urine cotinine at screening.
9. Has the following laboratory abnormalities at screening:
    a. ALT or AST Grade 2 or greater (≥ 2.0 times ULN)
    b. Creatinine Grade 2 or greater (≥1.6 times ULN)
    c. Pancreatic lipase Grade 2 or greater (≥1.6 times ULN)
    d. Amylase Grade 2 or greater (≥1.6 times ULN)
    e. Total bilirubin Grade 2 or greater
    f. CPK (> 1.25 times ULN)

    If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.
10. Has a positive test for hepatitis B surface antigen, hepatitis C antibody, or HIV at screening.
11. Seated blood pressure (BP) is less than 90/40 mmHg or greater than 140/90 mmHg at screening, Day -1 (check-in) or predose. Out-of-range vital signs may be repeated once for confirmation. Out of range values will not be considered AEs if the repeat assessment is in range.
12. Seated heart rate is lower than 40 beat per minute (bpm) or higher than 99 bpm at screening, Day -1 (check-in) or predose. Out-of-range vital signs may be repeated once for confirmation. Out of range values will not be considered AEs if the repeat assessment is in range.
13. Any clinically significant ECG abnormality at screening (as deemed by decision of the Investigator and the Sponsor's Medical Monitor).

NOTE: The following may be considered not clinically significant without consulting the Sponsor's Medical Monitor:

- Mild first degree A-V block (P-R interval <0.23 sec)
- Right or left axis deviation
- Incomplete right bundle branch block
- Isolated left anterior fascicular block (left anterior hemiblock) in younger athletic subjects

14. QTcF interval >450 msec for males or >470 msec for females at screening, Day -1, or Day 1 (predose), or history of prolonged QT syndrome. For the triplicate ECGs taken at screening and on Day -1, the average QTcF interval of the 3 ECG recordings will be used to determine qualification.
15. Family history of long-QT syndrome or sudden death without a preceding diagnosis of a condition that could be causative of sudden death (such as known coronary artery disease, congestive heart failure, or terminal cancer).
16. Use of any prescription medication within 14 days prior to dosing.
17. Use of any over-the-counter (OTC) medication, including herbal products and vitamins, within 7 days prior to dosing, except acetaminophen. Up to 3 grams per day of acetaminophen is allowed only at occasional use and at the discretion of the Investigator prior to dosing.
18. Use of any drugs or substances known to be significant inhibitors of cytochrome P450 (CYP) enzymes and/or significant inhibitors or substrates of P-glycoprotein (P-gp) and/or organic anion transporting polypeptides (OATP) within 14 days prior to the first dose of study drug.
19. Use of any drugs or substances known to be inducers of CYP enzymes and/or P-gp, including St. John's Wort, within 30 days prior to the first dose of study drug.
20. Blood donation or significant blood loss within 56 days before the first dose of study medication until the end-of-study visit.
21. Plasma donation within 7 days before the first dose of study medication until the end-of-study visit.
22. Has been on a significantly abnormal diet during the 4 weeks preceding the first dose of study medication.
23. Unwilling to remove any artificial nails (e.g. acrylic, gel) or fingernail polish and not use such products for the duration of the study.

24. History or presence of allergic or adverse response to Listerine breath strips or aspartame.
25. Is lactose intolerant.

5.3 Medication and Activity Restrictions

1. Subjects must not donate blood from 56 days or plasma from 7 days prior to the first dose of study medication until the last follow-up visit or early withdrawal visit is completed. It is recommended that blood/plasma donations not be made for at least 30 days after the last follow-up visit or early withdrawal visit.
2. Subjects must not use tobacco- or nicotine-containing products (including smoking cessation products) from 6 months prior to the first dose of study medication until the last follow-up visit or early withdrawal visit is completed.
3. Subjects must not consume alcohol from 72 hours prior to the first dose of study medication until the last follow-up visit or early withdrawal visit is completed. However, allowance for an isolated single incidental consumption may be evaluated and approved by the study Investigator based on the potential for interaction with the study drug.
4. Subjects must not consume beverages or foods that contain grapefruit or Mandarin oranges from 10 days before the first dose of study medication, or poppy seeds, broccoli, Brussels sprouts, pomegranate, star fruit, char-grilled meat, or caffeine/xanthine from 24 hours before the first dose of study medication, until the last follow-up visit or early withdrawal visit is completed. Subjects will be instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may be evaluated and approved by the study Investigator based on the potential for interaction with the study drug.
5. Subjects must not engage in strenuous exercise from 48 hours prior to the first dose of study medication until after discharge from the clinic. For follow-up visits, subjects must not engage in strenuous exercise during the 3 days prior to the visit. Any report of exercise will be documented and recoded as a protocol deviation. Subjects may continue in the study at the discretion of the study Investigator.
6. Subjects must be willing to remove any artificial nails (e.g., acrylic, gel) or fingernail polish and not use such products for the duration of the study.

5.4 Screening

The informed consent documents (ICDs) will be discussed with each potential participant, and each individual will sign an ICD for the study before any study-specific procedures being performed.

Each potential study participant will have the following assessments by the Investigator or designee within 28 days (21 days for Part 3) before study start:

- Demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and smoking habits.
- Medical history
- Physical examination
- Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry)
- Triplicate 12-lead safety ECGs
- Clinical laboratory tests (hematology, coagulation, chemistry, and urinalysis)
- Serology tests for HIV, hepatitis B and C
- Urine test for drugs of abuse and cotinine
- Serum pregnancy (all female subjects)
- FSH test (Post-menopausal females)
- Concomitant medication review

Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs within the defined parameters who fulfill all other inclusion criteria and meet none of the exclusion criteria outlined in the previous sections will be enrolled in the study.

Subjects will be assigned numbers in an ascending order, based on successful completion of the screening process.

6 STUDY PROCEDURES

6.1 Subject Assignment

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

In addition, 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 50 to 60.

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

Additional cohorts (8 subjects per cohort) 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).

Additional cohort, Cohort 7: Eight (8) subjects will be enrolled, 6 to receive active drug and 2 to receive placebo. Subjects will receive a single dose under fasted conditions. Subjects will receive 800 mg TBAJ-876 or matching dose of placebo for TBAJ-876 Oral Suspension.

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.

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.

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.

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.

6.2 Blinding (Parts 1 and 2)

All subjects and clinical staff (except for the unblinded pharmacy staff) will be blinded to treatment. An unblinded pharmacy staff will be required at the Clinical Site to comply with the study's randomization and blinding requirements. At the Clinical Site, prior to study initiation, the Principal Investigator will be responsible for designating a qualified pharmacy staff to serve as the unblinded pharmacy staff in the study. Unblinded pharmacy staff may dose subjects but may not participate in any subject assessments.

Throughout the study, the designated unblinded pharmacy staff will be responsible for all drug accountability issues, including preparing, labeling, dispensing, and dosing study drug according to the randomization code provided, yet remain independent of all

subject assessments. The pharmacy staff will follow the Standard Operating Procedures (SOPs) and Work Instructions related to pharmacy services and protocol-specific requirements.

Randomization codes will be provided to the unblinded pharmacy staff. Confirmation of receipt of the randomization code will be required by the Sponsor. The unblinded pharmacy staff will be responsible for maintaining the blind, consistent with protocol design, throughout the study. All blinded information will be kept in the pharmacy file. Access to the blinded information in the pharmacy file will be restricted.

The subjects, Principal Investigator, and all other study personnel involved with subject assessments will remain blinded to the actual treatment assignments of the subjects. The Principal Investigator will be ultimately responsible for ensuring that the integrity of the blind is maintained throughout the study at the site and will be required to notify the Sponsor in the event of any breaking of the blind for any reason.

Part 3 is open-label.

6.2.1 Clinical Research Staff

All observers who evaluate any reported AE, laboratory abnormalities, ECGs, and changes in the ECGs will be blinded as to what treatment each subject is assigned.

6.2.2 Study Subjects

All subjects will be blinded as to which treatment they are receiving at any dose.

6.2.3 Bioanalytical Laboratory

All samples will be sent to the bioanalytical laboratory for analysis. The bioanalytical laboratory will be unblinded and only run the analysis on active treatment subjects.

6.2.4 Pharmacokinetic Analysis

Pharmacokinetic analysis will be completed only on the active treatment subjects and will be blinded by subject for interim assessments.

6.2.5 Cardiac Vendor

Electrocardiogram data will be analyzed in a blinded fashion and then unblinded by the cardiac vendor in order to be presented by treatment group in aggregate (reviewers will remain blinded by subject).

6.2.6 Unblinding Procedures

As data from each cohort is informative for dose escalation decisions in subsequent cohorts, review of unblinded data will be conducted after completion of each cohort by 2 experienced individuals not directly involved in the study, one of whom must be a physician. Per protocol, the dose escalation meeting and decision require PK data through the morning of Day 8 and approximately 14 days of safety data, depending on the turnaround time of the bioanalysis. Upon completion of the review, they will

communicate to the study team modifications, if any, that should be implemented for subsequent cohorts.

The treatment assignment should be unblinded at the clinic only in the case of an emergency when knowledge of the study drug assignment is absolutely necessary for the clinical management or welfare of the subject. Breaking of the blind at the clinic under any other circumstances will be considered a protocol violation.

The Investigator is strongly encouraged to contact the Sponsor before unblinding the study drug assignment prior to the scheduled assessment of tolerance and safety data. If the blind is broken for any reason, the Investigator must notify the Sponsor within 1 day, and an SAE form must be completed, if appropriate. In addition, the Investigator will record the date and reason for revealing the blinded study drug assignment for that subject in the source documents and appropriate CRF page(s).

6.3 Check-In Procedures

Subjects will check into the clinic on Day -1.

At check-in, all subjects will be evaluated to confirm they continue to meet all the inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2).

Subjects will undergo the following assessments during the confinement period prior to dosing:

- Physical examinations
- Weight
- Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry)
- Triplicate 12-lead ECG
- Clinical laboratory tests (hematology, coagulation, chemistry, and urinalysis) – myoglobin will be collected but results will not be required for dose qualification.
- Urine drug, alcohol, and cotinine screens – results must be negative for the subject to continue study participation
- Serum pregnancy test (all female subjects) – results must be negative for the subject to continue study participation
- Concomitant medication review

6.4 Confinement

For Part 1, subjects will be admitted to the research center on Day -1 and remain in the research center until completion of the procedures on Day 8. Subjects will return for subsequent follow up visits on Days 10, 14, 17, 21, and 28. Available subjects from

Cohorts 4 and 5, and all subjects in Cohort 6 will also return bi-weekly (+/- 2 days) up to 10 weeks or longer postdose.

Additional cohort, Cohort 7: Subjects will check-in to the clinic on Day -1 and be confined through Day 8. Subjects will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21.

For Part 2, subjects will be admitted to the research center on the evening of Day -1 and remain in the research center until completion of the procedures on Day 21. Subjects will return for subsequent follow up visits on Days 42, 63, 84, 105, and 126 (+/- 1 day) and will receive a phone call on Day 133 (+/- 1 day).

For Part 3, subjects will be admitted to the research center on the evening of Day -1 and remain in the research center until completion of the procedures on Day 8. Subjects will return for subsequent follow-up visits on Days 10 and 14 and will receive a follow-up phone call on Day 21.

6.5 Fasting/Meals/Beverages

6.5.1 Fasting/Meals

Part 1, SAD

Optional meals (lunch, snack, and dinner) may be served the day of check-in. All subjects will then be required to fast for at least 10 hours before dosing. The subjects will fast for 4 hours after dosing. Standard meals will be provided at appropriate times after dosing.

In the food-effect cohort of Part 1, the 3 fasted subjects will fast for at least 10 hours before dosing and the 10 fed subjects will receive the required FDA standard high-fat, high-calorie breakfast to begin 30 minutes before scheduled administration of the dose and to end (last bite taken) within 5 minutes before dosing. The subjects will fast for 4 hours thereafter. The following high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast will be ingested 30 minutes before administration of the drug:

2 eggs fried in butter
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An equivalent meal may be substituted with documentation of the menu and caloric contents.

Standard meals will be provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter.

Part 2, MAD

An optional meal or snack will be served the evening of check-in.

All subjects will then be required to fast for at least 10 hours before consuming a required FDA standard high fat, high-calorie breakfast. Subjects will receive the required FDA standard high fat, high-calorie breakfast to begin 30 minutes before scheduled administration of the dose and to end (last bite taken) within 7 minutes before dosing. The subjects will fast for 4 hours thereafter. The following high-fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast will be ingested 30 minutes before administration of the drug:

2 eggs fried in butter
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An equivalent meal may be substituted with documentation of the menu and caloric contents.

Standard meals will be provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter.

Part 3, BA

An optional meal or snack will be served the evening of check-in.

Subjects in Group 1 and Group 3 will be required to fast for at least 10 hours before dosing. The subjects will fast for 4 hours after dosing.

Subjects in Group 2 will fast for at least 10 hours before consuming the required FDA standard high-fat, high calorie breakfast as described above in the food effect cohort in Part 1.

Standard meals will be provided at appropriate times after dosing for all groups.

6.5.2 Beverages

Part 1, SAD and Part 2, MAD

Each dose of TBAJ-876 Oral Suspension and placebo for TBAJ-876 Oral Suspension will be administered orally followed by approximately 240 mL of room temperature water.

Except for the room temperature water provided with the study treatment, no water may be consumed for 1 hour prior to each dose through 1 hour after each dose.

At other times, subjects will be encouraged to drink water ad libitum.

Part 3, BA

Each dose of TBAJ-876 Tablet(s) will be administered orally with approximately 240 mL of room temperature water.

Except for the room temperature water provided with the study treatment, no water may be consumed for 1 hour prior to each dose through 1 hour after each dose.

At other times, subjects will be encouraged to drink water ad libitum.

6.6 Drug Administration

6.6.1 Administration of Oral Care Strips (Parts 1 and 2)

Listerine® oral care strips (or similar product) will be used to blind subjects to treatment (TBAJ-876 Oral Suspension or placebo for TBAJ-876 Oral Suspension). One strip will be added to the subject's tongue immediately before administration of the study treatment. Another strip will be placed on the subject's tongue immediately after the subject has swallowed the study treatment and 240 mL of water. Research staff will place the strip on the midsection of the subject's tongue. The subject should keep the strip on the tongue while it dissolves but may swallow when they feel the need to. A mouth check will be performed, using a flashlight and tongue depressor, after each administration of Listerine oral care strip to ensure that all of the film has been dissolved.

6.6.2 Administration of TBAJ-876 Oral Suspension or Placebo for TBAJ-876 Oral Suspension

Note: Detailed instructions for preparing and dispensing TBAJ-876 Oral Suspension will be provided in a separate pharmacy manual. Any instructions in the pharmacy manual shall supersede those presented in this protocol.

TBAJ-876 Oral Suspension or placebo for TBAJ-876 Oral Suspension will be transferred and stored in Pyrex glass reagent bottles with a polypropylene (PP) screw cap without a liner. These bottles will be used for mixing, sampling, and storage prior to administration.

The required doses of the drug product will be dispensed using commercially available oral syringes of suitable capacity. The suspension will be dispensed just prior to dosing and not stored in the oral syringes.

Each dose of TBAJ-876 Oral Suspension or Placebo for TBAJ-876 Oral Suspension will be administered orally followed by approximately 240 mL of room temperature

water. A mouth check will be performed immediately after dose to ensure that the medication has been appropriately swallowed.

Subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after dosing on these days, subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary. Subjects will not be allowed to lie down, except as directed by clinical staff secondary to AEs, for the first 4 hours after dosing.

6.6.3 Administration of TBAJ-876 Tablet

Each dose of TBAJ-876 Tablet will be administered orally with approximately 240 mL of room temperature water. A mouth check will be performed immediately after dose to ensure that the medication has been appropriately swallowed.

Subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after dosing, subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary. Subjects will not be allowed to lie down, except as directed by clinical staff secondary to AEs, for the first 4 hours after dosing.

6.7 Blood Sampling, Processing and Shipment

Blood samples will be collected as detailed in Appendix 1.

Refer to the Schedule of Events (Table 15, Part 1, Table 16, Part 2, or Table 17, Part 3) for specific blood collection time points. The Principal Investigator, in conjunction with the Sponsor, may collect additional blood if necessary for repeat laboratory or safety evaluations including AE follow-up. Two aliquots of each blood sample will be prepared. One set aliquot of the plasma samples will be sent to bioanalytical lab. After receiving of the first set of plasma samples, the second set plasma samples (backup samples) will also be sent to the bioanalytical lab.

6.7.1 Part 1

For Cohorts 1-6, a total of 140 mL (35 x 4 mL samples) will be collected from each subject for PK analysis. Approximately 124.5 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing.

Table 8 Total Volume of Blood to be Collected for Testing: Part 1

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	12.5	12.5
Clinical labs during study (check-in, 6 and 48 hours and Days 5, 7, 10, 14, 17, 21, and 28 (end-of-study) [a]	10	8.5	85.0
Coagulation [a]	10	2.7	27.0
Pharmacokinetic analysis [a]	35	4.0	140.0
10 week postdose follow-up (includes clinical labs and coagulation) [a]	5	11.2	56
		Total	320.5

a. Subjects in Cohort 7 will not have collections after Day 14.

The scheduling of PK sample collection will be based on the PK data collected from previous cohorts and could involve a different sampling schedule during the first 5 days and may require subjects return to the clinic for up to 10 weeks after dosing, depending on what is learned about the PK of TBAJ-876. Available subjects from Cohorts 4 and 5, and all subjects in Cohort 6 will return bi-weekly (+/- 2 days) up to 10 weeks postdose. Subjects will have clinical labs and coagulation tests completed at each visit. The total volume of blood collected from each subject during the 10 week postdose follow-up will be approximately 56 mL. The total volume of blood collected from each subject in Part 1 Cohorts 1-6 will not exceed approximately 320.5 mL.

For Cohort 7, a total of 124 mL (31 x 4 mL samples) will be collected from each subject for PK analysis. Approximately 78.5 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing. The total volume of blood collected from each subject in Part 1 Cohort 7 will not exceed approximately 203 mL.

6.7.2 Part 2

A total of 212 mL (53 x 4 mL samples) will be collected from each subject for PK analysis. Approximately 110.6 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing. The total volume of blood collected from each subject in Part 2 is planned not to exceed approximately 322.6 mL, although more may be collected if a decision is made to prolong PK monitoring.

Table 9 Total Volume of Blood to be Collected for Testing: Part 2

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	12.5	12.5
Clinical labs during study (check-in, Days 7, 14, 21, 42, 63, 84, 105, and 126 (end-of-study)	9	8.5	76.5
Coagulation	8	2.7	21.6
Pharmacokinetic analysis (predose trough)	13	4.0	52.0
Pharmacokinetic analysis (postdose)	40	4.0	160.0
		Total	322.6

Additional PK samples may be collected at times to be determined based on the results from previous cohorts.

The Principal Investigator, in conjunction with the Sponsor, may collect additional blood if necessary, for repeat laboratory or safety evaluations including AE follow-up.

6.7.3 Part 3

A total of 128 mL (32 x 4ml samples) will be collected for PK Analysis. Approximately 91 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing.

Table 10 Total Volume of Blood to be Collected for Testing: Part 3

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	12.5	12.5
Clinical labs during study (check-in, 6 and 48 hours and Days 5, 7, 10, and 14 (end-of-study).	7	8.5	59.5
Coagulation	7	2.7	18.9
Pharmacokinetic analysis	32	4.0	128.0
		Total	218.9

The Principal Investigator, in conjunction with the Sponsor, may collect additional blood if necessary, for repeat laboratory or safety evaluations including AE follow-up.

6.7.4 Pharmacokinetic Sampling Time Windows

Blood samples collected outside the time windows listed below will be considered deviations.

Table 11 Acceptable Pharmacokinetic Sampling Time Windows, Part 1 and Part 3

Investigation and examination	Allowable Time Window		
	Postdose		
	≤24 hours	>24 hours to ≤Day 7	>Day 7
Plasma sample collection for pharmacokinetic assessment	± 2 minutes	± 5 minutes	± 10 minutes

Note: For the food-effect cohort, time windows are relative to dosing in each study period.

Table 12 Acceptable Pharmacokinetic Sampling Time Windows, Part 2

Investigation and examination	Allowable Time Window		
	Postdose		
	≤24 hours and Day 14	>24 hours to ≤Day 13	>Day 15
Plasma sample collection for pharmacokinetic assessment	± 5 minutes	± 5 minutes	± 10 minutes

Note: The 24-hour sample of Day 1 must be collected prior to the Day 2 dose.

6.8 End-of-Study Procedures

Subjects will return to the clinic for a follow-up visit after their final dose of study medication. During this visit, the following procedures will be conducted:

- Physical examination
- Triplicate ECG
- Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry)
- Blood sample collection for PK
- Clinical laboratory tests (hematology, coagulation, chemistry, and urinalysis)
- Urine pregnancy (all female subjects)

When possible, end-of-study procedures will be performed in the event of a subject's early termination from the study.

6.9 Safety Monitoring and Procedures

6.9.1 Adverse Events

Subjects will be instructed to inform the study physician and/or research personnel of any AEs that occur at any time during the study. Subjects will be monitored for AEs from the time of signing the ICD through the end-of-study visit.

Refer to Section 7 for details regarding AE reporting.

6.9.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the times noted on the appropriate schedule of events (Table 15, Table 16, or Table 17). A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform all clinical laboratory tests for this study.

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect, and total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, , magnesium, and bicarbonate, creatine phosphokinase of myocardial band (CPK-MB), lipase, and amylase.
- Serology: hepatitis B surface antigen, hepatitis C antibody, and HIV.
- Coagulation: prothrombin time (PT2) and activated partial thromboplastin time (aPTT2).
- Other Laboratory Tests: cardiac troponin I and glycosylated hemoglobin
- Urinalysis - The following will be evaluated by an automated or manual urine “dipstick” method: pH, specific gravity, protein, glucose, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, myoglobin, blood, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed. Myoglobin will be collected but results will not be required for dose qualification.
- Urine Drug, Cotinine, and Alcohol Screens - Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates) cotinine, and alcohol.
- Pregnancy test (all female subjects).
- FSH (female subjects claiming post-menopausal status).

6.9.3 Vital Signs

For Part 1, vital signs (blood pressure, pulse rate, temperature, respiration rate, and pulse oximetry) will be measured at the times noted on the appropriate events schedule (Table 15).

For Part 2, vital signs (blood pressure, pulse rate, temperature, respiration rate, and pulse oximetry) will be measured at the times noted on the appropriate events schedule (Table 16). Furthermore, vital signs will also be taken once daily on Day 2 through Day 14 (6 hours after dosing) and once daily on Days 15-21 and Days 42, 63, 84, 105, and 126 or at early withdrawal (to be done within 15 minutes before review of medication and collection of AEs).

For Part 3, vital signs (blood pressure, pulse rate, temperature, respiration rate, and pulse oximetry) will be measured at the times noted on the appropriate events schedule (Table 17).

Vitals signs will be measured within 90 minutes prior to dosing and within 15 minutes of the defined time points. Both blood pressure and pulse rate should be captured simultaneously. Blood pressure and pulse rate should be measured after subjects are in a seated position for at least 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs, or as deemed necessary by the Investigator.

Additional vital signs measurements may be performed as deemed medically necessary by research personnel.

6.9.4 Physical Examinations

Physical examinations including height and weight measurements, will be conducted at the times noted on the appropriate events schedule (Table 15, Table 16, or Table 17).

6.9.5 Electrocardiograms

For Part 1, triplicate ECGs will be completed at screening, Day -1, 48 hours, and Day 8 or early withdrawal only. All other time points will be single ECG readings within 15 minutes of time points on Table 15.

The predose ECG will be performed prior to the predose blood draw. If a subject experiences a postdose QTcF >500 msec or a change from baseline QTcF >60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline.

For Cohort 7, all ECGs will be triplicate at each time point. In addition, subjects in will have triplicate ECGs at 16 hours postdose.

For Part 2, triplicate ECGs will be completed at screening, Day -1, Day 15 or early withdrawal only. All other time points on Table 16 will be single ECG readings. ECGs

may be done within 2 hours prior to time of dosing and at 6 hours after dosing on Days 1, 2, 3, 8, 12, 14, and on Days 42, 63, 84, 105, and 126.

For Cohorts 2 and 3, an additional ECG extraction will occur at 16 hours postdose on Day 1 and Day 14. For Cohort 3, all ECGs performed will be triplicate ECGs at each time point listed in Table 16.

For Part 3, triplicate ECGs will be completed with 15 minutes at all timepoints on Table 17.

NOTE: Where possible, ECG extractions should be taken from the continuous 12-lead ECGs (Holter).

The predose ECG should be completed within 1 hour prior to the predose blood draw. If a subject experiences a postdose QTcF >500 ms with a change from baseline QTcF >60 ms, after repeat testing, the Principal Investigator should be notified, and additional ECGs should be recorded until normalization or return to baseline.

6.9.6 Cardiac Holter Monitoring and Cardiodynamic Assessment

In order to detect potential changes in ECG parameters, study subjects will undergo cardiac Holter monitoring. ECG data will be analyzed focusing in particular on changes of the QT segment although other ECG parameters will be analyzed, as specified in the Statistical Analysis Plan (SAP).

On Day -1, subjects should fast until lunch to avoid circadian fluctuations.

For Part 1, continuous 12-lead ECGs (Holter) will be recorded for 1 hour prior to dose and continue for at least 24 hours post dose.

For Part 2, continuous 12-lead ECGs (Holter) will begin at least 1 hour before and end at least 24 hours after dosing first dose (Day 1) and start again at least 1 hour before and end at least 24 hours after dosing dose 14 (Day 15).

For Part 3, continuous 12-lead ECGs (Holter) will be recorded for 1 hour prior to dose and continue for at least 24 hours post dose.

The ECG waveforms will be stored for analysis as appropriate after the completion of the study. Replicate 12-lead ECGs will be extracted prior to dosing and serially after dosing by the central ECG laboratory at the time points shown in Table 15, Table 16, and Table 17. At each time point for ECG extraction, subjects should be resting in the supine position for at least 10 minutes.

NOTE: When ECG extractions from the continuous 12-lead ECGs (Holter) coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order.

Details regarding the equipment and methods to be used for continuous Holter extraction and analysis are provided in Appendix 4.

6.9.7 Other Safety Measures

Medical emergency personnel trained in advanced cardiac life support will be on site to monitor subjects during the confinement period in the research center. Emergency medical equipment including but not limited to intubation equipment and pulse oximetry shall be maintained on site to administer appropriate medical care should it be required.

Procedures will be completed as specified in this protocol unless contraindicated due to a reported AE.

7 ADVERSE EVENTS

Subjects will be monitored for any AEs from the signing of the consent form until the end-of-study visit. Adverse events for subjects who fail screening will be recorded in the source documents and maintained on site. The Investigator or a medically qualified designee will review each event. The Investigator or a Sub-Investigator will assess its relationship to the study drug. Each sign or symptom will be graded for severity, and the date and time of onset, cessation and resolution will be recorded. Treatment of any adverse reactions will be evaluated and managed by a physician, either at the study site or at a nearby hospital emergency room, as appropriate. All non-serious AEs will be reported on a regular basis or as specified by the Sponsor.

7.1 Definitions

7.1.1 Adverse Event

Any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a trial treatment whether or not considered related to trial treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

7.1.2 Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (any event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization; In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE;

- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption;
- Is a congenital anomaly/birth defect; or
- Is a medically important event.

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

7.2 Attribution/Causality

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product).

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Table 13 Adverse Event Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An adverse event, which is not related to the use of the drug.
Unlikely	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
Possible	An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable	An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

Table 14 Definitions for Adverse Event Severity Gradings

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-Threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

See Appendix 3 for full DMID Toxicity Tables. The above ratings should be used to estimate the grade for abnormalities NOT found elsewhere in the Toxicity Tables. Lab results within the testing facility's normal range will not be considered AEs when referenced to the DMID assessment/grading scale (Appendix 3).

Laboratory abnormalities and cardiovascular findings of hypertension or hypotension Grade 2 or above on the DMID toxicity tables will be considered AEs.

7.3 Reporting

7.3.1 Adverse Event

Adverse Events will be collected by the Investigator or qualified designee(s) from the time a subject signs the Informed Consent Form through the end-of-study. Any AE (serious or non-serious) observed by the Investigator (or a suitably medically qualified designee) or reported by the subject will be recorded on the Adverse Event Case Report Form (CRF). The Investigator will review each AE and assess its relationship to drug treatment based on all available information at the time of the completion of the CRF. The following information will be recorded for each Adverse Event reported:

- Diagnosis of the AE, if possible. In the case where an overall diagnosis cannot be made, each specific sign and/or symptom will be recorded as individual AEs;
- Date of onset;
- Stop date (with duration, if applicable);
- Severity;
- Action taken with IMP;
- Other action taken;
- Outcome;
- Relationship to IMP;
- Occurrence;
- Seriousness

7.4 Serious Adverse Event Reporting

The Investigator or designee will notify the appropriate Sponsor contact immediately after the SAE detection, observation, or report of occurrence (regardless of the relationship to test article). The Sponsor contact information for SAE reporting is provided below:

TB Alliance Pharmacovigilance
Email: AE_inbox@tballiance.org

Questions relative to SAE case processing may also be sent to the above-mentioned email address. If there is ever an email failure upon trying to report an SAE, please call Dr. Lombardi at 1-917-601-0024 and he will notify the Safety team at TB Alliance.

Medical questions relative to AEs or SAEs can be directed to:

Antonio (Tony) Lombardi, MD

Global Alliance for TB Drug Development

40 Wall Street, 24th Floor
New York, NY 10005, United States of America

Mobile: +1 917.601.0024
Email: Antonio.Lombardi-Consultant@tballiance.org

These SAE reports must contain the following information:

A. Study name/number
B. Study drug
C. Investigator details (name, phone, fax, e-mail)
D. Subject number
E. Subject demographics
F. Clinical event:
    1) Description
    2) Date of onset
    3) Treatment (drug, dose, dosage form)
    4) Adverse event relationship to study drug
    5) Action taken regarding study drug in direct relationship to the AE
G. If the AE was fatal or life-threatening
H. If applicable, cause of death (whether or not the death was related to study drug)
I. If applicable, autopsy findings (if available)

Any new SAE that occurs within one month after the study period and is considered to be possibly related to the Investigational Product (IP) should be recorded and reported immediately to the Sponsor.

The person responsible for the study shall take care that the study has been carried out in accordance with pharmacovigilance local regulations.

All serious event reporting will adhere to U.S. Code of Federal Regulations (21 CFR Part 312.32) for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The IRB will be notified of the alert reports per FDA regulations.

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the CRF.

The Sponsor will be responsible for reporting and processing any SAEs to the FDA or other applicable regulatory agency.

7.5 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- End of the follow-up period; and
- All queries on these AEs have been resolved.

Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases, follow-up will be the responsibility of the treating physician. However, this will have to be agreed upon with the Sponsor Medical Monitor.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Investigator should contact Sponsor/designee to discuss appropriate medical follow-up if consultation required.

If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide Sponsor/representative with a copy of any post-mortem findings including histopathology.

New or updated information on an SAE will be recorded in the originally completed CRF and submitted to Sponsor within 24 hours of the information becoming known per SAE reporting guidelines.

7.6 Post-Trial Serious Adverse Events

Any new SAEs reported by the subject to the Investigator that occur up to 30 days after last contact and are determined by the Principal Investigator to be possible, probable, or very likely related to the use of the IMP, will be reported to the Sponsor, IRB and FDA on an expedited basis as required in accordance with local requirements and International Council for Harmonisation (ICH) guidelines for GCP.

7.7 Clinical Laboratory Adverse Events

Changes in the results of the Clinical Laboratory assessment results which the Investigator feels are clinically significant will be reported as AEs. It is the Investigators' responsibility to review the results of all laboratory tests as they become available. This review must be documented by the Investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. All laboratory changes greater than or equal to Grade 2 must be reported as an AE regardless of clinical significance.

7.8 Drug Interaction

If the Investigator becomes aware that the subject has experienced a drug interaction which has resulted in an AE, it will be recorded as an AE.

7.9 Pregnancy

The Investigator will immediately notify the Sponsor of any pregnancy that is discovered during the clinical trial. Pregnancy forms will be completed for all pregnancies reported during the study or in the 30 days after completion of the IMP. In addition, the Investigator will report to the Sponsor follow up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for 6 months.

If pregnancy is suspected while the subject is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the subject withdrawn from the trial. Protocol-required procedures for trial discontinuation and follow up will be performed unless contraindicated by the pregnancy.

If the Investigator becomes aware the female partner of a male subject becomes pregnant during the study or in the 30 days after the completion of IMP, consent will be requested from the female partner for collection of information on her pregnancy history and for information on the current pregnancy and birth.

7.10 Monitoring and Safety for Specific Toxicities

During preclinical testing, issues with increased heart rate and lowering of blood pressure were detected. Therefore, heart rate and blood pressure changes should be monitored carefully. When abnormalities are detected both blood pressure and pulse rate should be captured simultaneously

8 GENERAL CONSIDERATIONS

8.1 Basic Principles

This research will be carried out in accordance with the protocol, the ICH, Guideline for Good Clinical Practice: Consolidated Guidance (E6), and applicable regulatory requirements(s) including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).

8.2 Institutional Review Board

This protocol will be reviewed by an appropriate IRB and study enrollment will not commence until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in 21 CFR Part 56.

8.3 Informed Consent

Written informed consent will be obtained from each subject prior to performing any baseline study-specific evaluations. The ICD is prepared by the Investigator or designee, subject to review and approval by the Sponsor, and forwarded to a qualified IRB for final review and approval. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent. Only the most recently IRB-approved ICD must be used to consent prospective study subjects. One copy of the signed and dated ICD will be given to the subject and the original retained by the Investigator/site.

8.4 Indications for Subject Withdrawal

Subjects will be free to withdraw at any time for any reason, or they may be withdrawn if necessary, to protect their health and safety or the integrity of the study data.

Subjects who discontinue may be replaced at the Principal Investigator and Sponsor's discretion. Subjects who have a positive urine drug, alcohol, or cotinine screen result will be evaluated on a case-by-case basis and the Principal Investigator and Sponsor will decide whether the subject will continue in the study or will be withdrawn.

The final report will include reasons for withdrawals. In the event of an early termination, subjects will undergo the procedures described in Section 6.8.

Subjects who experience emesis may be replaced if the emesis could potentially impact drug absorption and therefore the PK data. Cases of emesis will be evaluated by the Sponsor and Principal Investigator to determine if subject replacement is needed.

8.5 Termination of the Study

The Principal Investigator reserves the right to terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

8.6 Documentation

All documents pertaining to the study, including a copy of the approved protocol, copy of the ICD and Health Insurance Portability and Accountability Act (HIPAA) documents, completed CRFs (where applicable), drug accountability and retention

records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the subject of this investigation; or, if no application is to be filed or if the application is not approved for such indication, until two years following the date on which the entire study is completed, terminated, or discontinued, and the FDA is notified.

Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors, and auditors, the FDA, other government offices, and the IRB.

8.7 Trial Monitoring

Sponsor personnel (or designees) will be responsible for monitoring the study to ensure compliance with the protocol and GCP. Compliance may be verified by one or more of the following methods: on-site visits, frequent communication with the Investigator, and/or review of CRFs and source documents. The Investigator agrees to permit such monitoring as well as audits or reviews by regulatory authorities and the IRB.

8.8 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

9 PHARMACOKINETIC ANALYSIS

9.1 Analytical Methodology

Plasma samples will be analyzed for TBAJ-876, M2, and M3 using validated assays. Plasma samples from subjects who receive placebo for TBAJ-876 oral suspension will not be analyzed.

9.2 Pharmacokinetic Analysis

Final PK calculations will be performed using appropriate software, e.g., 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 or higher, or comparable product, Certara, L.P.]) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.).

PK parameters will be calculated using non-compartmental analysis. The following PK parameters will be determined as appropriate for each study part and analyte.

AUC_{Extrap} (%)	The percentage of extrapolated AUC to AUC_{inf} based on extrapolation (Parts 1 and 3)
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated for Parts 1 and 3 as: $AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule (Parts 1 and 3)
AUC_{tau}	Area under the concentration-time curve during the dosing interval; calculated using the linear trapezoidal rule (Part 2)
C_{avg}	Average concentration during the dosing interval (Part 2)
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data (Parts 1, 2, and 3)
CL/F	Apparent total clearance after single administration (Parts 1 and 3)
CLss/F	Apparent total clearance after multiple administration (Part 2)
C_{max}	Maximum concentration, determined directly from individual concentration-time data (Parts 1, 2, and 3)
R_{AUC}	Accumulation factor during multiple dosing, based on AUC_{tau} (Part 2)
R_{Cmax}	Accumulation factor during multiple dosing, based on C_{max} (Part 2)
T_{last}	Time of the last quantifiable concentration (Parts 1, 2, and 3)
T_{max}	Time of the maximum concentration (Parts 1, 2, and 3)
$T_{1/2}$	The observed terminal half-life, calculated for Parts 1, 2, and 3 as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
Vz/F	Apparent volume of distribution in the terminal phase (Parts 1, 2, and 3)

λ_z	The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile (Parts 1, 2, and 3)

Additional PK analysis and modeling with multiple compartment model may be performed and will be reported separately, if conducted.

Food effect: The effect of food will be assessed comparing PK parameters under fed versus fasting conditions using an analysis of variance (ANOVA) approach.

For Part 2, the following PK parameters will be calculated from plasma concentrations of TBAJ-876 following doses on Days 1 and 14:

- Day 1: AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{max}, and C_{avg} λz, $t_{1/2}$, CLss/F, and Vz/F may be calculated as reasonable).
- Day 14: AUC_{tau}, C_{max}, C_{min}, T_{max}, C_{trough}, C_{avg}, CLss/F, Vz/F, R_{AUC}, and R_{Cmax}. Parameters such as λz, and $t_{1/2}$ may be calculated as reasonable.

For Parts 1 and 2, PK parameters will be summarized by cohort using descriptive statistics. Dose proportionality will be assessed using the power model approach.[4]

For Part 3, the following PK parameters will be calculated for Group 1 (1 x 100 mg tablet, fasted), Group 2 (1 x 100 mg tablet, fed), and Group 3 (4 x 25 mg tablets, fasted):

C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{Extrap}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, and Vz/F.

PK parameters will be summarized by group using descriptive statistics. Food effect (Group 2, fed, 1 x 100 mg tablet vs. Group 1, fasted, 1 x 100 mg tablet) and relative bioavailability of the two fasted groups (Group 3, 4 x 25 mg tablets vs. Group 1, 1 x 100 mg tablet) will be assessed using an analysis of variance (ANOVA) approach.

Additional details will be provided in the Statistical Analysis Plan (SAP).

9.3 Statistical Analysis

Final statistical analyses will be performed using appropriate software, e.g. 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 or higher, Certara, L.P.]) and SAS® (Version 9.4 or higher, SAS Institute Inc.).

For Parts 1, 2, and 3, PK parameters will be summarized by cohort using descriptive statistics. Summary statistics will also be presented by gender within each cohort.

For Part 1, dose proportionality for exposure parameters (C_{max}, AUCs) will be assessed using a power model approach. Food effect will be assessed using an analysis of variance (ANOVA) with food condition as the fixed effect.

For Part 2, dose proportionality for exposure parameters (C_{max}, AUCs) will be assessed using a power model approach. Steady state for each dose level will be assessed using an appropriate statistical methodology.

For Part 3, Food effect will be assessed using an 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 details will be provided in the SAP.

10 FACILITIES

CLINICAL TRIAL SITE

Worldwide Clinical Trials Early Phase Services, LLC
2455 N.E. Loop 410, Suite 150
San Antonio, Texas 78217
Telephone: 210.635.1500
Fax: 210.635.1646

CLINICAL LABORATORIES

Worldwide Clinical Trials Early Phase Services, LLC
2455 N.E. Loop 410, Suite 150
San Antonio, Texas 78217
Telephone: 210.635.1500
Fax: 210.635.1646

ANALYTICAL LABORATORY

Alliance Pharma, Inc.
Bioanalytical Principal Investigator: Natalie Auman
Contact for Sample Shipment: Ruth Guan
17 Lee Boulevard
Malvern, PA 19355
Phone: 610.296.3152
Fax: 610.296.3153
Email: rguan@alliancepharmaco.com;
samples@alliancepharmaco.com
Web: www.alliancepharmaco.com

CARDIAC VENDOR

iCardiac Technologies, Inc.
150 Allens Creek Road
Rochester, New York 14618
Phone: 585.295.7610
Fax: 585.285.4130

11 DRUG SUPPLIES

Global Alliance for TB Drug Development will supply sufficient a quantity of the study drug, TBAJ-876 for preparation of TBAJ-876 Oral Suspension, TBAJ-876 tablets 25 mg, and TBAJ-876 tablets 100 mg. Study drug will be shipped to Worldwide Clinical Trials Early Phase Services, LLC pursuant to site SOPs. Upon receipt of the study drug, the study drug will be inventoried and stored in an environmentally controlled and secure, limited access area. For oral suspension, the suspending vehicle (also used as Placebo) and other supplies will be procured, inventoried, and stored appropriately by Worldwide Clinical Trials Early Phase Services, LLC pursuant to site SOPs.

The lot numbers of the study drug, vehicle, and other supplies along with the expiration dates (where available) will be recorded and copies of the Certificate of Analysis (where available) will be maintained on file. Records will be maintained of the receipt and dispensation of the drugs supplied.

Samples will be collected from each batch of test product (TBAJ-876 Oral Suspension and Placebo for TBAJ-876 Oral Suspension) and stored frozen until the clinical study report is issued. At the conclusion of the study, any unused study drug will be returned to the Sponsor or destroyed by the site pursuant to written authorization by the Sponsor and applicable federal and state regulations.

12 ADMINISTRATIVE ISSUES

The Investigator is referred to the Investigator Brochure, or information provided during the study initiation visit, information provided by the study monitor, and ICH Guidelines for Good Clinical Practice for information regarding the study drug, details, or general considerations to be followed during the course of this study.

13 EVENTS SCHEDULES

Table 15 Schedule of Assessments and Procedures, Part 1 SAD

PART 1	**SCR**		**CONFINEMENT**																													***FU**
STUDY DAY**	-28 to -2	-1 CI	DAY 1														DAY 2								3				4			5, 6, 7, 8	10, 14, 17, 21, 28
			STUDY HOUR																														
EVENT**			0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16[a]	20	24	28	30	32	36	40	42	44	48	54	60	66	72	80	88		N/A
Informed consent and medical history	X																																
Height	X																																
Weight	X	X																															
Physical examination	X	X															X								X							X	
Heart murmur[b]	X	X	X									X					X								X							X	
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)	X[c]	X	X[c]	X	X	X		X	X		X		X		X		X	X		X		X				X				X		X	X
12-lead safety ECGs	X[d]	X	X[d]	X	X	X	X	X	X	X	X	X	X		X	X[d]	X	X								X							X[d]	X[d]
HIV/hepatitis B, C	X																																

PART 1	**SCR**		**CONFINEMENT**																													***FU**
STUDY DAY**	-28 to -2	-1 CI	DAY 1														DAY 2									3				4			5, 6, 7, 8	10, 14, 17, 21, 28
			STUDY HOUR																														
EVENT**			0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16[a]	20	24	28	30	32	36	40	42	44	48	54	60	66	72	80	88		N/A
Clinical laboratory tests (hematology, chemistry, and urinalysis)[e]	X	X									X														X							X	X
Coagulation tests[e]	X	X									X														X							X	X
Urine drug, alcohol, cotinine screen	X	X																															X
Serum pregnancy (females only)	X	X																															
Urine pregnancy (females only)[f]																																	X
FSH (post-menopausal females only)	X																																
Concomitant medication review	X	←																															→
Check-in questions		X																															
Adverse events[g]			X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PART 1	**SCR**		**CONFINEMENT**																														***FU**
STUDY DAY**	-28 to -2	-1 CI	DAY 1														DAY 2									3				4			5, 6, 7, 8	10, 14, 17, 21, 28
			STUDY HOUR																														
EVENT**			0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16[a]	20	24	28	30	32	36	40	42	44	48	54	60	66	72	80	88		N/A
Breath strip application[h]			X																														
Dose			X																														
PK blood collection[i]			X	X	X		X	X	X	X	X		X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X
Cardiac Telemetry; 12 – lead Holter monitoring[j]			X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	X	X																
ECG extractions from Holter recording[k]			X	X	X	X	X	X	X	X	X	X	X		X			X																

CI = check-in; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening; T and R = temperature and respirations

* Available subjects from Cohorts 4 and 5, and all subjects in Cohort 6 will return bi-weekly (+/- 2 days) up to 10 weeks postdose. Subjects will complete the same procedures as required for Day 28 at each visit.

** Subjects in Cohort 7 will be discharged from the clinic on Day 8. Subjects will return for one follow-up visit on Day 14 for PK and safety. Subjects will receive a follow-up phone call on Day 21. Subjects will complete the procedures specified for those study days only.

a. The 16-hour time point following dosing on Day 1 will either be on Day 1 or Day 2, depending upon time of dosing on Day 1.

b. Heart Murmur: Presence of heart murmur

c. Vital signs (blood pressure, pule rate, temperature, respiration rate, and pulse oximetry) will be measured at screening and check-in (Day -1). Vitals signs will be measured within 90 minutes prior to dosing and within 15 minutes of the defined time points. Both blood pressure and pulse rate should be captured simultaneously. Blood pressure and pulse rate will be measured after subjects are in a seated position for at least 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs, or as deemed necessary by the Investigator.

d. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Triplicate ECGs will be completed at screening, Day -1, at 48 hours and on Day 8 or upon early withdrawal only. All other time points will be single ECG readings within 15 minutes of the time points. The first ECG Day 1 may be done within 2 hours prior to dosing and must be completed 20 minutes prior to the predose blood draw. All safety ECGs on Day 1 and Day 2 will be extracted from a continuous 12 lead Holter recording at discrete

timepoints as noted in above flow chart. If a subject experiences a postdose QTcF >500 msec or a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs will be recorded until normalization or return to baseline. All ECGs in Cohort 7 will be triplicate at each time point. In addition, subjects in Cohort 7 will have triplicate ECGs at 16 hours postdose.

e. Safety laboratory assessments will be done at check-in (Day -1), 6 and 48 hours postdose and on Days 5, 7, 10, 14, 17, 21, and 28. The following analyses will be performed:
   - Full blood cell count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, reticulocyte count, platelet count), reticulocyte count
   - Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
   - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect, and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO2, creatine phosphokinase (CPK), creatine phosphokinase myocardial band (CPK-MB), lipase, and amylase
   - Other laboratory tests: cardiac troponin I and glycosylated hemoglobin
   - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, myoglobin, blood, leukocytes). If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed. Myoglobin will be collected but results will not be required for dose qualification.

f. Female subjects will have a urine pregnancy test at the end-of-study on Day 28 or early withdrawal.

g. Subjects will be monitored from the time of signing the informed consent and throughout the study via safety assessments, observation and subject reporting. A specific inquiry regarding AEs will be conducted prior to dosing and at time points specified postdose and upon return to clinic for subsequent visits.

h. TBAJ-876 or Placebo for TBAJ-876 Oral Suspension will be administered orally followed by 240 mL of water. Listerine® strips will be used as a blinding agent. A strip will be added to the subject's tongue before and after each dose.

i. Subjects will be followed up for safety and PK during follow-up at the following timepoints: **Dose Level 1**: PK samples to be collected at pre-dose, 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. **Other Dose Level Cohorts:** scheduling of PK sample collection will be based on the PK data collected from previous cohorts and could involve a different sampling schedule and require subjects return to the clinic for up to 10 weeks or longer after dosing.

j. Continuous 12-lead Holter recording (cardiac telemetry) will begin 1 hour before and end 24 hours after dosing.

k. ECGs on Day 1 will be extracted from a continuous 12 lead Holter recording at discrete timepoints as noted in above flow chart and will be extracted at the same time as vital sign measurements. If a subject experiences a post-dosing QTcF >500 msec or a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline.
   NOTE: when ECG extractions coincide with safety ECGs, vital sign assessments, and/or blood draws, then procedures should be carried out in said order.

Table 16 Schedule of Assessments and Procedures, Part 2 MAD

PART 2	SCREEN	CHECK-IN[a]	CONFINEMENT[a]			FOLLOW-UP			EARLY WITHDRAWAL
DAY	-28 to -2	-1	1 to 20	7, 14	21	42	63, 84, 105, 126	133	
EVENT									
Informed consent	X								
Check-in questions		X							
Medical history	X								
Height, weight	X								
HIV/ Hepatitis B, C	X								
Serum pregnancy test[b]	X	X							
FSH[b]	X								
Urine pregnancy[c]							X		X
Urine drug/alcohol/ cotinine screen	X	X							
Safety Labs hematology, chemistry, urinalysis)[d]	X	X		X	X	X	X		X
Coagulation	X	X		X	X	X	X		X
Physical exam	X	X		X	X	X	X		X
Heart murmur[e]	X	X	X	X	X	X	X		X
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)[f]	X	X	X[f]	X	X	X	X		X
Concomitant medication review	X	X	X	X	X	X	X		X
Adverse events[g]		X	X	X	X	X	X	X	X
Breath strip application[h]			X[i]	X					
Dose[i]			X[i]	X					
12-lead safety ECGs[j]	X	X	X[j]		X	X	X		X
Plasma for pre-dose trough PK[k]			X[k]	X					
Plasma for Post-dose PK[l]			X[l]	X	X	X	X		

PART 2	SCREEN	CHECK-IN[a]	CONFINEMENT[a]			FOLLOW-UP			EARLY WITHDRAWAL
DAY	-28 to -2	-1	1 to 20	7, 14	21	42	63, 84, 105, 126	133	
EVENT									
Cardiac telemetry; 12-lead Holter monitoring[m]			X[m]	X[m]					
ECG extractions from Holter recording[n]			X[n]	X[n]					

CI = check-in; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening; T and R = temperature and respirations

a. Confinement to start at check-in (Day -1) until the completion of procedures on Day 21.
b. Serum pregnancy test done at screening and at check-in for females only. FSH completed for perimenopausal females only.
c. Female subjects will have a urine pregnancy test done at the end-of-study Day 126 or early withdrawal.
d. Safety laboratory assessments. The following analyses will be performed:
    - Full blood cell count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, reticulocyte count, platelet count)
    - Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect, and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO2, creatine phosphokinase (CPK), lipase, and amylase
    - Other laboratory tests: creatine phosphokinase of myocardial band (CPK-MB), cardiac troponin I and glycosylated hemoglobin
    - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, myoglobin, leukocytes). If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed. Myoglobin will be collected but results will not be required for dose qualification.
e. Heart murmur: Presence of heart murmur
f. Vital signs (blood pressure, pule rate, temperature, respiration rate, and pulse oximetry) will measured at screening and check-in (Day -1). Vital sign measurements will be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points at study hours 0, 1, 6, and 12 on Days 1 and 14. Furthermore, vital signs will also be taken once daily on Day 2 through Day 14 (6 hours after dosing) and once daily on Days 15-21 and Days 42, 63, 84, 105, and 126 and at early withdrawal (to be done within 15 minutes before review of medication and collection of adverse experiences). Both blood pressure and heart rate will be captured simultaneously. Blood pressure and heart rate will be measured after subjects are in a seated position for 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.
g. AEs will be monitored from the time of signing the informed consent throughout the study via safety assessments, observation and participant reporting. Specific AE questions will be posed daily throughout the study until Day 21 and on all follow-up visits including a phone call on Day 133.
h. TBAJ-876 or Placebo to TBAJ-876 Oral Suspension will be administered orally followed by 240 mL of water. Listerine® strips will be used as a blinding agent. A strip will be added to the subject's tongue before and after each dose.

i. Dosing will only occur on Days 1-14.

j. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Triplicate ECGs will be completed at screening, Day -1, and on Day 15 or upon early withdrawal. All other time points will be single ECG readings. ECGs may be done within 2 hours prior to time of dosing and at 6 hours after dosing on Days 1, 2, 3, 8, 12, 14, and on Days 21, 42, 63, 84, 105, and 126. The predose ECG will be completed within 1 hour prior to the predose blood draw. If a participant experiences a postdose QTcF >500 ms or a change-from-baseline QTcF >60 ms, after repeat testing, additional ECGs should be recorded until normalization or return to baseline. All ECGs in Cohort 3 will be triplicate at each time point. In addition, subjects in Cohort 3 will have triplicate ECGs at 16 hours postdose on Day 1 and Day 14.

k. Predose trough plasma samples will be drawn daily Days 1 through 14.

l. Postdose blood plasma samples will be drawn at the following timepoints:
   - Day 1: 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.

m. Continuous 12 lead Holter recording (cardiac telemetry) will begin at least 1 hour before and end at least 24 hours after dosing (Day 1) and start again at least 1 hour before and end at least 24 hours after dosing on Day 14.

n. ECGs extractions from the 12 lead Holter monitor will occur only on Days 1 and 14 at the following time points: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 20, and 24 hours postdose. If a subject experiences a post-dosing QTcF >500 msec or a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline. For Cohorts 2 and 3, an additional extraction will be done at the 16 hour time point on Days 1 and 14.

   NOTE: when ECG extractions coincide with safety ECGs, vital sign assessments, and/or blood draws, then procedures should be carried out in said order.

Table 17 Schedule of Assessments and Procedures, Part 3 BA

PART 3	**SCR**		**CONFINEMENT**																													***FU**
STUDY DAY	-21 to -2	-1 CI	DAY 1														DAY 2								3				4			5, 6, 7, 8	10, 14, 21
			STUDY HOUR																														
EVENT			0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16[a]	20	24	28	30	32	36	40	42	44	48	54	60	66	72	80	88		N/A
Informed consent and medical history	X																																
Height	X																																
Weight	X	X																															
Physical examination	X	X															X								X							X	
Heart murmur[b]	X	X	X									X					X								X							X	
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)	X[c]	X	X[c]	X	X	X		X	X		X		X		X		X	X		X		X				X				X		X	X
12-lead safety ECGs	X[d]	X	X[d]	X	X	X	X	X	X	X	X	X	X		X	X	X	X								X							X[d]	X[d]
HIV/hepatitis B, C	X																																

PART 3	**SCR**		**CONFINEMENT**																												***FU**
STUDY DAY	-21 to -2	-1 CI	DAY 1														DAY 2									3				4			5, 6, 7, 8	10, 14, 21
			STUDY HOUR																														
EVENT			0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16[a]	20	24	28	30	32	36	40	42	44	48	54	60	66	72	80	88		N/A
Clinical laboratory tests (hematology, chemistry, and urinalysis)[e]	X	X									X															X							X	X
Coagulation tests[e]	X	X									X															X							X	X
Urine drug, alcohol, cotinine screen	X	X																																X
Serum pregnancy (females only)	X	X																																
Urine pregnancy (females only)[f]																																		X
FSH (post-menopausal females only)	X																																	
Concomitant medication review	X	←																																→
Check-in questions		X																																
Adverse events[g]			X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PART 3	**SCR**		**CONFINEMENT**																														***FU**
STUDY DAY	-21 to -2	-1 CI	DAY 1															DAY 2								3				4			5, 6, 7, 8	10, 14, 21
			STUDY HOUR																															
EVENT			0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16[a]	20	24	28	30	32	36	40	42	44	48	54	60	66	72	80	88		N/A
Dose[h]			X																														
PK blood collection[i]			X	X	X		X	X	X	X	X		X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X
Cardiac Telemetry; 12 – lead Holter monitoring[j]			X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	X	X																
ECG extractions from Holter recording[k]			X	X	X	X	X	X	X	X	X	X	X		X			X																

CI = check-in; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening; T and R = temperature and respirations

* Subjects will return for follow-up visits on Day 10 and 14. Subjects will receive a follow-up phone call on Day 21.

a. The 16-hour time point following dosing on Day 1 will either be on Day 1 or Day 2, depending upon time of dosing on Day 1.

b. Heart Murmur: Presence of heart murmur

c. Vital signs (blood pressure, pule rate, temperature, respiration rate, and pulse oximetry) will be measured at screening and check-in (Day -1). Vitals signs will be measured within 90 minutes prior to dosing and within 15 minutes of the defined time points. Both blood pressure and pulse rate should be captured simultaneously. Blood pressure and pulse rate will be measured after subjects are in a seated position for at least 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs, or as deemed necessary by the Investigator.

d. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Triplicate ECGs will be completed at screening, Day -1, each time point listed, and on Day 8 or upon early withdrawal. ECG readings will be within 15 minutes of the time points. The first ECG Day 1 may be done within 2 hours prior to dosing and must be completed 20 minutes prior to the predose blood draw. All safety ECGs on Day 1 and Day 2 will be extracted from a continuous 12 lead Holter recording at discrete timepoints as noted in above flow chart. If a subject experiences a postdose QTcF >500 msec or a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs will be recorded until normalization or return to baseline.

e. Safety laboratory assessments will be done at check-in (Day -1), 6 and 48 hours postdose and on Days 5, 7, 10, and 14. The following analyses will be performed:

- Full blood cell count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, reticulocyte count, platelet count), reticulocyte count
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect, and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO2, creatine phosphokinase (CPK), creatine phosphokinase myocardial band (CPK-MB), lipase, and amylase
- Other laboratory tests: cardiac troponin I and glycosylated hemoglobin
- Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, myoglobin, blood, leukocytes). If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed. Myoglobin will be collected but results will not be required for dose qualification.

f. Female subjects will have a urine pregnancy test at the end-of-study on Day 14 or early withdrawal.

g. Subjects will be monitored from the time of signing the informed consent and throughout the study via safety assessments, observation and subject reporting. A specific inquiry regarding AEs will be conducted prior to dosing and at time points specified postdose and upon return to clinic for subsequent visits.

h. TBAJ-876 Tablet will be administered orally with 240 mL of water.

i. Subjects will be followed up for safety and PK during follow-up at the following timepoints: pre-dose, 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 and 14.

j. Continuous 12-lead Holter recording (cardiac telemetry) will begin 1 hour before and end 24 hours after dosing.

k. ECGs on Day 1 will be extracted from a continuous 12 lead Holter recording at discrete timepoints as noted in above flow chart and will be extracted at the same time as vital sign measurements. If a subject experiences a post-dosing QTcF >500 msec or a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline.
NOTE: when ECG extractions coincide with safety ECGs, vital sign assessments, and/or blood draws, then procedures should be carried out in said order.

14 REFERENCES

1. Investigator's Brochure, TBAJ-876, TB Alliance, version 1.0, effective 19 Mar 2020.
2. Package insert: Sirturo. Janssen Therapeutics, September 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf.
3. FDA Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
4. Smith, B, Vandenhende, F, DeSante, K, Farid, N, Welch, P, Callaghan, J & Forgue, S. (2000). Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research. 17. 1278-1283. 10.1023/A:1026451721686.
5. FDA Food-Effect Guidance [https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf].

APPENDIX 1 PHARMACOKINETIC SAMPLE COLLECTION, PROCESSING, AND SHIPMENT INSTRUCTIONS

Collection and Processing

A more detailed description of plasma sample preparation requirements may be provided by the analytical laboratory. If such a description is provided, the method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the Investigator Site File (ISF).

Processing Instructions	
1	Samples will be collected via direct venipuncture at the time points delineated in the appropriate Events Schedule (Section 13).
2	Blood will be drawn into pre-chilled 4 mL evacuated tubes containing K_3-EDTA and immediately placed on wet ice and then processed to plasma within 60 minutes.
3	Samples will be centrifuged at 1500 g at approximately 4°C (± 10 degrees) for 10 minutes. After centrifugation, two aliquots of plasma (the first containing at least 0.5 mL and the second containing the remainder of the plasma) will be removed and placed in appropriately labeled 1 mL polypropylene vials.
4	The aliquots will be immediately placed on dry ice. Within 90 minutes of collection, the aliquots will be stored in a freezer set at -80°C ± 10°C and remain in the freezer until transferred for analysis.
5	Samples will be transferred at the agreed upon intervals.
6	The aliquots will be transferred on dry ice to the Alliance Pharma, Inc. bioanalytical laboratory for the determination of plasma concentrations of TBAJ-876 and its metabolites (M2 and M3) using a validated procedure at Alliance Pharma.
7	Blood sampling, plasma processing, and storage time will be documented in the study records.

Labeling of aliquot tubes

Labels will contain at least the following information:

a) Study number

b) Subject identification

c) Period or dosing phase; sampling time (relative to dosing)

d) Aliquot letter (a or b)

Shipment

1. The samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. The second set of samples will be shipped after the bioanalytical laboratory confirms receipt of the first set of samples.
2. Samples will be packaged into cryoboxes and sorted by subject
3. Before shipment, the samples will be appropriately packed in a cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 72 hours.
4. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. Expected samples that are not present will be identified.
5. All frozen pharmacokinetic samples will be transferred with accompanying documentation to:

   Alliance Pharma, Inc.
   17 Lee Blvd
   Malvern, PA 19355
   Telephone: 610.296.3152
   Fax: 610.296.3153
   Contact name: Ruth Guan
   Contact E-mail: rguan@alliancepharmaco.com
   samples@alliancepharmaco.com

APPENDIX 2 DESCRIPTION AND COMPOSITION OF TEST PRODUCT

Description of the Dosage Form

TBAJ-876 Oral Suspension is a compounded preparation at 5 mg/mL TBAJ-876 as tartrate, in ORA-Sweet®. The suspension is compounded at the clinical study site with TBAJ-876 tartrate and ORA-Sweet®, a commercially available flavored suspending vehicle.

Placebo for TBAJ-876 Oral Suspension is ORA-Sweet®, the same flavored vehicle used in the active oral suspension (without TBAJ-876). The placebo suspension, 100% ORA-Sweet®, is purchased commercially by the clinical site.

The required doses of the suspension drug product are dispensed using commercially available oral syringes of suitable capacity.

TBAJ-876 Tablets 25 mg are white to off white, round uncoated tablets, plain on both sides.

TBAJ-876 Tablets 100 mg are white to off white, capsule-shaped uncoated tablets, plain on both sides.

Composition of the Drug Product

TBAJ-876 Oral Suspension

The quantitative composition, function, and quality of each ingredient in the drug product (TBAJ-876 Oral Suspension, 5 mg/mL) is provided in the table below.

Qualitative and Quantitative Composition of the TBAJ-876 Oral Suspension, 5 mg/mL

Ingredient	Function	Quality Standard	Quantity in 5 mg/mL	Quantity per Dose					
				10 mg	25 mg	50 mg	100 mg	200 mg	400 mg
TBAJ-876 Tartrate[1], equivalent to TBAJ-876	Drug Substance	In-house	0.5 g	10 mg	25 mg	50 mg	100 mg	200 mg	400 mg
ORA-Sweet®[2]	Flavored Oral Suspending Vehicle	Commercially available	q.s to 100 mL	q.s. to 2 mL	q.s. to 5 mL	q.s. to 10 mL	q.s. to 20 mL	q.s. to 40 mL	q.s. to 80 mL
Total Volume			100 mL	2 mL	5 mL	10 mL	20 mL	40 mL	80 mL

[1]TBAJ-876 equivalent calculated using the assay value of free base from the certificate of analysis.

$$Quantity\ of\ Tartrate\ salt\ (g) = \frac{5\ \frac{\text{mg}}{\text{mL}} * 100\ \text{mL(volume of suspension)}}{\frac{\%\ \text{assay value as free base}}{100} * 1000\ \frac{\text{mg}}{\text{g}}}$$

[2]Purified water, sucrose, glycerin, sorbitol, and flavoring. Buffered with citric acid and sodium phosphate. Preserved with methylparaben and potassium sorbate.

TBAJ-876 Tablets

Each 25 mg tablet contains 25 mg of TBAJ-876 equivalent to 30.7 mg of TBAJ-876 tartrate. Each 100 mg tablet contains 100 mg of TBAJ-876 equivalent to 122.8 mg of TBAJ-876 tartrate. The composition of the tablets is as follows: lactose monohydrate, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. The formulation of the two strengths of tablets is identical and dose proportional.

Container and Closure System

TBAJ-876 tartrate drug substance is shipped to the clinical study site in double LDPE bags, with each bag individually twist-tied. The bags are then placed in an aluminum foil polybag with a silica gel pack in the foil bag, and heat-sealed.

TBAJ-876 Oral Suspension is transferred and stored in Pyrex glass reagent bottles with a polypropylene (PP) screw cap without a liner. These bottles are used for mixing, sampling, and storage prior to administration.

TBAJ-876 Tablets 25 mg are packaged as 30-count in 30 cc round high-density polyethylene (HDPE) bottles induction sealed and with 28 mm polypropylene (PP) child resistant closures (CRC). TBAJ-876 Tablets 100 mg are packaged as 30-count in 40 cc round HDPE bottles induction sealed and with 33 mm PP CRC. The tables are stored at 15-30 °C (59-86 °F).

APPENDIX 3 DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASE TOXICITY TABLE

Division of Microbiology and Infectious Disease (DMID) Toxicity Table

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of Patients in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.

- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria*	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

*Assessment does not apply if a subject is on menses.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment[1]	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	BP, No treatment required[1]			
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

1) For protocol TBI-223-CL-001, defined as increase from baseline in predose vital signs.

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

APPENDIX 4 HOLTER RECORDING AND ANALYSIS

Continuous 12-lead ECGs (Holters) will be recorded using the Mortara Surveyor system.

The continuous 12-lead digital ECG data will be stored and transmitted to iCardiac using the appropriate medium (e.g., file transfer protocol [FTP], disc, or flash drive). ECGs to be used in the analyses will be selected by pre-determined time points as defined in the Schedule of Assessments and Procedures, and will be read centrally by iCardiac Technologies, Inc.

The following principals will be followed in iCardiac's core laboratory:

- ECG analysts are blinded to the subject, visit and treatment allocation
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods utilized by iCardiac' core laboratory.

TQT Plus ECG Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the "TQT Plus method", a computer-assisted and statistical process utilized by iCardiac Technologies. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (e.g., the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

High-Precision QT Analysis

High-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc or RR from beat to beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" is performed using COMPAS software. All low confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR value from each extracted replicate is

calculated, and then the mean of all available medians from a nominal timepoint is used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

T-wave morphology categories (assessed manually)

Category	Description
Normal T-wave	Any T-wave not meeting any criterion below
Flat T-waves	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave

In addition to the T-wave categorical analysis, the presence of abnormal U-waves is noted.