PROTOCOL CLARIFICATION LETTER (29 July 2022)

A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects

TB Alliance PROTOCOL NO. TBAJ-876-CL002
TKL STUDY NO. P1980322
Version 1.0
Dated: 20-May-2022

The purpose of this protocol clarification letter is to update vital signs footnote, exclusion criteria, PK sampling time windows, Section 7.6.3 Vital Signs, and Section 7.6.5 Electrocardiograms.

Antonio (Tony) Lombardi, MD
Medical Officer

DocuSigned by:
Antonio Lombardi, MD
Signature
Signer Name: Antonio Lombardi, MD
Signing Reason: I approve this document
Signing Time: 8/1/2022 | 5:21:53 AM PDT
AAFDCEAAD2874D3382507893E2EDC27C

8/1/2022
Date

Suraj Saggar, MD
Principal Investigator

DocuSigned by:
Suraj Saggar, MD
Signature
Signer Name: Suraj Saggar, MD
Signing Reason: I approve this document
Signing Time: 7/30/2022 | 5:35:22 PM PDT
EC25660513764F079145B13EC902277D

7/30/2022
Date

Irina Krause, RN, MSN
Senior Director, Phase I Operations

DocuSigned by:
Irina Krause, RN, MSN
Signature
Signer Name: Irina Krause, RN, MSN
Signing Reason: I approve this document
Signing Time: 7/29/2022 | 9:55:32 AM EDT
0D9920D912154147852ACDECEE722A44

7/29/2022
Date

1. Updated Footnote g

Current footnote per PCL dated 13-July-2022:

g. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in (Day -1).
Furthermore, vital signs should also be taken once daily on Days 3-5, Days 7 - 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes before review of medication and collection of adverse experiences).
Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.
Orthostatic blood pressure and heart rate should be measured at study hours pre-dose, 2, 6 and 12 on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.
Both blood pressure and heart rate should be captured simultaneously.

Revised footnote:

g. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in (Day -1).
Furthermore, vital signs should also be taken once daily on Days 3-5, Days 7 - 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes ~~**before review**~~ of medication and collection of adverse experiences **review**).
Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.
Orthostatic blood pressure and heart rate should be measured at study hours pre-dose, 2, 6 and 12 on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.
Both blood pressure and heart rate should be captured simultaneously.

2. Updated Exclusion Language (Exclusion Section 5.2)

Current Exclusion #9:

9. Subjects with the following laboratory abnormalities at screening or Day -1:
a. ALT or AST >1.0 times upper limit of normal (ULN)
b. Creatinine grade 2 or greater (>1.5 times ULN)
c. Total lipase or amylase >1.0 times ULN
d. Total bilirubin grade 1 or greater (>1.0 times ULN)
e. CPK >1.25 times ULN

If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.

Revised Exclusion #9:

9. Subjects with the following laboratory abnormalities at screening or Day -1:

a. ALT or AST **grade 2 or greater** (**≥2.0** times upper limit of normal ULN)
b. Creatinine grade 2 or greater (**≥1.6** times ULN)
c. Total lipase or amylase ≥**1.6** times ULN
d. Total bilirubin grade **2** or greater (≥**1.5** times ULN)
e. CPK >1.25 times ULN
f. Glomerular Filtration Rate (eGFR) <60 ml/min/1.73m2

If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.

Current Exclusion #13:

13. Heart rate is lower than 60 beats per minute (bpm) or higher than 100 bpm at screening, Day -1 (check-in), or pre-dose. 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.

Revised Exclusion #13:

13. **Clinically significant heart rate abnormalities such as heart** rate is lower than 60 beats per minute (bpm) or higher than 100 bpm at screening, Day -1 (check-in), or pre-dose. 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.

3. Updated Table 7 Acceptable Pharmacokinetic Sampling Time Windows

Current Table 7:

Table 1 Acceptable Pharmacokinetic Sampling Time Windows

Investigation and Examination	**Allowable Time Window**		
	Pre-dose	**0-24 hours**	**>24 hours to Day 25**
Plasma sample collection for pharmacokinetic assessment	Within 1 hour pre-dose	+- 5 minutes	+- 15 minutes

Revised Table 7:

Table 2 Acceptable Pharmacokinetic Sampling Time Windows

Investigation and Examination	**Allowable Time Window**		
	Pre-dose	**Timepoints 0-24 hours**	**Timepoints >24 hours ~~to Day 25~~**
Plasma sample collection for pharmacokinetic assessment	Within 1 hour pre-dose	+- 5 minutes	+- 15 minutes

4. Updated Section 7.6.3 Vital Signs

Current wording per PCL dated 23-June-2022:

Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in, Day -1.

Furthermore, vital signs should also be taken once daily on Day 3-5, 7 through Day 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes before review of medication and collection of adverse experiences).

Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.

Orthostatic blood pressure and heart rate should be measured at study hours Pre-dose, 2, 6 and 12 on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.

Both blood pressure and heart rate should be captured simultaneously.

Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in, Day -1.

Furthermore, vital signs should also be taken once daily on Day 3-5, 7 through Day 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes ~~**before review**~~ of medication and collection of adverse experiences **review**).

Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.

Orthostatic blood pressure and heart rate should be measured at study hours Pre-dose, 2, 6 and 12 on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.

Both blood pressure and heart rate should be captured simultaneously.

5. Updated Section 7.6.5 Electrocardiograms

Current Wording:

Group 1

Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 3, 7, 20, 21, 22 and on Day 25 or upon early withdrawal**.** The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

Group 2

Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 7, 20, 21 and 25 or upon early withdrawal. The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

Revised Wording:

Group 1

Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 3, 7, 20, 21, 22 and on Day 25 or

upon early withdrawal**.** The pre-dose ECG should be completed ~~**within**~~ **at least** 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

Group 2

Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 7, 20, 21 and 25 or upon early withdrawal. The pre-dose ECG should be completed ~~**within**~~ **at least** 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

PROTOCOL CLARIFICATION LETTER (13 July 2022)

A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects

TB Alliance PROTOCOL NO. TBAJ-876-CL002
TKL STUDY NO. P1980322
Version 1.0
Dated: 20-May-2022

The purpose of this protocol clarification letter is to update vital signs footnote, exclusion criteria, and administration of TBAJ-876 oral suspension language.

Antonio (Tony) Lombardi, MD
Medical Officer

DocuSigned by:
Antonio Lombardi, MD
Signature
7/13/2022
Date
Signer Name: Antonio Lombardi, MD
Signing Reason: I approve this document
Signing Time: 7/13/2022 | 2:47:04 PM PDT
AAFDCEAAD2874D3382507893E2EDC27C

Suraj Saggar, MD
Principal Investigator

DocuSigned by:
Suraj Saggar, MD
Signature
7/15/2022
Date
Signer Name: Suraj Saggar, MD
Signing Reason: I approve this document
Signing Time: 7/15/2022 | 6:22:11 AM PDT
EC25660513764F079145B13EC902277D

Irina Krause, RN, MSN
Senior Director, Phase I Operations

DocuSigned by:
Irina Krause, RN, MSN
Signature
7/13/2022
Date
Signer Name: Irina Krause, RN, MSN
Signing Reason: I approve this document
Signing Time: 7/13/2022 | 4:13:39 PM EDT
0D9920D912154147852ACDECEE722A44

1. Updated the Schedule of Assessments & Procedures, Group 1: Midazolam, Digoxin Table, Section 1.2 Flow Chart; Footnotes a, d, g

Current footnotes per PCL dated 23-June-2022:

a. Confinement to start at check-in (Evening of Day 1) until 24 hours after dosing on Day 25.

d. Safety laboratory assessments. The following analyses will be performed at the following timepoints: **Screening, Day -1, Day 2, Day 3, Day 7, Day 20, Day 21, Day 22, and Day 25.**

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect, and total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na+), potassium (K+), chloride (CL-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, magnesium, and bicarbonate, lipase, and amylase
- **Note:** ***If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN), according to FDA guidance criteria (see Appendix 3), the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB) and cardiac troponin T I.***
- 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, blood, myoglobin, leukocyte esterase. If protein, occult blood, nitrate, 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 **Breathalyzer** Screens - Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates) cotinine, and alcohol **at screening and check-in only.**

g. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in (Day -1).
Furthermore, vital signs should also be taken once daily on Days 3-5, Days 7 - 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes before review of medication and collection of adverse experiences).

Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in ~~f~~lowchart **at study hours pre-dose, 0, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.**

Orthostatic blood pressure and heart rate should be measured at study hours pre-dose, 2, 6 and 12 ~~time points~~ on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.

Both blood pressure and heart rate should be captured simultaneously.

Revised footnotes:

a. Confinement to start at check-in (Evening of **Day -1**) until 24 hours after dosing on **Day 24**.

d. Safety laboratory assessments. The following analyses will be performed at the following timepoints: **Screening, Day -1, Day 2, Day 3, Day 7, Day 20, Day 21, Day 22, and Day 25.**

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect, and total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na+), potassium (K+), chloride (CL-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, magnesium, and bicarbonate, lipase, and amylase
- **Note:** ***If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN), according to FDA guidance criteria (see Appendix 3), the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB) and cardiac troponin T ~~I~~.***
- 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, blood, myoglobin, leukocyte esterase. If protein, occult blood, nitrate, 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, **Urine** Cotinine, and Alcohol Breathalyzer Screens - Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates) **and** cotinine**, in conjunction with an alcohol breathalyzer.~~, and alcohol~~ These tests will be performed at screening and check-in only.**

g. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in (Day -1).
Furthermore, vital signs should also be taken once daily on Days 3-5, Days 7 - 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes before review of medication and collection of adverse experiences).
Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose~~, 0~~, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.
Orthostatic blood pressure and heart rate should be measured at study hours pre-dose, 2, 6 and 12 on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.
Both blood pressure and heart rate should be captured simultaneously.

2. Updated Exclusion Language (Exclusion Section 5.2)

Current Exclusion #15 per PCL dated 23-June-2022:

15. QTcF interval >450 ms for males or >470 ms for females at screening, Day -1, or Day 2 (pre-dose), or history of prolonged QT syndrome. PR interval < 200 ms at screening, Day -1, or Day 2 pre-dose. Out of range values may be repeated twice for confirmation. The average QTcF or PR intervals of the three ECG recordings will be used to determine qualification.

Revised Exclusion #15:

15. QTcF interval >450 ms for males or >470 ms for females at screening, Day -1, or Day 2 (pre-dose), or history of prolonged QT syndrome. PR interval **> 200 ms** at screening, Day -1, or Day 2 pre-dose. Out of range values may be repeated twice for confirmation. The average QTcF or PR

intervals of the three ECG recordings will be used to determine qualification.

3. Administration of TBAJ-876 Oral Suspension, Section 6.1

Current Wording:

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 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.

Refer to Appendix 2: Description and Composition of Investigational Medicinal Product (IMP) for details.

Each dose of 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.

Revised Wording:

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 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.**~~

Refer to Appendix 2: Description and Composition of Investigational Medicinal Product (IMP) for details.

Each dose of TBAJ-876 Oral Suspension will be administered orally followed by approximately 240 mL of room temperature water. **The TBAJ-876 doses from the oral syringes may be transferred to a dosing container for the subjects to swallow. The dosing container will be**

rinsed with a portion of the approximately 240 mL of water, swallowed by the subject and followed by the remainder of the approximately 240 mL 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.

PROTOCOL CLARIFICATION LETTER (23 June 2022)

A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects

TB Alliance PROTOCOL NO. TBAJ-876-CL002
TKL STUDY NO. P1980322
Version 1.0
Dated: 20-May-2022

The purpose of this protocol clarification letter is to update the schedule of assessments and accompanying footnotes, inclusion/exclusion criteria, restrictions, check-in procedures, laboratory parameters, vital signs language, physical examination language, electrocardiograms language, PK processing instructions, plasma processing instructions, and tables for cardiovascular and laboratory abnormalities.

Antonio (Tony) Lombardi, MD
Medical Officer

DocuSigned by:
Antonio Lombardi
Signer Name: Antonio Lombardi
Signing Reason: I approve this document
Signing Time: June 23, 2022 | 2:37 PM PDT
AAFDCEAAD2874D3382507893E2E[illegible]

Signature — June 23, 2022 | 2:37 PM PDT — Date

Suraj Saggar, MD
Principal Investigator

DocuSigned by:
Suraj Saggar
Signer Name: Suraj Saggar
Signing Reason: I approve this document
Signing Time: June 24, 2022 | 12:27 PM EDT
EC25660513764F079145B13EC902277D

Signature — June 24, 2022 | 12:27 PM EDT — Date

Irina Krause, RN, MSN
Senior Director, Phase I Operations

DocuSigned by:
Irina Krause
Signer Name: Irina Krause
Signing Reason: I approve this document
Signing Time: June 24, 2022 | 7:33 AM EDT
0D9920D912154147852ACDECEE722A44

Signature — June 24, 2022 | 7:33 AM EDT — Date

1. **Updated the Schedule of Assessments & Procedures, Group 1: Midazolam, Digoxin Table, Section 1.2 Flow Chart**

Current Table and Footnotes:

Table 1.2.1: Schedule of Assessments & Procedures, Group 1: Midazolam, Digoxin

	SCR	CHECK-IN	TREATMENT									CHECK-OUT	FOLLOW UP	
DAY	-21 to -1	-1	1	2-5	6-16	17	18	19	20	21	22-24	25	32	EARLY WITHDRAWAL
Informed consent	X													
Check-in questions		X												
Medical history	X													
Height, weight, BMI	X	X												
HIV/ Hepatitis B, C	X													
Serum pregnancy test[b]	X	X										X		
FSH[b]	X													
Urine drug/alcohol/ cotinine screen	X	X												
Safety Labs hematology, chemistry, urinalysis)[c]	X	X		X	X				X	X	X	X		X
Coagulation[c]	X	X		X	X				X	X	X	X		X
Physical exam	X	X		X								X		X
Heart Murmur[d]	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs (blood pressure, pulse, temperature,	X	X	X	X	X	X	X	X	X	X	X	X		X

	SCR	CHECK-IN	TREATMENT									CHECK-OUT	FOLLOW UP	
DAY	-21 to -1	-1	1	2-5	6-16	17	18	19	20	21	22-24	25	32	EARLY WITHDRAWAL
respiration rate, and pulse oximetry)[e]														
Concomitant medication review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[g]		X	X	X	X	X	X	X	X	X	X	X	X	X
Midazolam Dose[h]			X						X					
Digoxin Dose[i]				X						X				
TBAJ-876[j]					X	X	X	X	X	X	X			
12-lead safety ECGs[k]	X	X		X	X				X	X	X	X		X
Plasma for PK[l]			X	X		X			X	X	X	X		

SCR=screening; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening

a. Confinement to start at check-in (Evening of Day 1) until 24 hours after dosing on Day 25.
b. Serum pregnancy test done at screening, check-in, and Day 25 for females only. FSH completed for perimenopausal females only.
c. Safety laboratory assessments. The following analyses will be performed at the following timepoints: **Screening, Day -1, Day 2, Day 3, Day 7, Day 20, Day 21, Day 22, and Day 25.**

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect, and total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na+), potassium (K+), chloride (CL-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, magnesium, and bicarbonate, lipase, and amylase
- **Note:** ***If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN), according to FDA guidance criteria (see Appendix 3), the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB), trypsin like immunoreactivity, and cardiac troponin I.***

- 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, blood, myoglobin, leukocyte esterase. If protein, occult blood, nitrate, 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.

d. Heart murmur: Presence of heart murmur
e. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in, Day -1. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart **at study hours 0, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.** Furthermore, vital signs should also be taken once daily on Day 7 through Day 20 (6 hours after Dosing) and Day 25 or early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences). Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should be measured after subjects are in supine position for at least 2 minutes and then again after standing for at least 1 minute (starting with 2-hr post dose VS), except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.
f. On Day 32, follow-up questioning on concomitant medications will be completed by a phone call.
g. Adverse events to be monitored from the time of informed consent signing throughout the study via safety assessments, observation, and participant reporting. Specific adverse event questions will be posed daily throughout the study until Day 25 and a follow-up phone call on Day 32.
h. Midazolam Dose on Day 1 and Day 20 under fasted conditions
i. Digoxin Dose on Day 2 and Day 21 under fasted conditions
j. TBAJ-876 will be dosed as following:
    a. 200 mgTBAJ-876 on Day 6 - 13 under fed conditions
    b. ***165 mg TBAJ-876 on Day 14 – 19 under Fed conditions***
    c. ***200 mg TBAJ-876 on Day 20 - 21 under fasted conditions***
    d. 150 mg TBAJ-876 on Day 22 - 24 under fed conditions
k. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single **ECGs will be completed at screening, Day -1, 2, 3, 7, 20, 21, 22 on Day 25 or upon early withdrawal. Furthermore, ECGs should also be taken on Digoxin dosing days, on Day 2 and Day 21, at study hours 0, 0.5, 1, 2, 6, and 12** within 15 minutes of the defined time points**.** The pre-dose ECG should be completed within 90 minutes prior to dosing and all ECGs should be completed prior to blood draws. If a participant experiences a post-dosing 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
l. Blood plasma samples will be drawn at the following timepoints:
    - **Midazolam: Day 1 and Day 20**: pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours
    - **TBAJ-876: Day 17**: pre-dose, 0.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24 hours
    - **Digoxin:**
        - **Day 2:** pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 3), 48 (D4), 72 (D5), 96 (D6) hours

- **Day 21:** pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (D22), 48 (D23), 72 (D24), 96 (D25)

Revised table and footnotes:

	SCR	CHECK-IN	TREATMENT									CHECK-OUT	FOLLOW UP	
DAY	**-21 to -2**	-1	1	2-5	6-16	17	18	19	20	21	22-24	25	32	EARLY WITHDRAWAL
Informed consent	X													
Check-in questions		X												
Medical history	X													
Height, weight, BMI[b]	X	X												
HIV/ Hepatitis B, C	X													
Serum pregnancy test[c]	X	X										X		
FSH[c]	X													
Urine drug/alcohol **breathalyzer**/ **urine** cotinine screen	X	X												
Safety Labs hematology, chemistry, urinalysis)[d]	X	X		X	X				X	X	X	X		X
Coagulation[d]	X	X		X	X				X	X	X	X		X
Physical exam[e]	X	X		X							**X**	X		X
Heart Murmur[f]	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs (blood pressure,	X	X	X	X	X	X	X	X	X	X	X	X		X

	SCR	CHECK-IN	TREATMENT									CHECK-OUT	FOLLOW UP	
DAY	**-21 to -2**	-1	1	2-5	6-16	17	18	19	20	21	22-24	25	32	EARLY WITHDRAWAL
pulse, temperature, respiration rate, and pulse oximetry)[g]														
Concomitant medication review[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Midazolam Dose[j]			X						X					
Digoxin Dose[k]				X						X				
TBAJ-876[l]					X	X	X	X	X	X	X			
12-lead safety ECGs[m]	X	X		X	X				X	X	X	X		X
Plasma for PK[n]			X	X		X			X	X	X	X		

SCR=screening; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening

a. Confinement to start at check-in (Evening of Day 1) until 24 hours after dosing on Day 25.
b. **Height will be done at screening only and used for BMI calculation at screening and day -1 check in.**
c. Serum pregnancy test done at screening, check-in, and Day 25 for females only. FSH completed for **postmenopausal** females only.
d. Safety laboratory assessments. The following analyses will be performed at the following timepoints: **Screening, Day -1, Day 2, Day 3, Day 7, Day 20, Day 21, Day 22, and Day 25.**

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect, and total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na+), potassium (K+), chloride (CL-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, magnesium, and bicarbonate, lipase, and amylase

- **Note:** ***If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN), according to FDA guidance criteria (see Appendix 3), the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB) and cardiac troponin T ~~I~~.***
- 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, blood, myoglobin, leukocyte esterase. If protein, occult blood, nitrate, 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 **Breathalyzer** Screens - Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates) cotinine, and alcohol **at screening and check-in only.**

e. **Physical exam will be performed on Screening, Check-in (Day-1), Day 3, Day 22, and Day 25.**
f. Heart murmur: Presence of heart murmur
g. **Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in (Day -1).**
Furthermore, vital signs should also be taken once daily on Days 3-5, Days 7 - 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes before review of medication and collection of adverse experiences).

Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose, 0, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.

Orthostatic blood pressure and heart rate should be measured at study hours pre-dose, 2, 6 and 12 ~~time points~~ on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.

Both blood pressure and heart rate should be captured simultaneously.

h. On Day 32, follow-up questioning on concomitant medications **and adverse events** will be completed by a phone call.
i. Adverse events to be monitored from the time of informed consent signing throughout the study via safety assessments, observation, and participant reporting. Specific adverse event questions will be posed daily throughout the study until Day 25 ~~**within**~~ ± 15 minutes and a follow-up phone call on Day 32.
j. Midazolam Dose on Day 1 and Day 20 under fasted conditions
k. Digoxin Dose on Day 2 and Day 21 under fasted conditions
l. TBAJ-876 will be dosed as following:
    a. ***200 mgTBAJ-876 on Day 6 - 13 under fed conditions***
    b. ***165 mg TBAJ-876 on Day 14 – 19 under Fed conditions***
    c. ***200 mg TBAJ-876 on Day 20 - 21 under fasted conditions***
    d. ***150 mg TBAJ-876 on Day 22 - 24 under fed conditions***
m. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single **ECGs will be completed at screening, Day -1, ~~2~~, 3, 7, 20, ~~21~~, 22 on Day 25 or upon early withdrawal. Furthermore, ECGs should also be taken on Digoxin dosing**

days, on Day 2 and Day 21, at study hours ~~0~~ pre-dose, 0.5, 1, 2, 6, and 12 within 15 minutes of the defined time points**.** The pre-dose ECG should be completed within 90 minutes prior to dosing and all ECGs should be completed prior to blood draws. If a participant experiences a post-dosing 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

n. Blood plasma samples will be drawn at the following timepoints:
   - **Midazolam: Day 1 and Day 20**: pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours
   - **TBAJ-876: Day 17**: pre-dose, 0.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24 hours
   - **Digoxin:**
     - **Day 2:** pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 3), 48 (D4), 72 (D5), 96 (D6) hours
     - **Day 21:** pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (D22), 48 (D23), 72 (D24), 96 (D25)

2. Updated Inclusion/Exclusion Language (Inclusion Section 5.1 / Exclusion Section 5.2)

Current Inclusion #8:

8. If a non-vasectomized male (or male vasectomized less than 6 months 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.

Revised Inclusion #8:

8. If a non-vasectomized male (or male vasectomized less than 6 months 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***~~ ***6 months*** *before study start.*

Current Exclusion #12:

12. Seated or supine blood pressure is less than 90/40 mmHg or greater than 150/90 mmHg at screening, Day -1 (check-in), or pre-dose. Out of range vital signs may be repeated twice for confirmation. Out of range values will not be considered AEs if the repeat assessment is in range.

Revised Exclusion #12:

12. Seated or supine blood pressure is less than 90/40 mmHg or greater than 150/90 mmHg at screening, Day -1 (check-in), or pre-dose **Day 1**. Out of range vital signs may be repeated twice for confirmation. Out of range values will not be considered AEs if the repeat assessment is in range.

Current Exclusion #13:

13. Heart rate is lower than 60 beats per minute (bpm) or higher than 100 bpm at screening, Day -1 (check-in), or pre-dose. 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.

Revised Exclusion #13:

13. Heart rate is lower than 60 beats per minute (bpm) or higher than 100 bpm at screening, Day -1 (check-in), or pre-dose **Day 1**. 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.

Current Exclusion #15:

15. QTcF interval >450 ms for males or >470 ms for females at screening, Day -1, or Day 2 (pre-dose), or history of prolonged QT syndrome. PR interval < 200 ms at screening, Day -1, or Day 2 pre-dose. Out of range values may be repeated twice for confirmation. The average QTcF and PR intervals of the three ECG recordings will be used to determine qualification.

Revised Exclusion #15:

15. QTcF interval >450 ms for males or >470 ms for females at screening, Day -1, or Day 2 (pre-dose), or history of prolonged QT syndrome. PR interval < 200 ms at screening, Day -1, or Day 2 pre-dose. Out of range values may be repeated twice for confirmation. The average QTcF ~~**and**~~**or** PR intervals of the three ECG recordings will be used to determine qualification.

3. Restrictions Section 5.3

Current Wording:

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 (Day 32 phone call) 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.

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.

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.

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, cherries, 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.

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.

Revised Wording:

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 (Day 32 phone call) 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.

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.

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.

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, cherries, char grilled meat, or caffeine/xanthine from 24 hours before the first dose of study medication, until Day 25 ~~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.

Subjects must not engage in strenuous exercise from 48 hours prior to the first dose of study medication until **Day 32 follow up call.** ~~**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.

4. Check-in Procedures, Section 7.2

Current Wording:

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)
- 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

Revised Wording:

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 **and BMI (height from screening will be used to calculate the BMI)**
- Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry)
- 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 **breathalyzer, and urine** 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

5. Laboratory parameters, Section 7.6.2

Current Wording:

Clinical laboratory evaluations will be performed at the times noted on the appropriate schedule of events (Section 1.2). A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform all clinical laboratory tests for this study.

- Hematology: hemoglobin, hematocrit, , red blood cell (RBC) count, white blood cell count with differential, 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, lipase, and amylase.

Note: If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN) the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB), trypsin like immunoreactivity, and cardiac troponin I.

- Serology: hepatitis B surface antigen, hepatitis C antibody, and HIV
- Coagulation: prothrombin time (PT2) and activated partial thromboplastin time (aPTT2).
- 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).

Revised Wording:

Clinical laboratory evaluations will be performed at the times noted on the appropriate schedule of events (Section 1.2). A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform all clinical laboratory tests for this study.

- Hematology: hemoglobin, hematocrit, , red blood cell (RBC) count, white blood cell count with differential, 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, lipase, and amylase.

Note: If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN) the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB), ~~trypsin like immunoreactivity~~, and cardiac troponin T.

- Serology: hepatitis B surface antigen, hepatitis C antibody, and HIV
- Coagulation: prothrombin time (PT2) and activated partial thromboplastin time (aPTT2).
- 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, **Urine** Cotinine, and Alcohol **Breathalyzer** Screens - Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates) cotinine, and alcohol **at screening and check-in only**.
- Pregnancy test (all female subjects).
- FSH (female subjects claiming post-menopausal status).

6. Vital Signs, Section 7.6.3

Current Wording:

Vital signs (blood pressure, heart rate [pulse], temperature, respiration rate, and pulse oximetry) should be measured at screening, check-in, and Day -1. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart **at study hours 0, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.** Furthermore, vital signs should also be taken once daily on Day 7 through Day 20 (6 hours after Dosing) and Day 25 or early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences)Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should be measured after subjects are in supine position for at least 2 minutes and then again after standing for at least 1 minute (starting with 2 hours post dose), except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.

Revised Wording:

Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in, Day -1.

Furthermore, vital signs should also be taken once daily on Day 3-5, 7 through Day 19 (6 hours post dose on dosing days and around the same time on non-dosing days), Day 22-Day 23 (6 hours after Dosing) and Day 25 (prior to discharge) or early withdrawal (vital signs must be done within 15 minutes before review of medication and collection of adverse experiences).

Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart at study hours pre-dose, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.

Orthostatic blood pressure and heart rate should be measured at study hours Pre-dose, 2, 6 and 12 ~~time points~~ on Days 1, 2, 6, 20, 21 and 24, after subjects are in supine position for at least 2 minutes and then again after standing for at least 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.

Both blood pressure and heart rate should be captured simultaneously.

7. Physical Examination, Section 7.6.4

Current Wording:

Physical examinations including height and weight measurements and presence of heart murmur, will be conducted in the times noted on the appropriate events schedule (Section 1.2).

Revised Wording:

Physical examinations ~~**including height and weight measurements**~~ and presence of heart murmur, will be conducted in the ~~**times**~~**days** noted on the appropriate events schedule (Section 1.2).

8. **Electrocardiograms, Section 7.6.5**

Current Wording:

Group 1
Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 3, 7, 20, 21, 22 and on Day 25 or upon early withdrawal**.** The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

Revised Wording:

Group 1
Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, ~~**2,**~~ 3, 7, 20, ~~**21,**~~ 22 and on Day 25 or upon early withdrawal**. Furthermore, ECGs should also be taken on Digoxin dosing days, on Day 2 and Day 21, at study hours ~~0,~~predose, 0.5, 1, 2, 6, and 12 within 15 minutes of the defined time points.** The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

9. **Appendix 1 , PK Processing Instructions Table and Plasma from whole blood Midazolam, Digoxin and TLD samples Processing Instructions Table**

Current Table for PK Processing Instructions:

Processing Instructions	
1	Samples will be collected via direct venipuncture at the time points delineated in the appropriate Events Schedule (Section 1.2).
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.

Revised Table for PK Processing Instructions:

Processing Instructions	
1	Samples will be collected via direct venipuncture **or peripheral venous catheter** at the time points delineated in the appropriate Events Schedule (Section 1.2).
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.

Current Table for Processing Instructions of Plasma from whole blood Midazolam, Digoxin and TLD samples:

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 evacuated tubes containing K2-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 will be removed and placed in appropriately labelled 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 Pyxant bioanalytical laboratory for the determination of plasma concentrations of Midazolam and Digoxin using a validated procedure.
7	Blood sampling, plasma processing, and storage time will be documented in the study records.

Revised Table for Processing Instructions of Plasma from whole blood Midazolam, Digoxin and TLD samples:

Processing Instructions	
1	Samples will be collected via direct venipuncture **or peripheral venous catheter** at the time points delineated in the appropriate Events Schedule (Section 13).
2	Blood will be drawn into pre-chilled evacuated tubes containing K2-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 will be removed and placed in appropriately labelled 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 Pyxant bioanalytical laboratory for the determination of plasma concentrations of Midazolam and Digoxin using a validated procedure.
7	Blood sampling, plasma processing, and storage time will be documented in the study records.

10. Appendix 3, Cardiovascular Table

Current table:

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 BP, No treatment required[1]	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
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

Revised table – added footnotes:

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 BP, No treatment required[1]	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment[2]	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
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] In this healthy volunteer study, asymptomatic transient orthostatic hypotension will be defined as heart rate increased by 20 ≥ beats/min or systolic BP decreased by ≥10 mm Hg. This will be captured as a Grade 1 Adverse Event.

[2] In this healthy volunteer study, Grade 2 orthostatic hypotension will be defined as symptoms due to systolic BP decreased by ≥20 mm Hg; correctable with oral fluid treatment. This will be captured as a Grade 2 Adverse Event.

11. Appendix 3, A. Tables for Laboratory Abnormalities

Current Language above the table:

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Revised Language above the table:

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. **In all cases PI should consult the DMID (toxicity) table (Appendix 3) when assessing laboratory abnormalities.**

DocuSign

Certificate Of Completion

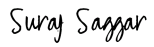
Envelope Id: 8D180E63D96C4FCFB02C70E97A6F2DC9
Status: Completed
Subject: Please DocuSign: TB Alliance_PCL_TBAJ-876-CL002_Final_v1.0_23June2022.pdf
Source Envelope:
Document Pages: 21
Signatures: 3
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Envelope Originator:
Marie Messina
40 Wall St FL 24
New York, NY 10005
marie.messina@tballiance.org
IP Address: 142.255.111.146

Record Tracking

Status: Original
23 June 2022 | 16:26
Holder: Marie Messina
marie.messina@tballiance.org
Location: DocuSign

Signer Events	Signature	Timestamp
Antonio Lombardi Antonio.Lombardi-Consultant@tballiance.org Dr. Security Level: Email, Account Authentication (Required)	DocuSigned by: Antonio Lombardi Signer Name: Antonio Lombardi Signing Reason: I approve this document Signing Time: June 23, 2022 | 2:37 PM PDT AAFDCEAAD2874D3382507893E2EDC27C Signature Adoption: Pre-selected Style Signed by link sent to Antonio.Lombardi-Consultant@tballiance.org Signature ID: AAFDCEAA-D287-4D33-8250-7893E2EDC27C Using IP Address: 69.112.138.78 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23 June 2022 | 16:29 Viewed: 23 June 2022 | 17:37 Signed: 23 June 2022 | 17:37
Electronic Record and Signature Disclosure: Accepted: 23 June 2022 | 17:37 ID: 21902c7a-0a67-4f12-b458-b8bde21513d7		
Irina Krause ikrause@tklresearch.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Irina Krause Signer Name: Irina Krause Signing Reason: I approve this document Signing Time: June 24, 2022 | 7:33 AM EDT 0D9920D912154147852ACDECEE722A44 Signature Adoption: Pre-selected Style Signed by link sent to ikrause@tklresearch.com Signature ID: 0D9920D9-1215-4147-852A-CDECEE722A44 Using IP Address: 70.36.31.130 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23 June 2022 | 16:29 Viewed: 24 June 2022 | 07:33 Signed: 24 June 2022 | 07:33
Electronic Record and Signature Disclosure: Accepted: 24 June 2022 | 07:33 ID: 5c626be0-68ff-4db1-9faa-d325a7670009		

Signer Events	Signature	Timestamp
Suraj Saggar ssaggar@tklresearch.com Suraj Saggar Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signed by link sent to ssaggar@tklresearch.com Signature ID: EC256605-1376-4F07-9145-B13EC902277D Using IP Address: 64.183.8.188 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23 June 2022 | 16:29 Viewed: 24 June 2022 | 12:27 Signed: 24 June 2022 | 12:27
Electronic Record and Signature Disclosure: Accepted: 11 January 2021 | 22:58 ID: 0be413f4-c8bd-491c-8e67-362e061ead00		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	23 June 2022 | 16:29
Certified Delivered	Security Checked	24 June 2022 | 12:27
Signing Complete	Security Checked	24 June 2022 | 12:27
Completed	Security Checked	24 June 2022 | 12:27

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Global Alliance for TB Drug Development-Sub Account (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through your DocuSign, Inc. (DocuSign) Express user account. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. For such copies, as long as you are an authorized user of the DocuSign system you will have the ability to download and print any documents we send to you through your DocuSign user account for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of your DocuSign account. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use your DocuSign Express user account to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through your DocuSign user account all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Global Alliance for TB Drug Development-Sub Account:
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: christi.baine@tballiance.org

To advise Global Alliance for TB Drug Development-Sub Account of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at christi.baine@tballiance.org and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..
In addition, you must notify DocuSign, Inc to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in DocuSign.
To request paper copies from Global Alliance for TB Drug Development-Sub Account
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to christi.baine@tballiance.org and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.
To withdraw your consent with Global Alliance for TB Drug Development-Sub Account
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
ii. send us an e-mail to christi.baine@tballiance.org and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will

have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I Agree' box, I confirm that:

- I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC RECORD AND SIGNATURE DISCLOSURES document; and

- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and

- Until or unless I notify Global Alliance for TB Drug Development-Sub Account as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by Global Alliance for TB Drug Development-Sub Account during the course of my relationship with you.

TB Alliance

Protocol Number:	TBAJ-876-CL002
Title:	A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects
Drug(s)/Combination(s):	TBAJ-876
Protocol Version/Date:	VERSION 1.0 / 20May2022 (Final)
Protocol Name:	TBAJ-876-CL002

PROTOCOL SIGNATURE PAGE

Protocol Title: A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects

Protocol Number: **TBAJ-876-CL002**

Protocol Date: **20 May 2022**

Protocol Name: **TBAJ-876-CL002**

SPONSOR

I agree to the terms of this study protocol.

DocuSigned by:
Antonio Lombardi
Signer Name: Antonio Lombardi
Signing Reason: I approve this document
Signing Time: May 20, 2022 | 10:44 AM PDT
AAFDCEAAD2874D3382507893E2EDC27C

Signature of Medical Officer

May 20, 2022 | 10:44 AM PDT

Date

Antonio (Tony) Lombardi, MD
Printed Name

TB Alliance
40 Wall Street, 24th Floor
New York, NY, 10005, United States of America
Phone/ Mobile: +1 917 601 0024
email: Antonio.lombardi-consultant@tballiance.org

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol Title: A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects

Protocol Number: **TBAJ-876-CL002**

Protocol Date: **20 May 2022**

Protocol Name: **TBAJ-876-CL002**

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein and in accordance with the principals of Good Clinical Practice (GCP) and local regulations.

I will provide copies of the protocol and access to all the information required to conduct the clinical study according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all study requirements.

DocuSigned by:
Suraj Saggar
Signer Name: Suraj Saggar
Signing Reason: I approve this document
Signing Time: May 24, 2022 | 6:57 AM PDT
CACB0F0EFD3D4987B37FD80E1850DA67

Signature

Suraj Saggar, MD

May 24, 2022 | 6:57 AM PDT

Date

Table of Contents

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT2	activated partial prothrombin time
AST	aspartate aminotransaminase
AUC	area under the (plasma concentration vs. time) curve
AUC_{Extrap} (%)	the percentage of AUC_{inf} based on extrapolation
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
AUC_{tau}	area under the concentration-time curve at the end of a dosing interval
BDQ	bedaquiline
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
bpm	beats per minute
Ca	calcium
C_{avg}	average steady-state plasma concentration
CL/F	apparent total clearance after oral administration
CFR	Code of Federal Regulations
CI	confidence interval
Cl-	chloride

C_{last}	the last quantifiable concentration determined directly from individual concentration-time data
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
CPK	creatine phosphokinase
CPK-MB	creatine phosphokinase myocardial band
CRF	case report form
cTnT	cardiac troponin T
C_{trough}	trough plasma concentration
CV	Cardiovascular
CYP	cytochrome P450
DARQ	diarylquinoline
DIC	disseminated intravascular coagulation
dL	decilitre
DMID	Division of Microbiology and Infectious Diseases
DTG	dolutegravir
ECG	electrocardiogram
FDA	Food and Drug Administration
FE	food-effect
FIH	first-in-human
FOB	Functional observational battery
FSH	follicle-stimulating hormone
g	gram(s)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B Surface Antigen
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HCl	hydrochloride
HCV	Hepatitis C Virus
HR	Heart rate
IB	Investigator Brochure
ICD	informed consent document
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
IV	intravenous
kg	kilogram(s)
K2-EDTA	ethylenediaminetetraacetic acid

K+	potassium
L	litre(s)
LDH	lactate dehydrogenase
LDPE	Low density polyethylene
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
m	meter(s)
MAD	multiple ascending dose
MAOI	monoamine oxidase inhibitor
max.	maximum
mcg	micrograms
MDD	major depressive disorder
MDR	multi drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
min.	minute(s)
mIU	milli international units
mL	millilitre(s)
mmHg	millimetre of mercury
ms	millisecond
MTB / *M.tb*	Mycobacterium tuberculosis
MTD	maximum tolerated dose
n or N	number of occurrences
NA	Not assessed
N/A	Not applicable
Na+	sodium
NC	Not calculated
ND	Not determined
ng	nanogram(s)
NOAEL	no observed adverse effect level
NS	Nervous System
OATP	organic anion transport protein
OTC	over the counter
PaL	pretomanid + linezolid
PCR	Polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic
PP	polypropylene
PRBC	packed red blood cells
PT	prothrombin time
PTT	partial thromboplastin time
QTcF	QTc interval corrected with Fridericia formula
R_{AUC}	accumulation ratio for AUC
R_{Cmax}	accumulation ratio for C_{max}
rbc	red blood cell
Resp	Respiratory
rpm	revolutions per minute
SAD	single ascending dose
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	screening

SAE	serious adverse event
SAP	statistical analysis plan
SAUC	sum of the AUC_{0-24} values of parent drug and its M3 metabolite
SOC	System organ class
SOP	standard operating procedure
SP	Safety Pharmacology Study
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TK	toxicokinetic
TLD	A fixed-dose combination of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and dolutegravir (DTG)
T½ or t½	terminal elimination half-life
T_{lag}	time prior to the first measurable (non-zero) concentration
T_{last}	time of the last quantifiable concentration
T_{max}	time of the maximum concentration
ULN	Upper limit of normal
Vz/F	apparent volume of distribution
WHO	World Health Organization
β-hCG	beta-human chorionic gonadotropin
λz	observed terminal elimination rate constant (Lambda-z)
°C	degrees Celsius/Centigrade
3TC	lamivudine

1 Synopsis

1.1 Synopsis Summary

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	TBAJ-876
Protocol Number/Title:	A Phase 1, Drug-Drug Interaction Study to Evaluate the Safety, Tolerability, and the Induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the Inhibition potential of TBAJ-876 on P-glycoprotein in Healthy Adult Subjects
Treatment Indication:	Tuberculosis
Study Objectives:	The **primary objective** of the study is: • To evaluate the induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein (P-gp) and the inhibition potential of TBAJ-876 on P-gp in healthy adult subjects. The **secondary objectives** of the study are: • To evaluate the effects of multiple-dose administrations of TBAJ-876 on the safety and tolerability of midazolam and digoxin. • To evaluate the effects of multiple-dose administration of TBAJ-876 on the safety and tolerability of Dolutegravir administered as a fixed dose formulation with Tenofovir and Lamivudine.(If Group 2 is conducted).
Study Design Overview	This is a two-part (Group 1 and Group 2) open label drug-drug interaction study to be conducted in one study center in the United States. **Group 1**: Will assess the induction potential of TBAJ-876 on the sensitive CYP3A4 substrate **Midazolam** and the inhibition and induction potential of TBAJ-876 on the sensitive P-glycoprotein substrate **Digoxin**. **Group 2**: To be conducted only if the results of Group 1 show that TBAJ-876 is a moderate inducer of either CYP3A4 (geometric mean ratio [GMR] of midazolam area under the curve [AUC] <0.50 when co-administered with TBAJ-876 versus alone) or P-glycoprotein (GMR of digoxin AUC <0.50 when co-administered with TBAJ-876 versus alone) or a moderate inhibitor of P-glycoprotein (GMR of digoxin AUC ≥2.0 when co-administered with TBAJ-876 versus alone).

	Group 2 will quantify the magnitude of inhibition or induction of TBAJ-876 on the antiretroviral regimen **TLD, a** fixed-dose combination of tenofovir disoproxil fumarate **(TDF)**, lamivudine **(3TC)**, and dolutegravir **(DTG**), a regimen likely to be used in future clinical trials of TBAJ-876 by participants living with HIV.
Study Design	**Group 1:** All subjects will be admitted in the clinic from Day -1 until Day 25 for safety and PK assessments. Subjects will check-in to the clinic following a 21-day screening period. • **On Day 1,** subjects will receive a single dose of **Midazolam (2 mg) under fasted conditions**. • **On Day 2**, subjects will receive a single dose of **Digoxin (0.25 mg under fasted conditions**. • **On Day 6 – 13,** subjects will receive a single daily dose of **200 mg TBAJ-876 under Fed conditions.** • **On Day 14 – 19, subjects** will receive **a single daily dose of 165 mg TBAJ-876 under Fed conditions.** • **On Day 20,** subjects will receive **a single dose of Midazolam (2 mg) + a single dose of 200 mg TBAJ-876 under fasted conditions.** • **On Day 21,** subjects will receive **a single dose of Digoxin (0.25 mg) + a single dose of 200 mg TBAJ-876 under fasted conditions.** • **On Day 22 – 24,** subjects will receive **a single daily dose of 150 mg TBAJ-876 under Fed conditions**. • **On Day 25,** subjects will be discharged from the clinic following completion of all procedures. • **On Day 32,** subjects will receive a follow-up phone call to check for AEs and any concomitant medications. **Group 2: (To be conducted based on the Group 1 results)** All subjects will be admitted in the clinic from Day -1, until Day 25 for safety and PK assessments. • **On Day 1**, subjects will receive **a single dose of a Fixed Dose combination (TLD) of: Dolutegravir (DTG 50 mg) + Tenofovir disoproxil fumarate (TDF 300 mg) + Lamivudine (3TC 300 mg) under fasted conditions.** • **On Day 6 – 13,** subjects will receive **a single daily dose of 200 mg TBAJ-876 under fed conditions.** • **On Day 14 – 19,** subjects will receive **a single daily**

	dose of 165 mg TBAJ-876 under fed conditions. - • **On Day 20,** subjects will receive **a single dose of the fixed dose combination (TLD) of DTG/TDF/3TC plus a single dose of 200 mg TBAJ-876 under fasted conditions.** • **On Day 21 - 24,** subjects will receive **a single daily dose of 150 mg TBAJ-876 under fed conditions.** • **On Day 25,** subjects will be discharged from the clinic following completion of all procedures**.** • **On Day 32,** subjects will receive a follow-up phone call to check for AEs and concomitant medications**.**
Participant Population:	Healthy adult male and female subjects, ages 18-55 inclusive. **Group 1:** Plan to enroll: • 28 subjects **Group 2**: Plan to enroll: • 16 subjects
Investigational Medicinal Product, Dose and Mode of Administration:	**Group 1:** The Investigational Medicinal Product (IMP) is TBAJ-876 5 mg/mL oral suspension formulation at the following doses: • 200 mg administered on Day 6 - 13 under Fed conditions • 165 mg administered on Day 14 - 19 under Fed conditions • 200 mg administered on Day 20 - 21 under Fasted conditions • 150 mg administered on Day 22 - 24 under Fed conditions **Group 2:** The Investigational Medicinal Product (IMP) is TBAJ-876 5 mg/mL oral suspension formulation at the following dose: • 200 mg administered on Day 6 - 13 under Fed conditions • 165 mg administered on Day 14 - 19 under Fed conditions • 200 mg administered on Day 20 under Fasted conditions • 150 mg administered on Day 21 - 24 under Fed conditions
Interaction Products:	The interaction products are: **Group 1:** • Midazolam oral syrup (2 mg) administered on Day 1 and Day 20 under Fasted conditions • Digoxin (0.25 mg) tablets administered on Day 2 and Day 21 under Fasted conditions. **Group 2**: **TLD** is a fixed dose combination pill composed of: Dolutegravir (50 mg) plus Tenofovir disoproxil fumarate (300 mg) plus Lamivudine (300 mg) and is commonly identified as: DTG + TDF +3TC.

	• DTG + TDF + 3TC will be administered on Day 1 and Day 20 under Fasted conditions.

Criteria for Evaluation:

Pharmacokinetic Sample Collection

Serial blood samples will be collected at the time points defined in the Flow Chart (Section 1.2) to determine concentrations of:

- TBAJ-876 and its metabolites (M2 and M3).
- Midazolam and its metabolite 1-hydroxymidazolam
- Digoxin
- Dolutegravir
- Tenofovir (TFV, the active moiety for which tenofovir disoproxil fumarate is a prodrug)
- Lamivudine

Safety Assessments:

Safety assessments will be performed at the time points defined in the Flow Chart (Section 1.2). For all cohorts, physical examination (including heart murmurs), vital signs, electrocardiograms (ECGs), adverse events, hematology, serum chemistry, coagulation and urinalysis will be used to assess safety and tolerability. Blood and urine samples will be collected for clinical laboratory evaluations. Female subjects will have pregnancy testing during screening and at check-in. Females claiming postmenopausal status will have blood collected to measure follicle stimulating hormone (FSH) levels during screening.

Given the key safety findings in the nonclinical safety studies regarding observed myocardial, skeletal muscle, pancreas, and minimal liver injury, it is planned to have extensive monitoring with emphasis on cardiovascular monitoring including 12 lead ECGs, as well as monitoring to evaluate potential pancreatic, hepatocellular and skeletal muscle injury. This will occur at both protocol-defined time points (see Schedule of Assessments and Procedures-Section 1.2) and whenever deemed necessary by the study investigator.

Statistical Methods

Analysis Population

Safety population will include data from all subjects who received at least one dose of IMP and/or 1 dose of the interaction product. This population will be used to analyse the safety and tolerability endpoints.

Pharmacokinetic (PK) population will include data from all subjects who received at least one dose of IMP and/or 1 dose of the interaction product and whose plasma concentration data is available. This population will be used for the presentation of plasma concentration results as well as PK analysis.

All statistical reports must clearly indicate the group for the which the results are being summarised with a mention of the group in the report title. Demographics and other baseline characteristics will be summarized by safety population. Medical history and major protocol deviations will be listed.

The continuous variables will be summarized using number of eligible subjects (N), mean, standard deviation, median, minimum, and maximum. Frequency counts and percentages will be reported for categorical data.

Pharmacokinetics (PK) Sample Collection and Analysis

Group 1:

- PK for Midazolam: **Day 1** and Day **20:** pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours
- PK for TBAJ-876**: Day 17:** pre-dose, 0.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 hours
- PK for digoxin **Day 2**: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 3), 48 (D4), 72 (D5), 96 hours (D6 pre TBAJ-876 dose)
- PK for digoxin **Day 21**: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (D22), 48 (D23), 72 (D24), 96 hours (D25)

Group 2:

- PK for DTG, TFV, and 3TC**: Day 1:** pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24 (D2), 48 (D3), 72 (D4), 96 (D5), 120 (Day 6 pre TBAJ-876 dose).
- PK for TBAJ-876: **Day 17**: pre-dose, 0.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24
- PK for DTG, TFV, and 3TC: **Day 20:** pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24 (D21), 48 (D22), 72 (D23), 96 (D24), 120 (D25)

Pharmacokinetic Analysis:

Plasma concentrations of TBAJ-876 and interaction products will be listed by participant and visit details as applicable by group. Mean and individual concentrations (TBAJ-876, TBAJ-876 metabolites, and interaction products) will be plotted versus time.

Analysis for Group 1 will be conducted for induction potential of TBAJ-876 on the sensitive CYP3A4 substrate midazolam (M) and inhibition and induction potential of TBAJ-876 on the sensitive P-glycoprotein substrate Digoxin (D).

TBAJ-876 will be considered a moderate inducer of either CYP3A4, if the GMR of midazolam AUC <0.50 when co-administered with TBAJ-876 versus alone, or P-glycoprotein, if the GMR of digoxin AUC <0.50 when co-administered with TBAJ-876 versus alone. TBAJ-876 will be considered a moderate inhibitor of P-glycoprotein if the GMR of digoxin AUC ≥2.0 when co-administered with TBAJ-876 versus alone. These results will be used to decide whether to conduct of Group 2 of the study.

To compare pharmacokinetic parameters of the interaction products with TBAJ-876 versus alone, analyses of variance (ANOVA) will be performed by the SAS Mixed Linear Models procedure. The model will include subject as a random effect and treatment (with TBAJ-876 versus alone) as a fixed effect. Following log transformation, geometric least-squares mean values and 95% confidence intervals (CIs) will be tabulated for each pharmacokinetic parameter. GMRs and 95% CIs will be calculated for pharmacokinetic parameters of interaction products, with TBAJ-876 versus alone.

Safety Analysis:

The number of subjects for each cohort is expected to provide sufficient safety and tolerability. This study has not been formally powered for safety.

All clinical safety data will be listed by subject. Continuous variables will be summarized using sample size (N), mean, standard deviation, median, minimum, and maximum. Frequency counts will be reported for categorical data.

Every cardiovascular adverse event will be listed by time point with accompanying symptoms and with blood pressure (BP) and heart rate (HR) measurements.

Safety ECG results will be classified as normal or abnormal and summarized using frequency counts by dose group and time point of collection. HR and blood pressure values and changes from pre-dose will be summarized using descriptive statistics.

Study Duration:

Group1: The planned length of participation in the study is approximately 33 days from check-in on Day -1 through completion of the Day 25 procedures and follow-up phone call on Day 32.

Group 2: The planned length of participation in the study is 33 days from check-in on Day -1 through completion of the Day 25 procedures and follow-up phone call on Day 32.

1.2 Flow Chart

1.2.1 Schedule of Assessments & Procedures, Group 1: Midazolam, Digoxin

	SCR	CHECK-IN	TREATMENT									CHECK-OUT	FOLLOW UP	
DAY	-21 to -1	-1	1	2-5	6-16	17	18	19	20	21	22-24	25	32	EARLY WITHDRAWAL
Informed consent	X													
Check-in questions		X												
Medical history	X													
Height, weight, BMI	X	X												
HIV/ Hepatitis B, C	X													
Serum pregnancy test[b]	X	X										X		
FSH[b]	X													
Urine drug/alcohol/ cotinine screen	X	X												
Safety Labs hematology, chemistry, urinalysis)[c]	X	X		X	X				X	X	X	X		X
Coagulation[c]	X	X		X	X				X	X	X	X		X
Physical exam	X	X		X								X		X
Heart Murmur[d]	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)[e]	X	X	X	X	X	X	X	X	X	X	X	X		X

	SCR	CHECK-IN	TREATMENT									CHECK-OUT	FOLLOW UP	
DAY	-21 to -1	-1	1	2-5	6-16	17	18	19	20	21	22-24	25	32	EARLY WITHDRAWAL
Concomitant medication review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[g]		X	X	X	X	X	X	X	X	X	X	X	X	X
Midazolam Dose[h]			X						X					
Digoxin Dose[i]				X						X				
TBAJ-876[j]					X	X	X	X	X	X	X			
12-lead safety ECGs[k]	X	X		X	X				X	X	X	X		X
Plasma for PK[l]			X	X		X			X	X	X	X		

SCR=screening; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening

a. Confinement to start at check-in (Evening of Day 1) until 24 hours after dosing on Day 25.
b. Serum pregnancy test done at screening, check-in, and Day 25 for females only. FSH completed for perimenopausal females only.
c. Safety laboratory assessments. The following analyses will be performed at the following timepoints: **Screening, Day -1, Day 2, Day 3, Day 7, Day 20, Day 21, Day 22, and Day 25.**

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect and total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na+), potassium (K+), chloride (CL-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, magnesium, and bicarbonate, lipase, and amylase
- **Note: *If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN), according to FDA guidance criteria (see Appendix 3), the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB), trypsin like immunoreactivity, and cardiac troponin I.***
- 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, blood, myoglobin, leukocyte esterase. If protein, occult blood, nitrate, 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.

d. Heart murmur: Presence of heart murmur
e. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate, pulse oximetry) should be measured at screening, and check-in, Day -1. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart **at study hours 0, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.** Furthermore, vital signs should also be taken once daily on Day 7 through Day 20 (6 hours after Dosing) and Day 25 or early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences). Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should be measured after subjects are in supine position for at least 2 minutes and then again after standing for at least 1 minute (starting with 2-hr post dose VS), except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.
f. On Day 32, follow-up questioning on concomitant medications will be completed by a phone call.
g. Adverse events to be monitored from the time of informed consent signing throughout the study via safety assessments, observation and participant reporting. Specific adverse event questions will be posed daily throughout the study until Day 25 and a follow-up phone call on Day 32..
h. Midazolam Dose on Day 1 and Day 20 under fasted conditions
i. Digoxin Dose on Day 2 and Day 21 under fasted conditions
j. TBAJ-876 will be dosed as following:
    a. ***200 mgTBAJ-876 on Day 6 - 13 under fed conditions***
    b. ***165 mg TBAJ-876 on Day 14 – 19 under Fed conditions***
    c. ***200 mg TBAJ-876 on Day 20 - 21 under fasted conditions***
    d. ***150 mg TBAJ-876 on Day 22 - 24 under fed conditions***
k. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single **ECGs will be completed at screening, Day -1, 2, 3, 7, 20, 21, 22 on Day 25 or upon early withdrawal. Furthermore, ECGs should also be taken on Digoxin dosing days, on Day 2 and Day 21, at study hours 0, 0.5, 1, 2, 6, and 12** within 15 minutes of the defined time points**.** The pre-dose ECG should be completed within 90 minutes prior to dosing and all ECGs should be completed prior to blood draws. If a participant experiences a post-dosing 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
l. Blood plasma samples will be drawn at the following timepoints:
    - **Midazolam: Day 1 and Day 20**: pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours
    - **TBAJ-876: Day 17**: pre-dose, 0.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24 hours
    - **Digoxin:**
        - **Day 2:** pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 3), 48 (D4), 72 (D5), 96 (D6) hours
        - **Day 21:** pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (D22), 48 (D23), 72 (D24), 96 (D25)

1.2.2 Schedule of Assessments & Procedures Group 2: Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine

	SCR	CHECK-IN	TREATMENT								CHECK-OUT	FOLLOW-UP	
DAY	-21 to -1	-1	1	2-5	6-16	17	18	19	20	21-24	25	32	EARLY WITHDRAWAL
Informed consent	X												
Check-in questions		X											
Medical history	X												
Height, weight BMI	X	X											
HIV/ Hepatitis B, C	X												
Serum pregnancy test[b]	X	X									X		
FSH[b]	X												
Urine drug/alcohol/ cotinine screen	X	X											
Safety Labs hematology, chemistry, urinalysis)[c]	X	X		X	X				X	X	X		X
Coagulation [c]	X	X		X	X				X	X	X		X
Physical exam	X	X		X							X		X
Heart Murmur[d]	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)[e]	X	X	X	X	X	X	X	X	X	X	X		X

	SCR	CHECK-IN	TREATMENT								CHECK-OUT	FOLLOW-UP	
DAY	-21 to -1	-1	1	2-5	6-16	17	18	19	20	21-24	25	32	EARLY WITHDRAWAL
Concomitant medication review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[g]		X	X	X	X	X	X	X	X	X	X	X	X
DTG+TDF+3TC Dose[h]			X						X				
TBAJ-876[i]					X	X	X	X	X	X			
12-lead safety ECGs[j]	X	X		X	X				X	X	X		X
Plasma [k]			X	X	X	X			X	X	X		

SCR=Screening; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FU = follow up; HIV = human immunodeficiency virus; N/A = not applicable; PK = pharmacokinetic; SCR = screening

a. Confinement to start at check-in (Evening of Day -1) until 24 hours after dosing on Day 24.
b. Serum pregnancy test done at screening and at check-in for females only. FSH completed for perimenopausal females only.
c. Safety laboratory assessments. The following analyses will be performed on **Screening, Day -1, 2, 7, 20, 21, and 25.**

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC) count, reticulocyte count, and platelet count.
- Coagulation Tests: Activated partial thromboplastin time (aPTT2), Prothrombin time (PT2)
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), direct, indirect and total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na+), potassium (K+), chloride (CL-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, total protein, magnesium, and bicarbonate, lipase, and amylase
- **Note:** ***If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN), according to FDA guidance criteria (see Appendix 3), the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB), trypsin like immunoreactivity, and cardiac troponin I.***
- 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, blood, myoglobin, leukocyte esterase. If protein, occult blood, nitrate, 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.

d. Heart murmur: Presence of heart murmur
e. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate) should be measured at screening, check-in, and Day -1. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart

at study hours 0, 1, 6, and 12 on Days 1, 6, and 20. Furthermore, vital signs should also be taken once daily on Day 2 through Day 5 and Day 7-19 and Day 21-25 or early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences). Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should 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.

f. On Day 32, follow-up questioning on concomitant medications AEs will be completed by a phone call.
g. Adverse events to be monitored from the time of informed consent signing throughout the study via safety assessments, observation, and participant reporting. Specific adverse event questions will be posed daily throughout the study until Day 25 and a follow-up phone call on Day 32.
h. DTG (50 mg) +TDF (300 mg) + 3TC (300 mg) on Day 1 and Day 20 under fasted conditions
i. TBAJ-876 will be dosed as follows:
    a. 200 mg TBAJ-876 on Day 6 - 13 under Fed conditions
    b. 165 mg TBAJ-876 on Day 14 - 19 under Fed conditions
    c. 200 mg TBAJ-876 on Day 20 under fasted conditions
    d. 150 mg TBAJ-876 on Day 21 - 24 under Fed conditions
j. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. **Single ECGs will be completed at screening, Day -1, 2, 7, 20, 21, and 25 or upon early withdrawal**. The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.
k. Blood plasma samples will be drawn at the following timepoints:
    a. **TLD: Day 1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24 (D2), 48 (D3), 72 (D4), 96 (D5), 120 (D6)**
    b. **TBAJ-876: Day 17: pre-dose, 0.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24**
    c. **TLD: Day 20: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24 (D21), 48 (D22), 72 (D23), 96 (D24), 120 (D25**)

2 Introduction

2.1 Background

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] (IB) Unless noted otherwise, the TB Alliance provided the information in this introduction.

2.2 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 (BDQ) is a first-in-class diarylquinoline (DARQ) 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 DARQ with the potential to safely deliver superior efficacy to 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) and lower minimal inhibitory concentrations (MICs) against Mtb, including strains with mutations causing reduced susceptibility to BDQ. In preclinical models of TB, lower doses of TBAJ-876 demonstrate superior efficacy as monotherapy and within regimens when compared to BDQ given at standard doses. Taken together, these attributes may allow TBAJ-876 to safely deliver superior efficacy compared to BDQ.

2.3 Preclinical Studies

2.3.1 Primary pharmacology

In primary pharmacology studies, TBAJ-876 had clear and potent anti-mycobacterial activity in vitro and in animal models and provided faster time to sterilization in relapsing mouse models, than did similar BDQ containing regimens; therefore, it is a good candidate for clinical investigation.

2.3.2 Safety Assessment

2.3.2.1 Toxicology

The toxicological profile of TBAJ-876 was characterized in rats and dogs including two pivotal Good-Laboratory-Practice (GLP)-compliant 13-week toxicity studies. In the 13-week toxicity studies, safe TBAJ-876 dose levels and systemic exposures for TBAJ-876 and several of its metabolites were identified. This information was used to select a safe starting dose, identify potential adverse effects in human subjects, and inform the dose-escalation schedule and clinical safety monitoring plan in the first clinical study.

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 creatine kinase (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 or 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 mucosa, 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 of the glandular mucosa 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 was observed 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 preliminary non-GLP 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.

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.

Pharmacokinetic exposures in the toxicity studies are summarized in Table 1.

2.3.2.2 Safety Pharmacology

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.

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, pulse 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.

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 15 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 1.

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 1.

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 1.

Table 1 Plasma Exposure to TBAJ-876 and Metabolites in Toxicity and Safety Pharmacology Studies

		NOAEL			LOAEL			Higher Dose		
	Study Duration	**NOAEL Dose (mg/kg)**	**NOAEL AUC_{0-24}[A], (ug·h/mL)**	**NOAEL C_{max}[A], (ug·h/mL)**	**LOAEL Dose, (mg/kg)**	**LOAEL AUC_{0-24}[A], (ug·h/mL)**	**LOAEL C_{max}[A], (ug·h/mL)**	**Higher Dose (mg/kg)**	**Higher AUC_{0-24}[A], (ug·h/mL)**	**Higher C_{max}[A], (ug·h/mL)**
Rat / Tox	3-months	10	**876:** 8.4 **M2:** 1.6 **M3:** 5.2	**876:** 0.7 **M2:** 0.1 **M3:** 0.3	25	**876:** 29.6 **M2:** 10.8 **M3:** 25.4	**876:** 2.1 **M2:** 1.0 **M3:** 2.3	60[E]	**876:** 64.6 **M2:** 6.3 **M3:** 47.5	**876:** 4.1 **M2:** 0.4 **M3:** 2.2
Dog / Tox	2-weeks[B]	5	**876:** 7.6 **M2:** NA **M3:** 14.7	**876:** 0.6 **M2:** NA **M3:** 0.8	15	**876:** 14.1 **M2:** NA **M3:** 55.0	**876:** 0.9 **M2:** NA **M3:** 2.8	45	**876:** 22.7 **M2:** NA **M3:** 128	**876:** 1.8 **M2:** NA **M3:** 6.4
Dog / Tox	3-months	2.5	**876:** 10.0 **M2:** 1.8 **M3:** 17.3	**876:** 0.6 **M2:** 0.08 **M3:** 0.8	7.5	**876:** 18.1 **M2:** 6.9 **M3:** 50.1	**876:** 1.3 **M2:** 0.3 **M3:** 2.3	15	**876:** 25.0 **M2:** 15.2 **M3:** 102.5	**876:** 1.7 **M2:** 0.7 **M3:** 4.7
Rat/ NS SP	13-days[C]	60	**876:** 64.6 **M2:** 6.3 **M3:** 47.5	**876:** 4.1 **M2:** 0.4 **M3:** 2.2	ND (>60)	ND	ND			
Rat / Resp. SP	8-days	75	**876:** 92.1 **M2:** 0.7 **M3:** 16.2	**876:** 6.2 **M2:** 0.04 **M3:** 0.9	ND (>75)	ND	ND			
Dog / CV SP	12-days[D]	30	**876:** 26.9 **M2:** 3.4 **M3:** 33.5	**876:** 2.3 **M2:** 0.2 **M3:** 1.6	ND (>30)	ND	ND			

NOAEL = No Observed Adverse Effect Level; LOAEL = Lowest Observed Adverse Effect Level NC = Not calculated; NA = Not assessed; ND = Not determined; NS = Nervous System; Resp. = Respiratory; SP = safety pharmacology study; CV = Cardiovascular

[A]Exposure (AUC_{0-24} and C_{max}) is presented after the last dose of the study
[B]The 2-week dog toxicity study with TBAJ-876 was non-GLP
[C]Nervous system function safety pharmacology study was conducted within the 3-month toxicity study
[D]Doses were administered in an escalating fashion from 3 mg/kg (Days 1-4), 10 mg/kg (Days 5-8), and 30 mg/kg (Days 9-12)
[E]Rats were administered TBAJ-876 for 16 days then dosing was stopped due to toxicity.

2.3.2.3 Potential adverse effects in human subjects

Table 1 summarizes pharmacokinetic exposures in nonclinical toxicity and safety pharmacology studies. As discussed in Section 2.6, a potential clinical dose of TBAJ-876 is 100 mg QD for eight weeks. Based on a mathematical model developed using data from the first-in-human study, predicted mean values of AUC_{0-24} for TBAJ-876 and M3 at the end of treatment are 9.90 and 1.47 µg.h/mL, and the corresponding predicted mean values of C_{max} are 0.596 and 0.063 µg/mL. In humans, the concentration of the parent species, TBAJ-876, is much greater than that of the M3 metabolite; whereas in rats, the two species generally have similar exposures, and in dogs M3 exposures are higher. Considering TBAJ-876 alone, predicted human exposures are approximately equivalent to slightly higher than the NOAEL from the toxicity studies and substantially lower than the NOAEL from the safety pharmacology studies in Table 1. The predicted M3 metabolite exposures are lower to substantially lower than the NOAELs from the toxicology and safety pharmacology studies. Considering the sum of TBAJ-876 and M3 metabolite exposures, predicted human exposures are less than all NOAEL exposures.

Based on the nonclinical safety studies, human subjects were monitored in a first-in-human clinical study 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 or female 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] (Bedaquiline circular).

2.3.3 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 representing 0.2x of parent AUC in both species. Female rabbits also showed a similar profile after receiving a single dose of TBAJ-876 0.6x and 0.02x to 0.3x of parent AUC, respectively. 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 2). TBAJ-876-M3, TBAJ-876-M2, and BDQ-M2 AUC_{0-24} was 5x of parent AUC_{0-24h}.

Table 2 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. The K_m and V_{max} values of TBAJ-876 were 43.4µM and 299 pmol/min/mg, respectively, in human liver microsomes and 2.20µM and 4.06 pmol/min/pmol P450 for recombinant human CYP3A4.

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 of 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 300x the predicted mean TBAJ-876-M3 C_{max} in humans at the end of eight weeks of treatment with the potential clinical 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 activate AhR, CAR, or PXR nuclear receptors in vitro. However, TBAJ-876 at 1 µM (i.e., approximately 1x the predicted mean TBAJ-876 C_{max} in humans

at the end of eight weeks of treatment with the potential clinical dose of 100 mg) induced CYP3A4 mRNA in one of three lots of human hepatocytes tested.

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.

2.4 Clinical Findings

2.4.1 Safety

A Phase 1 study combined single ascending dose (SAD) study with food-effect cohort and multiple ascending dose (MAD) clinical study to evaluate the safety, tolerability, and pharmacokinetics of TBAJ-876 in healthy subjects is ongoing. Dosing is completed however some subjects are still being followed up for safety and PK. (Protocol TBAJ-876-CL001). Below is a summary of the blinded safety data as of the most recent review of the data.

The first subject was dosed on 08Jun20. The SAD study included 7 Cohorts of 8 subjects (6 on study drug, 2 on placebo) each. The doses studied were: 10, 25, 50, 100, 200, 400 and 800 mg under fasted conditions and then subjects were followed from 14 days and up to 10 weeks during which time they returned to the clinic for safety and PK. The MAD study included 3 cohorts (9 on study drug and 3-5 on placebo). The doses studied were: 25, 75 and 200 mg for 14 days under fed conditions. Subjects were then followed for up to 18 weeks during which time they returned to the clinic every 3 weeks for safety (including safety labs, ECGs) and PK.

Prior to escalating to the next dose both for the SAD and MAD, a meeting was held to review all the safety and PK data. Review of the blinded safety data showed that TBAJ-876 was generally safe and well tolerated at single doses between 10 and 800 mg and 14-day dosing with 25, 75 and 200 mg. There were no serious or severe AES. Most of the AEs were mild and all resolved. There were very few clinically significant changes in clinical safety tests, and all resolved. There were also no reported clinically significant QT prolongations based on ECG review.

AEs of interest, based on nonclinical findings, included myocardial damage, skeletal muscle injury, gastrointestinal irritation, elevated pancreatic enzymes, elevated liver enzymes, and cytopenia. Observations related to these AEs in the first-in-human study, where the data are still blinded, were:

- Myocardial: there was no evidence of myocardial toxicity
- Skeletal muscle:
    - 2 events of rhabdomyolysis, secondary to strenuous physical activity, not related, both resolved.
    - A few events of muscle pain, all resolved.
- GI: only mild to moderate GI adverse events
- Liver: no signal identified
- Pancreas: no signal identified

2.4.2 Pharmacokinetics

Concentrations of the two metabolites, M2 and M3, as well as of the parent TBAJ-876 were measured in the SAD and the MAD. Because of M2's low exposures, the focus is centered on the parent and M3.

TBAJ-876 and M3 exposures were approximately dose proportional in both the SAD study, over a dose range of 10 – 800 mg, and the MAD study, over a dose range of 25 – 200 mg QD for 14 days.

The food effect of TBAJ-876 was studied in the SAD study using a single 100 mg dose. After a high-fat breakfast, the AUC and C_{max} of TBAJ-876 increased by approximately 60% and 100% respectively, while M3 AUC and C_{max} decreased by approximately 30% and 40%, respectively. In the MAD study, TBAJ-876 was administered daily with a high-fat breakfast.

TBAJ-876 and M3 exhibited multi-compartmental pharmacokinetics with long terminal half-lives of approximately 60 and 20 days, respectively. Consequently, TBAJ-876 and M3 accumulate with multiple dosing.

Table 3 shows mean C_{max} and AUC_{0-24} of TBAJ-876 and M3 after the 1st and 14th doses in the MAD study.

Table 3 Mean C_{max} and AUC_{0-24} of TBAJ-876 and M3 in the MAD study.

Dose (mg)	TBAJ-876				M3			
	C_{max} (µg/mL)		AUC_{0-24} (µg.h/mL)		C_{max} (µg/mL)		AUC_{0-24} (µg.h/mL)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
25	0.096	0.148	0.938	1.67	0.0013	0.0106	0.015	0.209
75	0.322	0.401	3.010	4.25	0.0040	0.0354	0.068	0.650
200	0.873	1.160	7.270	12.90	0.0110	0.0858	0.175	1.620
Note: TBAJ-876 was administered daily with a high-fat breakfast.								

2.5 Rationale for Drug-Drug Interaction Studies

Interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug's safety and effectiveness. The objective of drug-drug interaction studies is to determine whether potential interactions between the investigational drug and other drugs exist and, if so, whether the potential for such interactions indicates the need for dosage adjustments, additional therapeutic monitoring, a contraindication to concomitant use, or other measures to mitigate risk.

In vitro studies of TBAJ-876 identified the potential for CYP3A4 induction and P-gp inhibition. In particular, TBAJ-876 at 1 µM, approximately equal to the predicted mean C_{max} in humans after 90 days of dosing at a potential clinical dose of 100 mg, induced CYP3A4 mRNA in one of three lots of human hepatocytes tested. A positive signal for induction of CYP3A4 in this assay may also indicate potential induction of P-gp. However, in another assay a signal for potential inhibition of P-gp was observed, with an IC_{50} of 5.08 µM. A dose of 100 mg of TBAJ-876 would yield a value of I_{gut}/IC_{50} > 10 and thus satisfy the criterion for potentially inhibiting P-gp in vivo according to FDA's guidance "In Vitro Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" of January 2020.

Because of potential interactions with TBAJ-876, the pharmacokinetics of midazolam, a CYP3A4 substrate, and digoxin, a P-gp substrate, will be studied before and after two weeks of daily dosing with TBAJ-876. Depending on the outcome of this investigation, a similar investigation may be undertaken with the antiretroviral regimen TLD (tenofovir disoproxil fumarate (TDF), lamivudine (3TC), dolutegravir (DTG)). This regimen is likely to be used in future clinical trials of TBAJ-876 by participants with HIV. DTG is a substrate of CYP3A4 and P-gp, and TDF is a substrate of P-gp.

The following sections contain safety information excerpted from the Prescribing Information for midazolam syrup, digoxin, and TLD tablets listed in the reference section of the protocol.

Midazolam Syrup[3]

Midazolam hydrochloride (HCl) syrup is indicated for use as a single dose (0.25 to 1 mg/kg with a maximum dose of 20 mg) for preprocedural sedation and anxiolysis in pediatric patients. Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.

Adverse events: In a randomized, double-blind, parallel-group trial, the most commonly reported adverse events among patients during the premedication period (before the introduction of anesthesia) were emesis, nausea, laryngospasm, and sneezing/rhinorrhea.

Other adverse events that have been reported in the literature with the oral administration of midazolam (not necessarily Midazolam Syrup), are listed below. The incidence rate for these events was generally <1%.

Respiratory: apnea, hypercarbia, desaturation, stridor.

Cardiovascular: decreased systolic and diastolic blood pressure, increased heart rate.

Gastrointestinal: nausea, vomiting, hiccoughs, gagging, salivation, drooling.

Central nervous system: dysphoria, disinhibition, excitation, aggression, mood swings, hallucinations, adverse behavior, agitation, dizziness, confusion, ataxia, vertigo, dysarthria.

Special senses: diplopia, strabismus, loss of balance, blurred vision.

The midazolam syrup label carries a boxed warning for risks with concomitant use of benzodiazepines and opioids.

Pregnancy Category: Midazolam is rated Pregnancy Category D. Although midazolam HCl syrup has not been studied in pregnant patients, an increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) have been suggested in several studies.

Digoxin[4]

Digoxin tablets are indicated for the treatment of mild to moderate heart failure in adults and indicated for the control of ventricular response rate in adults with chronic atrial fibrillation.

Adverse events: In patients who are being treated with digoxin for heart failure or certain types of irregular heartbeat the most common (1% to 10%) adverse events include:

Cardiovascular: arrhythmia, conduction disturbances, PR prolongation and sinus bradycardia.

Gastrointestinal: nausea, vomiting, loss of appetite, lower stomach pain and diarrhea.

Central nervous system: dizziness, drowsiness, and headache

Other adverse events that are unlikely but serious may occur with digoxin include: weakness, mental/mood changes, vision changes (such as blurred or yellow/green vision) and enlarged/tender breasts in males.

Pregnancy Category: Digoxin is rated Pregnancy Category C. Underlying maternal condition (e.g., heart failure, atrial fibrillation) may increase risk of adverse pregnancy outcomes.

Dolutegravir/lamivudine/tenofovir (DTG/3TC/TDF)[5]

DTG/3TG/TDF (TLD) is a fixed dose combination tablet containing 50 mg dolutegravir, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg. As of 2019, it is listed by the World Health Organization (WHO) as first line treatment for adults.[6]

Adverse events: Potential side effects of TLD include insomnia, headache, agitation, nausea, diarrhea, and skin rash.

Warnings and Precautions: Previous hypersensitivity reaction to DTG, uncontrolled diabetes, renal impairment (creatinine clearance <50 ml/min), liver impairment, ascites, albumin <2.8 g/dL, total bilirubin >50 mmol/L and encephalopathy.

Pregnancy: In an initial study, exposure to DTG around the time of conception and during the first 8 weeks of pregnancy was previously thought to be associated with an increased risk of neural tube defects in the fetus. However, new data from two large clinical trials comparing the efficacy and safety of DTG and efavirenz have expanded the evidence base to suggest that the risk of neural tube defects are significantly lower than what the initial studies suggested. In July 2019, WHO announced that DTG is safe for women of child-bearing age.[6]

2.6 Rationale for the TBAJ-876 Dose Regimen

The finding of cardiac muscle damage in the 13-week dog toxicity study (Section 2.3.2) is being used to guide dose selection in this and other clinical studies. Clinical doses are being selected to keep exposure in humans below a limit determined by exposure in the dogs at the dose of 15 mg/kg/day where the cardiotoxicity was seen. Exposure for this purpose is quantified by the sum of the 24-hour AUCs of TBAJ-876 and its M3 metabolite, referred to as SAUC. The limit for the mean SAUC in humans is 12.8 µg.h/mL, which is 1/10th the mean SAUC in dogs after 13 weeks of dosing at 15 mg/kg/day. To achieve maximal efficacy, it is expected that the maximum clinical dose will be selected to yield exposures just below this limit.

A 100 mg QD dose of TBAJ-876 administered for eight weeks is a projected clinical efficacious dose. Based on a pharmacokinetic model developed using the data from the SAD and MAD studies, where a suspension formulation of TBAJ-876 was used, dosing TBAJ-876 at 100 mg QD for eight weeks, an aspirational treatment duration, is predicted to yield a mean SAUC at the end of treatment of 11.4 µg.h/mL. The separate mean values of $AUC_{0\text{-}24}$ for TBAJ-876 and M3 at the end of treatment are predicted to be 9.90 and 1.47 µg.h/mL, and the corresponding values of C_{max} are predicted to be 0.596 and 0.063 µg/mL, which were described above for comparison with the exposures listed in Table 1.

The goal for this drug-drug interaction study is to find a regimen that is expected to provide daily mean SAUC values close to, but not above, 12.8 µg.h/mL for a long enough duration to achieve a clinically relevant extent of induction, if TBAJ-876 is indeed an inducer of CYP3A4 or P-gp. The regimen chosen is:

- Day 6 to Day 13: 200 mg TBAJ-876, fed
- Day 14 to Day 19: 165 mg TBAJ-876, fed
- Day 20 and Day 21 in Group 1, Day 20 in Group 2: 200 mg TBAJ-876, fasting
- Day 22 to Day 24 in Group 1, Day 21 to Day 24 in Group 2: 150 mg TBAJ-876, fed

This regimen is predicted to keep the mean SAUC between 80% and 100% of 12.8 µg.h/mL from Day 9 through Day 24.

3 Study Objectives

3.1 Primary Objectives

The **primary objective** of the study is:

- To evaluate the induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein (P-gp) and the inhibition potential of TBAJ-876 on P-gp in healthy adult subjects.

3.2 Secondary Objectives

The **secondary objectives** of the study are:

- To evaluate the effects of multiple-dose administrations of TBAJ-876 on the safety and tolerability of midazolam and digoxin.
- To evaluate the effects of multiple-dose administration of TBAJ-876 on the safety and tolerability of an antiretroviral regimen (If Group 2 is conducted).

4 Study Design

4.1 Summary of Study Design

This study is a two-part, open-label drug-drug interaction study conducted in one study center in the United States. Two groups are planned, **Group 1** and **Group 2**. Group 2 will be conducted based on the Group 1 results.

Group 1 will assess the induction potential of TBAJ-876 on the sensitive CYP3A4 substrate midazolam (M) and inhibition and induction potential of TBAJ-876 on the sensitive P-glycoprotein substrate Digoxin (D).

Group 2 will only be conducted if the results of Group 1 show that TBAJ-876 is a moderate inducer of either CYP3A4 (midazolam AUC <0.50 when co-administered with TBAJ-876) or P-glycoprotein (digoxin AUC <0.50 when co-administered with TBAJ-876) or a moderate inhibitor of P-glycoprotein (digoxin AUC ≥2.0 when co-administered with TBAJ-876.

This group will quantify the magnitude of inhibition or induction of TBAJ-876 on the antiretroviral regimen TLD, a fixed dose combination of tenofovir disoproxil fumarate (TFD), lamivudine (3TC) and dolutegravir (DTG), a regimen likely to be used in future clinical studies of TBAJ-876 by subjects living with HIV.

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

Serial blood samples for PK will be collected at the timepoints according to the Schedule of Assessments & Procedures: Flow Chart (Section 1.2) and sent to a bioanalysis lab where they will be analysed for the for the following analytes using validated analytical methods:

- TBAJ-876 and its metabolites M2 and M3
- Midazolam and its metabolite 1-hydroxymidazolam
- Digoxin
- Dolutegravir
- Tenofovir (TFV, the active moiety for which tenofovir disoproxil fumarate is a prodrug)
- Lamivudine

4.2 Treatment Plan; Schedule of Assessments

In both Group 1 and Group 2, the dosing regimen for TBAJ-876 is listed in Table 4. Also listed in the table are the doses of the interaction products, dosing schedule, and if taken under Fed or fasted conditions.

Table 4 Investigational Medicinal Product (IMP) Details

Day	Dose	Fed/Fasted*
TBAJ-876		
Groups 1 & 2: Day 6 - 13	TBAJ-876 oral suspension: 200 mg dose	Fed
Groups 1 & 2: Day 14 - 19	TBAJ-876 oral suspension: 165 mg dose	Fed
Group 1: Day 20 - 21	TBAJ-876 oral suspension: 200 mg dose	Fasted
Group 2: Day 20	TBAJ-876 oral suspension: 200 mg dose	Fasted
Group 1: Day 22 - 24	TBAJ-876 oral suspension: 150 mg dose	Fed
Group 2: Day 21 - 24	TBAJ-876 oral suspension: 150 mg dose	Fed
Midazolam (Group 1)		
Day 1 and Day 20	Midazolam oral syrup: 2 mg	Fasted
Digoxin (Group 1)		
Day 2 and Day 21	Digoxin tablet: 0.25 mg	Fasted
TLD (fixed dose combination of dolutegravir 50 mg + tenofovir disoproxil fumarate 300 mg + Lamivudine 300 mg) (Group 2)		
Day 1 and Day 20	TLD	Fasted

*Refer to Section 6.3 for details on the intake of meals and beverages

Group 1:
Subjects will be housed in the clinic from at least 24 hours prior to dosing (from Day -1) and remain in the research center until completion of the procedures on Day 25 and will receive a phone call on Day 32 to check for AEs and concomitant medications.

- Subjects will check-in to the clinic following a 21-day screening period.
- On Day 1, subjects will receive a single dose of **Midazolam** (2 mg syrup) under fasted conditions.
- On Day 2, subjects will receive a single dose of **Digoxin** (0.25 mg) under fasted conditions.
- On Day 6 - 13, subjects will receive single daily doses of **200 mg TBAJ-876** under fed conditions.
- On Day 14 - 19, subjects will receive single daily doses of **165 mg TBAJ-876** under fed conditions
- On Day 20, subjects will receive a single dose of **Midazolam** + a single dose of **200 mg TBAJ-876** under fasted conditions.
- On Day 21, subjects will receive a single dose of **Digoxin** + a single dose of **TBAJ-876 200 mg** under fasted conditions.

- On Day 22 – 24, subjects will receive a single daily dose of **150 mg TBAJ-876** under Fed conditions and will be discharged from the clinic on Day 25.

Group 2:

To be conducted based on the Group 1 results. Subjects will be housed in the clinic from at least 24 hours prior to dosing (Day -1) and remain in the research center until completion of the procedures on Day 25 and receive a follow-up phone call on Day 32 to check for AEs and concomitant medications.

- Subjects will check into the clinic on Day -1 following a 21-day screening period**.**
- On Day 1, subjects will receive a single dose of a **Fixed Dose combination (TLD) of: Dolutegravir (DTG 50 mg) + Tenofovir disoproxil fumarate (TDF 300 mg) + Lamivudine (3TC 300 mg)** under fasted conditions.
- On Day 6 – 13, subjects will receive a single daily dose of **200 mg TBAJ-876** under fed conditions.
- On Day 14 – 19, subjects will receive a single daily dose of **165 mg TBAJ-876** under fed conditions.
- On Day 20, subjects will receive a single dose of the fixed dose combination **(TLD)** of DTG/TDF/3TC plus a single dose of **200 mg TBAJ-876** under fasted conditions.
- On Day 21 – 24, subjects will receive a single daily dose of **150 mg TBAJ-876** under fed conditions.
- On Day 25, subjects will be discharged from the clinic following completion of all procedures.

5 Study Population

Healthy adult male and female subjects, ages 18 – 55 inclusive. Subjects must meet all inclusion and no exclusion criteria within the screening period

Group 1: Plan to enroll:

Twenty- eight (28) subjects.

Group 2: Plan to enroll:

Sixteen (16) subjects.

5.1 Inclusion Criteria

All subjects 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, 18 to 55 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 Division of Microbiology and Infectious Diseases (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 and until 17 weeks after the last dose of TBAJ-876. The following are allowed birth control methods for this study:
    - Double barrier method (e.g., diaphragm with spermicide; condoms with spermicide).
    - Intrauterine device.
    - 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.
8. If a non-vasectomized male (or male vasectomized less than 6 months 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. Is willing and able to consume the entire high-calorie, high-fat breakfast meal in the timeframe required.

5.2 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History or presence of significant cardiovascular abnormalities, Heart Murmur, pulmonary, hepatic, renal, haematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological, or psychiatric disease as determined by the Investigator to be clinically relevant.
2. Any musculoskeletal abnormality (severe tenderness with marked impairment of activity) or musculoskeletal toxicity (frank necrosis).
3. History of any illness that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
4. Surgery within the past 90 days prior to dosing or other previous surgery as determined by the Investigator to be clinically relevant.
5. History or presence of alcoholism or drug abuse within the past 2 years as determined by the Investigator to be clinically relevant.
6. Female subjects who are pregnant or lactating.
7. Positive results for the urine drug/alcohol breath screen at screening or check-in.
8. Positive urine cotinine at screening or check-in.
9. Subjects with the following laboratory abnormalities at screening or Day -1:
   a. ALT or AST >1.0 times upper limit of normal (ULN)
   b. Creatinine grade 2 or greater (>1.5 times ULN)
   c. Total lipase or amylase >1.0 times ULN
   d. Total bilirubin grade 1 or greater (>1.0 times ULN)
   e. CPK >1.25 times ULN

   If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.
10. Positive results at screening for Human Immunodeficiency Virus (HIV), Hepatitis B Surface Antigen (HBsAg), or Hepatitis C antibodies (HCV**). Note: Subjects with positive HCV antibody but negative polymerase reaction (PCR) can be allowed in the study.**
11. Positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results within 6 days prior to Day 1.
12. Seated or supine blood pressure is less than 90/40 mmHg or greater than 150/90 mmHg at screening, Day -1 (check-in), or pre-dose. Out of range vital signs may be repeated twice for confirmation.

    Out of range values will not be considered AEs if the repeat assessment is in range.
13. Heart rate is lower than 60 beats per minute (bpm) or higher than 100 bpm at screening, Day -1 (check-in), or pre-dose. 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.
14. Any clinically significant electrocardiogram abnormality at Screening (as deemed by decision of the Investigator and the Sponsor's Medical Monitor).

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

a. Right or left axis deviation
b. Incomplete right bundle branch block
c. Isolated left anterior fascicular block (left anterior hemiblock) in younger athletic subjects

15. QTcF interval >450 ms for males or >470 ms for females at screening, Day -1, or Day 2 (pre-dose), or history of prolonged QT syndrome. PR interval < 200 ms at screening, Day -1 or Day 2 pre-dose. Out of range values may be repeated twice for confirmation. The average QTcF and PR intervals of the three ECG recordings will be used to determine qualification.
16. 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).
17. Use of any prescription medication within 14 days prior to dosing.
18. Use of any over the counter (OTC) medication, including herbal products and vitamins, within the 7 days prior to dosing, except acetaminophen. Up to 3 grams per day of acetaminophen is allowed at the discretion of the Investigator prior to dosing.
19. 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.
20. 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.
21. Participation in another clinical study within 30 days prior to dosing.
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. Is lactose intolerant
25. Current diagnosis of bulimia or anorexia nervosa
26. History or presence of allergic, or adverse response to midazolam, digoxin, dolutegravir, tenofovir, lamivudine or any related drugs.

5.3 Restrictions

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 (Day 32 phone call) 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.

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.

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.

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, cherries, 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.

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.

5.4 Stopping Rules

If any of the stopping rules are met, dosing must be stopped to allow review of the data by the Sponsor and the Investigator.

Rules for stopping dosing in all patients include the following:

- One subject experiences one or more drug-related serious adverse events (SAEs).
- 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).
- Two or more subjects have a QTcF ≥ 500 ms with an increase from baseline > 60 ms.
- 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.

5.5 Discontinuation from Treatment/Study

The following may result in the discontinuation of study treatment:

- Pregnancy
- Withdrawal of informed consent
- Investigator considers it for safety reasons in the best interest of the participant that he/she be discontinued
- Adverse event resulting in death
- Lost to follow-up
- Termination of the study by the sponsor

A subject may withdraw from the study at any time at his/her request (withdrawal of consent) or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues. All subjects withdrawn from study having received at least one dose of IMP will be requested to return for an early withdrawal visit and applicable safety Follow Up visits, as per Flow Chart (Section 1.2).

Subjects who withdraw from the study after having received study drug can be replaced after agreement between the Sponsor and investigator.

5.6 Trial Duration

Group 1 and Group 2

The planned length of participation in the study for each subject is approximately 34 Days from Check-in on Day -1 through completion of the clinical procedures on Day 25 and a follow-up phone call on Day 32.

6 Treatment

6.1 Administration of 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 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.

Refer to Appendix 2: Description and Composition of Investigational Medicinal Product (IMP) for details.

Each dose of 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.

6.2 Administration of the Interaction Products

When the TBAJ-876 is administered with the interaction products the interaction product will be administered first followed by TBAJ-876. The time of interaction product dosing will be considered ‘0’ hour. The elapsed time from start to finish for administration of both medications should not exceed 5 minutes. The time of dosing for each of the medications must be recorded on the CRF.

Each dose of the interaction products will be orally administered in accordance with individual package insert provided with the drug.

The 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 each dose, 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.

6.3 Fasting/Meals/Beverages

Optional meals (lunch, snack, and dinner) may be served the day of check-in and Day -1.

All subjects will then be required to fast for at least 10 hours before dosing on Days 1, 2, 20 and, in Group 1, 21. The subjects will fast for 4 hours after dosing.

Subjects during the Fed period will receive the required FDA standard high-fat, high-calorie breakfast that has to begin 30 minutes before the scheduled administration of the dose and end (last bite taken) within 5-10 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 (details below) should be ingested within 30 minutes or less.

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.

Beverages

Each dose of TBAJ-876 Oral Suspension and Interaction Product 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.

6.4 Subject Compliance

The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.5 Method of Treatment Assignment

Subjects will be randomized sequentially. All subjects will receive active drug.

6.6 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions as per details on IMP labelling, have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Upon completion or termination of the study, all unused and/or partially used IMPs must either be returned to Sponsor (or designated vendor) who will arrange for destruction or destroyed at site as agreed by Sponsor after final accountability has been confirmed.

The Investigator/designee will immediately inform the Sponsor of any quality issues arising with respect to the study medication. The Sponsor will take whatever action is required should such a situation arise.

Further guidance and information for the handling, storage, accountability, and final disposition of unused study treatment are provided in the Drug Preparation Protocol and/or Pharmacy Manual.

7 Study Procedures

7.1 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 21 days before study start:

- Demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m2), and smoking habits.
- Medical history
- Physical examination
- Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry)
- 12-lead safety ECG
- 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 fulfil 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.

7.2 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)
- 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

7.3 Subject Assignment

Subjects will receive a 4-digit number on Day 1 before IMP drug administration. The assignment of a number and code for participant identification is based on the obligation for anonymity.

7.4 Confinement

Group 1 and Group 2: Subjects will be admitted to the research center on Day -1 and remain in the research center until completion of procedures on Day 25.

7.5 Blood Sampling, Processing and Shipment

Blood samples will be collected as detailed in the Appendix 1.

Refer to the Schedule of Assessments & Procedures (Group 1: Section 1.2.1 or Group 2: Section 1.2.2) for specific blood collection time points. The PI, 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 the bioanalytical lab. After receiving the first set of plasma samples (back-up samples) will also be sent to the bioanalytical lab.

7.5.1 Group 1

A total of 144 mL (12 x 4 mL samples + 48 x 2 mL samples) will be collected from each participant for PK analysis. Approximately 141.1 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing. The total volume of blood collected from each participant in Group 1 will not exceed approximately 285.1 mL (Table 5).

Table 5 Total predicted Volume of Blood to be Collected for Testing: Group 1

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	19.5	19.5
Clinical labs during study (check-in and Days 2, 3, 7, 20, 21, 22 and 25 or early withdrawal	8	12.5	100
Coagulation	8	2.7	21.6
Pharmacokinetic analysis (TBAJ-876 Day 17)	12	4	48
Pharmacokinetic analysis (Midazolam Day 1 and Day 20)	22	2	44
Pharmacokinetic analysis (Digoxin Day 2 and Day 21)	26	2	52
Total			285.1

7.5.2 Group 2

A total of 172 mL (43 x 4 mL samples) will be collected from each participant for PK analysis. Approximately 100.7 mL of blood will be collected for the clinical laboratory evaluations and coagulation testing. The total volume of blood collected from each participant in Group 2 will not exceed approximately 294.7 mL (Table 6).

Table 6 Total predicted Volume of Blood to be Collected for Testing: Group 2

Reason for Collection Group 2	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	19.5	19.5
Clinical labs during study (check-in and Days 2, 7, 20, 21, 25 + early withdrawal	6	12.5	75
Coagulation	6	2.7	16.2
Pharmacokinetic analysis (TBAJ-876 Day 17)	12	4	48
Pharmacokinetic analysis (TLD Day 1)	17	4	68
Pharmacokinetic analysis (TLD Day 20)	17	4	68
		Total	294.7

7.5.3 Pharmacokinetic Sampling Time Windows

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

Table 7 Acceptable Pharmacokinetic Sampling Time Windows

Investigation and Examination	Allowable Time Window		
	Pre-dose	**0-24 hours**	**>24 hours to Day 25**
Plasma sample collection for pharmacokinetic assessment	Within 1 hour pre-dose	+- 5 minutes	+- 15 minutes

7.6 Safety Monitoring and Procedures

Refer to the Flow Chart in Section 1.2 for full details on the visit window periods.

The following safety and tolerability variables will be collected at the time points described in the study flow chart and assessed for evaluation of the safety endpoints:

7.6.1 Adverse Events

Subjects will be instructed to inform the study physician and/or research personnel of any Adverse Events (AE) 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 8 for details regarding AE reporting.

7.6.2 Laboratory parameters

Clinical laboratory evaluations will be performed at the times noted on the appropriate schedule of events (Section 1.2). A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform all clinical laboratory tests for this study.

- Hematology: hemoglobin, hematocrit, , red blood cell (RBC) count, white blood cell count with differential, 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, lipase, and amylase.

Note: If a subject experiences an increase in CPK Grade 2 (≥1.6 x ULN) the following tests should be performed: creatine phosphokinase of myocardial band (CPK-MB), trypsin like immunoreactivity, and cardiac troponin I.

- Serology: hepatitis B surface antigen, hepatitis C antibody, and HIV
- Coagulation: prothrombin time (PT2) and activated partial thromboplastin time (aPTT2).
- 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).

7.6.3 Vital Signs

Vital signs (blood pressure, heart rate [pulse], temperature, respiration rate, and pulse oximetry) should be measured at screening, check-in, and Day -1. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the defined time points in flowchart **at study hours 0, 0.5, 1, 2, 6, and 12 on Days 1, 2, 6, 20, 21, and 24.** Furthermore, vital signs should also be taken once daily on Day 7 through Day 20 (6 hours after Dosing) and Day 25 or early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences)Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should be measured after subjects are in supine position for at least 2 minutes and then again after standing for at least 1 minute (starting with 2 hours post dose), except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.

7.6.4 Physical Examination

Physical examinations including height and weight measurements and presence of heart murmur, will be conducted in the times noted on the appropriate events schedule (Section 1.2).

7.6.5 Electrocardiograms

Group 1

Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 3, 7, 20, 21, 22 and on Day 25 or upon early withdrawal**.** The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

Group 2

Single 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be completed at screening, Day -1, 2, 7, 20, 21 and 25 or upon early withdrawal. The pre-dose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a participant experiences a post-dosing 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.

7.6.6 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 centre. Emergency medical equipment including but not limited to resuscitation 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.

8 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.

8.1 Definitions

8.1.1 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.

8.1.2 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 fulfils 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".

8.1.3 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 considering follow-up information and send a SAE follow-up report with the updated causality assessment.

Table 8 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 9 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 Scale. 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 FDA assessment/grading scale (Appendix 3, A).

8.2 Reporting

8.2.1 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

8.3 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 related 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:

- Study name/number
- Study drug
- Investigator details (name, phone, fax, e-mail)
- Subject number
- Subject demographics
- Clinical event:
    - Description
    - Date of onset
    - Treatment (drug, dose, dosage form)
    - Adverse event relationship to study drug
    - Action taken regarding study drug in direct relationship to the AE
- If the AE was fatal or life-threatening
- If applicable, cause of death (whether or not the death was related to study drug)
- 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 Investigational New Drugs (IND) and 21 CFR 314.80 for marketed drugs (15-day alerts). The Institutional Review Board (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.

8.4 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.

8.5 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.

8.6 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.

8.7 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.

8.8 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.

8.9 Monitoring and Safety for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies Investigator's Brochure.

Considering the safety findings in the toxicology studies regarding observed myocardial, skeletal muscle and minimal and mild liver injury, extensive monitoring with emphasis on cardiovascular monitoring as well as monitoring to evaluate potential hepatocellular and skeletal muscle injury will be performed.

AEs still ongoing at the end of treatment in the study will be followed until satisfactory clinical resolution or stabilization or until the follow-up period and until all queries on those AEs have been resolved. Grade 3 and Grade 4 abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

Note: For Grade 3 or 4 laboratory toxicities, subjects should have a confirmatory measurement within 48 hours where possible. The recommendations for managing subjects below assume the laboratory abnormalities of concern have been confirmed.

If any of the following events occurs, the investigator should contact the Sponsor Medical Monitor to review:

- Grade 3 or 4 myalgia
- QTcF ≥ 500 ms with an increase from baseline > 60 ms (based on the mean of the replicate ECGs collected from the initial 12 lead ECG recording) confirmed within 30 minutes if subject is symptomatic, and as soon as possible for asymptomatic subjects.
- Grade 3 or Grade 4 adverse events in any one of the following laboratory parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase, total amylase or lipase confirmed within 48 hours.

9 General Principles

9.1 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).

9.2 Institutional Review Board

This protocol will be reviewed by an appropriate IRB and study enrolment 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.

9.3 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.

9.4 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 5.5.

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.

9.5 Termination of 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.

9.6 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.

9.7 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.

9.8 Reimbursement, Indemnity, and Insurance

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

10 Statistical Analysis

Statistical analyses will be performed using appropriate software, e.g. Phoenix™ WinNonlin® (Version 8.1 or higher, Pharsight Corporation) and SAS® (Version 9.4 or higher, SAS Institute Inc.). Pharmacokinetic parameters will be summarized using descriptive statistics.

All statistical reports must clearly indicate the group for the which the results are being summarised with a mention of the group in the report title.

The safety and tolerability and Pharmacokinetic Statistical Analysis Plan (SAP) which will contain details of the analyses specified in this section, will be drafted, and signed off prior to data lock. The SAP will be written by TKL.

10.1 Analysis Population

Safety population will include data from all subjects who received at least one dose of IMP and/or 1 dose of the interaction product. This population will be used to analyse the safety and tolerability endpoints.

Pharmacokinetic (PK) population will include data from all subjects who received at least one dose of IMP and/or 1 dose of the interaction product and whose plasma concentration data is available. This population will be used for the presentation of plasma concentration results as well as PK analysis.

10.2 Sample Size

Sample sizes were determined with the objective of demonstrating no relevant impact of TBAJ-876 on the probe substrates midazolam and digoxin or the components of the ARV combination TLD. Impact was measured by the geometric mean ratio (GMR), i.e., the ratio of the geometric mean AUC of the other drug with TBAJ-876 to the geometric mean AUC of the other drug without TBAJ-876, and similarly for C_{max}. Absence of relevant impact would be concluded if a 90% confidence interval for the GMR falls within an acceptable target range.

Per FDA's Guidance for Industry "Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions", the investigation of midazolam and digoxin is an Index Study, where the goal is to show no clinically significant interaction with a sensitive substrate. Therefore, the target range is the default no-effect range of 80% - 125%.

The investigation of the ARVs is a Concomitant Use Study, where the target range is based on concentration-response or other available information about the substrate drug. DTG and TDF (active moiety TFV) are the two components of TLD where an interaction might be possible based on their involvement with CYP3A4 and/or P-gp.

DTG is a CYP3A4 substrate, so induction of CYP3A4 may reduce DTG concentrations enough to impair efficacy. In the DTG label, the GMR for DTG was 0.65 when co-administered with fosamprenavir/ritonavir, and a doubling of the DTG dose was recommended. The GMR for DTG was 0.67 when co-administered with a multivitamin, and no change of the DTG dose was recommended. No dose adjustments were indicated due to interactions that increased DTG concentrations. Therefore, 67% seems to be a reasonable lower bound of the target range for DTG; a symmetric upper bound on the log scale would be 150%.

TDF is a substrate for P-gp, so inhibition of TDF may increase TDF concentrations enough to compromise safety. In the TDF label, TFV increased 32% when TDF was co-administered with lopinavir/ritonavir, and monitoring for toxicity was recommended but no dose change. No dose adjustments were indicated due to interactions that decreased DTG concentrations. Therefore,

133% seems to be a reasonable upper bound of the target range for TFV; a symmetric lower bound on the log scale would be 75%.

Sample sizes were determined assuming a two-period-fixed-sequence design, with the other drug given in Period 1 and the other drug plus TBAJ-876 in Period 2. Inference is then based on the within-subject differences $\log(AUC_{Period\ 2}) - \log(AUC_{Period\ 1})$ and similarly for C_{max}. Given the target range and desired power, the necessary input for determining sample size is the standard deviation of such a difference, σ_{AUC} or σ_{Cmax}.

The desired power was taken to be 90%. Table 10 shows relevant standard deviations and implied sample sizes:

Table 10 Standard Deviations and Sample Sizes

Drug	Maximum of σ_{AUC} and σ_{Cmax}.	Sample Size for 90% Power
Midazolam	0.290	20
Digoxin	0.325	25
Dolutegravir	0.290	8
Tenofovir	0.289	13
Source for midazolam and digoxin: 485516 (karger.com); standard deviations here are √2 x the values reported there. For dolutegravir and tenofovir, standard deviations were inferred from results reported in in the respective labels.		

For Group 1 of the study, the maximum of the required sample sizes for midazolam and digoxin was used, augmented by three additional subjects to allow for dropouts.

Similarly for Group 2.

10.3 Interim analysis

No formal interim analyses are planned for this study.

10.4 Demographics and Other Baseline Characteristics Analysis

Demographics and other baseline characteristics will be summarized by safety population. Medical history and major protocol deviations will be listed. Any abnormal findings judged to be clinically significant will be documented as medical history or as a treatment-emergent adverse event, depending upon time of observation, as appropriate.

Prior (prior to the start of treatment) medication use and concomitant (after the start of treatment) medication use will be summarized separately. If the end date of a prior medication occurs after treatment starts, then the medication will be reported in both the prior and concomitant tables and listings. These tables will present the number and percentage of subjects for each medication.

10.5 Safety and Tolerability Analysis

All safety analysis will be performed using the Safety analysis population and will be presented by group

All safety and tolerability data collected in the study will be listed by participant. The continuous variables will be summarized using number of eligible subjects (N), mean, standard deviation, median, minimum, and maximum. Frequency counts and percentages will be reported for categorical data.

Every cardiovascular safety incidence will be listed by timepoint with accompanying symptoms and with BP and HR measurements.

Laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis) will be summarized using descriptive statistics.

ECG results will be classified as normal or abnormal and summarized using frequency counts by group and time point of collection. HR and blood pressure values and changes from pre-dose will be summarized using descriptive statistics for continuous variables.

All adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of finalisation of the Protocol and will be presented by Preferred Term within each MedDRA System Organ Class (SOC). Details related to pregnancy will only be listed.

10.6 Pharmacokinetic analysis

Plasma concentrations of TBAJ-876 and interaction products will be listed by participant and visit details as applicable by group.

Summary statistics for analyte concentrations and the pharmacokinetic parameters, excluding T_{max}, will be arithmetic mean, geometric mean, standard deviation (SD), geometric coefficient of variation (%CV), minimum (min), median, maximum (max) and number of subjects (n). Median, min, max, and n will be reported for T_{max}. The reports will be presented by group.

Mean and individual concentrations (TBAJ-876, TBAJ-876 metabolites, and interaction products) will be plotted versus time.

For pharmacokinetic and statistical calculations, all digits will be used for calculation. The final reportable results or data will be presented by rounding off to two decimal digits, (this applies to individual data and descriptive statistics but not to CV (%), which is rounded off to one decimal digit).

Analysis for Group 1 will be conducted for induction potential of TBAJ-876 on the sensitive CYP3A4 substrate midazolam (M) and inhibition and induction potential of TBAJ-876 on the sensitive P-glycoprotein substrate Digoxin (D).

TBAJ-876 will be considered a moderate inducer of either CYP3A4, if the GMR of midazolam AUC <0.50 when co-administered with TBAJ-876 versus alone, or P-glycoprotein, if the GMR of digoxin AUC <0.50 when co-administered with TBAJ-876 versus alone. TBAJ-876 will be considered a moderate inhibitor of P-glycoprotein if the GMR of digoxin AUC ≥2.0 when co-administered with TBAJ-876 versus alone. These results will be used to decide whether to conduct of Group 2 of the study.

Pharmacokinetic parameters for TBAJ-876 and interaction products will be calculated as defined in Table 11 below.

Only subjects with measured concentrations adequate to determine PK parameters will be included in the PK parameter estimation.

Table 11 Pharmacokinetic Parameters

PK parameter	Definition
C_{max}	Maximum plasma concentration
AUC_{0-24}	Area under the concentration curve from 0 to 24 h post-dose, calculated by trapezoidal integration (only for TBAJ-876 and its metabolites on Day 17)
SAUC	Sum of AUC_{0-24} of TBAJ-876 and the M3 metabolite on Day 17.
AUC_{last}	Area under the concentration curve from 0 to the last measurable concentration (only for interaction products)
AUC_{inf}	Area under the concentration curve extrapolated to complete elimination (only for interaction products)
T_{max}	Time of the maximum plasma concentration, given as the nominal time point
C_{trough}	Trough concentrations (pre-dose or 24-hour) (only for TBAJ-876 and its metabolites on Day 17)
Λ_z	Elimination rate constant, calculated as the slope of log transformed concentration vs time during the elimination phase (only for interaction products)
$t_{½}$	Elimination half-life (only for interaction products)
CL/F	Apparent plasma drug clearance (only for interaction products)
V_Z/F	Apparent volume of distribution (only for interaction products)

To compare pharmacokinetic parameters of the interaction products with TBAJ-876 versus alone, analyses of variance (ANOVA) will be performed by the SAS Mixed Linear Models procedure. The model will include subject as a random effect and treatment (with TBAJ-876 versus alone) as a fixed effect. Following log transformation, geometric least-squares mean values and 95% confidence intervals (CIs) will be tabulated for each pharmacokinetic parameter. GMRs and 95% CIs will be calculated for C_{max}, AUC_{inf}, and AUC_{last} of interaction products, with TBAJ-876 versus alone.

11 Facilities

CLINICAL TRIAL SITE

TKL Research, Inc.
One Promenade Blvd. Suites 1101 & 1201
Fair Lawn, New Jersey 07410
Telephone: 201.587.0500

CLINICAL LABORATORIES

Laboratory Corporation of America Holdings

69 First Ave
Raritan NJ 08869

ANALYTICAL LABORATORIES

TBAJ-876 Analysis
Alliance Pharma, Inc
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

Interaction Products Analysis
Pyxant Labs
Contact: Adam Winstrom
4720 Forge Rd, Suite 108
Colorado Springs, CO 80907
Phone: 719.593.1165 ext. 42
Fax: 719.593.1625
Email: awinstrom@pyxant.com

12 Drug Supplies

Global Alliance for TB Drug Development will supply a sufficient quantity of the study drug, TBAJ-876 tartrate for preparation of TBAJ-876 Oral Suspension. Study drug will be shipped to TKL Research, Inc. 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 Ora-Sweet® (or equivalent) and other supplies will be procured, inventoried, and stored appropriately by TKL Research, Inc. 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 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.

TKL will procure the interaction products for Group 1: Midazolam syrup (2 mg) and Digoxin tablets (0.25 mg).

For Group 2, the fixed dose combination of dolutegravir (50 mg) plus tenofovir disoproxil fumarate (300 mg) plus lamivudine (300 mg), may not be available in the United States. TB Alliance will assist in procuring if needed.

13 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 this study.

14 References

1.TBAJ-876 Investigator's Brochure. Edition: Version 2.0, Dated 03 March 2021

2. Package Insert: Sirturo. Janssen Therapeutics, September 2014. Available at: https:www.accessdata.fda.gov/drugsatfda_docs/label/2012/20484s000lbl.pdf

3. Package Insert for Midazolam Hydrochloride Syrup

4. Digoxin Package Circular

5. ACRIPTEGA (Fixed Dose Combination Dolutegravir/Lamivudine/Tenofovir disoproxil fumarate) Clinical Professional information and Patient Information Leaflet

6. Tenofovir, Lamivudine, and Dolutegravir (TLD) Transition: General Information for Clients, Counselors, and other Service Providers

APPENDICES

APPENDIX 1 PHARMACOKINETIC SAMPLE COLLECTION, PROCESSING, AND SHIPMENT INSTRUCTIONS

Collection and Processing TBAJ-876

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 1.2).
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

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.

1. Samples will be packaged into cryoboxes and sorted by subject
2. 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.
3. 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.
4. 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

Collection and Processing: Midazolam, Digoxin and TLD

Plasma from whole blood Midazolam, Digoxin and TLD samples will be analyzed by Pyxant bioanalytical laboratory.

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 evacuated tubes containing K2-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 will be removed and placed in appropriately labelled 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 Pyxant bioanalytical laboratory for the determination of plasma concentrations of Midazolam and Digoxin using a validated procedure.
7	Blood sampling, plasma processing, and storage time will be documented in the study records.

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.

1. Samples will be packaged into cryoboxes and sorted by subject
2. 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.
3. 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.
4. All frozen pharmacokinetic samples will be transferred with accompanying documentation to:

   Pyxant Labs Inc.
   4720 Forge Road
   Suite 108 Colorado Springs, CO 80907

APPENDIX 2 DESCRIPTION AND COMPOSITION OF TEST PRODUCT

TBAJ-876 Oral Suspension

Description of the Dosage Form

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

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

Composition of the Drug Product

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	Quantity per Dose		
		150 mg	165 mg	200 mg
TBAJ-876 free base (equivalent amount of TBAJ-876 tartrate API[1])	Drug Substance	150 mg (185.4 mg)	165 mg (203.9)	200 mg (247.2 mg)
Ora-Sweet®,[2] (or equivalent)	Suspending vehicle	q.s. to 30 mL	q.s. to 33 mL	q.s. to 40 mL
Total Volume		30 mL	33mL	40mL

[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.

Container and Closure System

TBAJ-876 tartrate drug substance is shipped to the clinical study site in double low density polyethylene (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.

Interaction Products

Midazolam hydrochloride, Digoxin, Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine will be obtained by TKL pharmacy in original manufacturing packaging. Individual doses will be prepared by TKL pharmacy as per manufacturing instructions.

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
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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 BP, No treatment required[1]	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
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

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
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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	
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

A. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 - 12.0	9.5 - 10.9	8.0 - 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 - 12.4	8.5 - 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 - 15,000	15,001 - 20,000	20,001 - 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 - 3,500	1,500 - 2,499	1,000 - 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 - 1,000	500 - 749	250 - 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 - 2,000	1,000 - 1,499	500 - 999	< 500
Eosinophils - cell/mm^3	650 - 1500	1501 - 5000	> 5000	Hypereosinophilic syndrome
Platelets Decreased - cell/mm^3	125,000 - 140,000	100,000 - 124,000	25,000 - 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 - 1.10 x ULN**	1.11 - 1.20 x ULN	1.21 - 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 - 1.2 x ULN	1.21 - 1.4 x ULN	1.41 - 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 - 500	501 - 600	> 600	--
Fibrinogen decrease - mg/dL	150 - 200	125 - 149	100 - 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) - red blood cells per high power field (RBC/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.