Abbreviated CLINICAL STUDY REPORT FOR

CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)

Short Title: Novel **E**xperimental **C**OVID **T**herapies **A**ffecting Host **R**esponse (**NECTAR)**

COVID-19 Inpatient Host Tissue Master Protocol

ClinicalTrials.gov Number: NCT04924660

Supported by: NHLBI-CONNECTS

1 TITLE PAGE

Protocol Number:	ClinicalTrials.gov Identifier: NCT04924660 NECTAR EudraCT: 2022-000715-31 sIRB study number: 210982
Test Drugs:	TXA-127, TRV-027, Fostamatinib
Study Design:	Double blind, placebo-controlled, randomized, multi-site, platform trial
Study Phase:	III
Study Dates:	Trial / First participant randomized / Last participant completed TXA-127 / 2021-07-22 / 2022-10-01 TRV-027 / 2021-07-22 / 2022-07-26 Fostamatinib / 2021-11-17 / 2023-12-31
Early Termination:	TXA-127: 2022-04-20 TRV-027: 2022-04-20 Fostamatinib: 2023-09-27
Principal Investigator:	Study Chair: Sean P. Collins, MD, MSCI CCC PI: Wesley H. Self, MD, MPH DCC PI: Matthew S. Shotwell, PhD
Sponsor Signatory:	US: Sean P. Collins, MD, MSCI; Ex-US: Anton Pozniak, MD
Sponsor:	US: Vanderbilt University Medical Center ex-US: NEAT-ID
Document Date:	June 5, 2024

This study was conducted in compliance with Good Clinical Practices, including the archiving of essential documents.

Sponsor: Sean Collins, MD, MSCI

Clinical Protocol Number: IND 154000

Drug Name: TRV-027, TXA-127, Fostamatinib

Protocol Title: CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)

Approved by:

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Ex-U.S. Sponsor

Sean P. Collins — 2024-07-10

Sean P. Collins, MD, MSCI — Date

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Matthew Shotwell — 2024-07-09

Matt S. Shotwell, PhD — Date

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2024-07-09

Wesley H. Self, MD, MPH

Date

CCC PI

2 SYNOPSIS

Name of Sponsor/Company	Name of Finished Product	Active ingredient
• Trevena Inc. (TRV-027) • Constant Therapeutics (TXA-127) • Rigel Pharmaceuticals (Fostamatinib)	• TRV-027 • TXA-127 • Fostamatinib	• TRV-027: TRV027 • TXA-127: Angiotensin (1-7) (as the acetate salt) • Fostamatinib: R940406 (R406)
Protocol Number: IND 154000		
Title of Study: CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)		
Investigators and Study Centers: 65 sites across 6 countries (44 U.S., 21 ex-U.S.)		
Publication (reference): Self WH, Shotwell MS, Gibbs KW, et al. Renin-Angiotensin System Modulation With Synthetic Angiotensin (1-7) and Angiotensin II Type 1 Receptor–Biased Ligand in Adults With COVID-19: Two Randomized Clinical Trials. *JAMA.* 2023;329(14):1170–1182. doi:10.1001/jama.2023.3546		
Study Period (years): 2 years Date of First Enrollment: July 22, 2021 Date of Last Completed: September 27, 2023	Phase of Development: 3	
Objectives: The primary objective of the Master Protocol was to find effective strategies for inpatient management of patients with COVID-19. Therapeutic goals for patients hospitalized for COVID-19 include hastening recovery and preventing progression to critical illness, multiorgan failure, or death. Our objective was to determine whether modulating the host tissue response improves clinical outcomes among patients with COVID-19.		
Methodology: This platform was a randomized, placebo-controlled trial of agents targeting the host response in COVID-19 in hospitalized patients. The Master Protocol was designed to be flexible in the number of study arms, the use of a single placebo group, and the stopping and adding of new therapies.		
Number of Subjects (planned and analyzed): It was anticipated that approximately 1100 subjects (~300 per interventional treatment arm) would be randomized across approximately 50 U.S. and ex-U.S. sites. The actual number of subjects randomized was 899 across 65 investigative sites.		
Diagnosis and Main Criteria for Inclusion: 1. Hospitalized for COVID-19 2. ≥18 years of age 3. SARS-CoV-2 infection, documented by: a. a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR b. documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator (For non-NAT tests, only those deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests is maintained in protocol Appendix E. Non-NAT Tests Deemed with Equivalent Specificity to NAT by the Protocol Team). 4. Hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy 5. Symptoms or signs of acute COVID-19, defined as one or more of the following: a. cough b. reported or documented body temperature of 100.4° F or greater c. shortness of breath d. chest pain e. infiltrates on chest imaging (x-ray, CT scan, lung ultrasound)		
Subject Disposition: Subject dispositions are summarized in Table 5.		
Test Product, Dose and Mode of Administration, Batch Number: • TRV-027: a 12 mg/h as a continuous 24-hour infusion, infused 5 days or until hospital discharge, whichever came first. Batch number: P04920 • TXA-127: 0.5 mg/kg/day infused 3 hours daily for 5 days or until hospital discharge, whichever comes first. Batch number: 072I0520 • Fostamatinib: Study dose of 150mg orally twice daily for 14 days (28 doses). Study medication was continued as an outpatient if the patient was discharged prior to completing 28 doses. Batch numbers: CFTTM and CFTTN		

Name of Sponsor/Company	Name of Finished Product	Active ingredient
• Trevena Inc. (TRV-027) • Constant Therapeutics (TXA-127) • Rigel Pharmaceuticals (Fostamatinib)	• TRV-027 • TXA-127 • Fostamatinib	• TRV-027: TRV027 • TXA-127: Angiotensin (1-7) (as the acetate salt) • Fostamatinib: R940406 (R406)

Duration of Treatment:

- TRV-027: 5 days or until hospital discharge, whichever came first
- TXA-127: 5 days or until hospital discharge, whichever came first
- Fostamatinib: 14 days

Reference Therapy, Dose and Mode of Administration, Batch Number:
Commercially available, sterile saline was supplied and masked by an unblinded pharmacist at each study site to serve as the matching placebo for TXA-127 and TRV-027. Placebo tablets to match fostamatinib 100 mg and 150 mg (2 strengths of orange film-coated, plain, bioconvex tablets; the 150 mg tablet was oval, and the 100 mg tablet was round) were provided by Rigel Pharmaceuticals, Inc. (batch numbers CDYVH and CDYVM)

Endpoints for Evaluation:
Efficacy endpoints are not presented in this abbreviated CSR.
The primary efficacy endpoint was Oxygen free days through day 28. This is defined as days alive and without supplemental oxygen use during the first 28 days following randomization. Patients who die prior to day 28 were assigned -1 oxygen free days.
The secondary efficacy endpoints were:

- In hospital mortality
- Proportion of patients alive and oxygen free at days 14 and 28
- Proportion of patients with new invasive mechanical ventilation at day 28
- 28-day mortality
- 60-day mortality
- 90-day mortality
- WHO 8-point ordinal scale at 14, 28, and 60 days
  1: Ambulatory – Not hospitalized and no limitation of activities
  2: Ambulatory – Not hospitalized with limitation of activities or home oxygen use
  3: Hospitalized Mild Disease – Hospitalized, no oxygen therapy
  4: Hospitalized Mild Disease – Hospitalized, oxygen by mask or nasal prongs
  5: Hospitalized Severe Disease – Non-invasive ventilation or high-flow nasal cannula
  6: Hospitalized Severe Disease –Invasive mechanical ventilation
  7: Hospitalized Severe Disease – Invasive mechanical ventilation plus additional organ support with-vasopressors, RRT, or ECMO
  8: Dead
- Support-free days through Day 28, including: Hospital-free days, Ventilator-free days, Respiratory failure free days

The safety variables evaluated were:

- Adverse Events
- Protocol Specified Exempt Serious Events (PSESEs)
- Hypotension as defined by low arterial blood pressure leading to either [1] initiation or increase in vasopressor therapy, [2] administration of a fluid bolus of 500 ml or more, or [3] modification of the dose or discontinuation of the study drug.
- Allergic reaction, including angioedema and rash
- Incident renal replacement therapy during hospitalization
- Fostamatinib-specific safety variables included neutropenia, hypertension and liver transaminases at day 28

Statistical Methods:
Analysis Populations: For each trial, the following analysis datasets are defined for participants that were assigned to the active drug group and placebo participants that were *eligible* for the active drug group at the time of randomization:

Modified intention-to-treat dataset: The mITT analysis dataset includes all randomized participants grouped by study arm and active/placebo assignment at randomization, regardless of subsequent compliance or protocol violations, with the

following exceptions: 1. Participants who have not received the study drug assigned at randomization will be excluded. 2. Participants who were randomized and later found to be ineligible based on assessments initiated prior to randomization will be excluded. All statistical analyses will be implemented using mITT dataset unless otherwise explicitly specified in this statistical analysis plan.

Intention-to-treat dataset: The intention-to-treat (ITT) analysis dataset consists of all randomized participants grouped by study arm and active/placebo assignment at randomization regardless of subsequent compliance or protocol violations.

Safety dataset: The safety analysis dataset consists of all randomized participants grouped by study arm and active/placebo assignment at randomization regardless of subsequent compliance or protocol violations, with the following exceptions: Participants that were mistakenly administered an active medication when assigned to placebo, or vice versa, were grouped according to the medication administered.

Interim Analysis:
Two planned interim analyses were planned to occur separately for each study arm when the number of participants with complete 28-day follow-up (or were deceased, withdrawn, or lost-to-follow-up by day 28) reaches 33% and 67% of maximum enrollment for that arm. Interim analyses were executed by unblinded personnel only. Participant records that inform the primary outcome must undergo monitoring prior to interim (and final) analysis. At each interim analysis, a study arm may be stopped early if there is evidence for inferiority/harm. Enrollment in the trial will be stopped early if the posterior probability for inferiority/harm exceeds 0.95.

Final analysis occurred once enrollment, follow-up, and the required monitoring were completed. Should additional data be collected after enrollment is halted at an interim analysis, the final analysis will incorporate this additional data. If the trial was stopped early at an interim analysis due to evidence of inferiority/harm, a conclusion of inferiority/harm will be indicated if the posterior probability for inferiority/harm remains greater than 0.95 at the final analysis. If the trial was not stopped early at an interim analysis due to evidence of inferiority/harm, efficacy will be indicated if the posterior probability for efficacy regarding the primary outcome exceeds a threshold as follows: For studies under this master protocol, the efficacy threshold was selected using statistical simulation to ensure a type-I error probability of 2.5% for each study arm. In all other scenarios, the trial is inconclusive.

Primary Endpoint:
The primary outcome for the ACTIV-4 Host Tissue platform is oxygen free days (OFD) at day 28. OFD will be calculated as the number of calendar days during the first 28 days after randomization during which the patient was alive and not receiving supplemental oxygen therapy. Participants who chronically used supplemental oxygen prior to their COVID-19 illness will be considered oxygen free when their use of supplemental oxygen does not exceed the level of oxygen support (measured in daily L/min·h by nasal canula) used prior to COVID-19 illness. Supplemental oxygen therapy includes the following: supplemental oxygen by nasal cannula, supplemental oxygen by face mask, high flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). The day of randomization is defined as day 0. Starting with study day 1 (the day after randomization) and continuing for 28 days, study personnel will document whether the participant received supplemental oxygen therapy on each day for any duration of time. Use of supplemental oxygen at home after discharge will be assessed via telephone follow-up calls to the participant or surrogates. OFD will be calculated as 28 minus the number of days between and including the first and last days of supplemental oxygen use during the first 28 days after randomization. OFD will be coded as -1 for patients who died on or before study day 28. Hence, OFD may take any integer value between -1 and 28. OFD is an ordered categorical (i.e., ordinal) outcome that may be interpreted as a count of days.

The effect of the active drug versus placebo will be quantified using an odds ratio – the primary estimand – which quantifies the treatment effect on the odds of greater oxygen-free days at day 28. Based on the behavior of similar outcomes in prior trials,[2-6] we anticipate the distribution of the primary outcome to be irregular, with peaks around -1 to 0 and between 22 and 28 days. Thus, we will use a flexible semi-parametric approach for the primary outcome analysis. Estimation and inferences about the odds ratio will be made using Bayesian proportional odds (PO) logistic regression

methods, adjusting for the active drug vs placebo indicator variable, age group (18-30, 31-65, >65 years), sex at birth, and WHO COVID ordinal outcome score at baseline (4, 5, and 6-7).[7] Evidence for efficacy will be quantified using the posterior probability that the active drug versus placebo odds ratio is greater than one (i.e., treatment is associated with greater oxygen free days at day 28). This is denoted the "efficacy probability" or $P(\mathrm{OR} > 1|\mathrm{Data})$, where OR represents the odds ratio, and Data represents the mITT analysis dataset. The "inferiority/harm probability" is defined as $P(\mathrm{OR} \leq 1|\mathrm{Data})$. The primary analysis will be implemented separately for each study arm, where the placebo comparator group will consist of placebo participants that were eligible for the corresponding study arm at randomization, regardless of the study arm assigned. The primary and supplementary estimates will be presented with 95% credible intervals.

Secondary Endpoint:
Listed below are the ACTIV-4 Host Tissue platform secondary outcomes. The "Test Order" field indicates the order in which key secondary outcomes will be tested, using the fixed-sequence method, to control the familywise type-I error probability across the primary and key secondary outcomes.

Description	Type	Test Order	Analysis Method
Alive and oxygen free at day 14	Binary		LogR
Alive and oxygen free at day 28	Binary		LogR
Alive and respiratory failure-free at day 14	Binary		LogR
Alive and respiratory failure-free at day 28	Binary	1	LogR
Alive and free of new IMV at day 14	Binary		LogR
Alive and free of new IMV at day 28	Binary		LogR
Mortality in-hospital	Binary		LogR
Mortality at day 28	Binary	3	LogR
Mortality at day 60	Binary		LogR
Mortality at day 90	Binary		LogR
WHO 8-point ordinal scale at day 14	Ordinal		POLR
WHO 8-point ordinal scale at day 28	Ordinal	2	POLR
WHO 8-point ordinal scale at day 60	Ordinal		POLR
Hospital-free days at day 28	Ordinal		POLR
Respiratory failure-free days at day 28	Ordinal		POLR
Ventilator-free days at day 28	Ordinal		POLR

LogR – Logistic Regression; POLR – Proportional Odds Logistic Regression

The WHO 8-point ordinal scale is defined as most severe clinical status among the following on the day of assessment:

1. Ambulatory – Not hospitalized, no limitation of activities
2. Ambulatory – Not hospitalized with limitation of activities or home oxygen therapy
3. Hospitalized Mild Disease – Hospitalized, no oxygen therapy
4. Hospitalized Mild Disease – Oxygen by mask or nasal prongs
5. Hospitalized Severe Disease – Non-invasive ventilation of high-flow oxygen
6. Hospitalized Severe Disease – IMV
7. Hospitalized Severe Disease – IMV + organ support with-vasopressors, RRT, or ECMO
8. Dead

Alive and respiratory failure-free at day 28, the WHO 8-point ordinal scale at day 28, and Mortality at day 28 are key secondary outcomes that will be treated as a family for testing purposes, even though the studies will not be adequately powered to detect anything but a very strong treatment effect on these outcomes. A supplementary analysis to assess the evidence that treatment lowers the risk of death in a way that is consistent with its effect on nonfatal outcomes will be performed. A respiratory failure-free day is defined as a day alive without the use of HFNC, NIV, IMV, or ECMO.

Name of Sponsor/Company	Name of Finished Product	Active ingredient
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Safety Analysis:
Safety outcomes include the following events, assessed daily during hospitalization or intermittently following hospital discharge. For each event, we will analyze two composite binary outcomes: 1) the occurrence of one or more such events by the end of study day 7 and 2) the occurrence of one or more such events by the end of study day 28.

Description	Type	Analysis Method
Hypotension	Binary	LogR
Allergic reaction, rash, or angioedema	Binary	LogR
Incident renal replacement therapy	Binary	LogR
Other PSESE	Binary	LogR

LogR – Logistic Regression

Hypotension is defined by low arterial blood pressure leading to either [1] initiation or increase in vasopressor therapy, [2] administration of a fluid bolus of 500 ml or more, or [3] modification of the dose or discontinuation of the study drug.

Summary of Results:

Efficacy results for the TRV-027 and TXA-127 trials[1]:

Both trials met prespecified early stopping criteria for a low probability of efficacy. Of 343 patients in the TXA-127 trial (226 [65.9%] aged 31-64 years, 200 [58.3%] men, 225 [65.6%] White, and 274 [79.9%] not Hispanic), 170 received TXA-127 and 173 received placebo. Of 290 patients in the TRV-027 trial (199 [68.6%] aged 31-64 years, 168 [57.9%] men, 195 [67.2%] White, and 225 [77.6%] not Hispanic), 145 received TRV-027 and 145 received placebo. Compared with placebo, both TXA-127 (unadjusted mean difference, −2.3 [95% CrI, −4.8 to 0.2]; adjusted OR, 0.88 [95% CrI, 0.59 to 1.30]) and TRV-027 (unadjusted mean difference, −2.4 [95% CrI, −5.1 to 0.3]; adjusted OR, 0.74 [95% CrI, 0.48 to 1.13]) resulted in no difference in oxygen-free days. In the TXA-127 trial, 28-day all-cause mortality occurred in 22 of 163 patients (13.5%) in the TXA-127 group vs 22 of 166 patients (13.3%) in the placebo group (adjusted OR, 0.83 [95% CrI, 0.41 to 1.66]). In the TRV-027 trial, 28-day all-cause mortality occurred in 29 of 141 patients (20.6%) in the TRV-027 group vs 18 of 140 patients (12.9%) in the placebo group (adjusted OR, 1.52 [95% CrI, 0.75 to 3.08]). The frequency of the safety outcomes was similar with either TXA-127 or TRV-027 vs placebo.

Efficacy results for the fostamatinib trial:

Of the 400 participants randomized (234 [58.5%] were aged over 65 years, 210 [52.5%] men, 298 [74.5%] White, and 329 [82.3%] not Hispanic), 199 received fostamatinib and 201 received placebo. The mean number of oxygen-free days was 13.4 (standard deviation, 12.4) in the fostamatinib group and 14.2 (standard deviation, 12.1) in the placebo group (unadjusted mean difference, -1.26 [95% CI -3.52 to 1.00]; adjusted OR, 0.82 [95% CI: 0.58 to 1.17]). Mortality at 28 days occurred in 22 of 195 participants (11.3%) in the fostamatinib group and 16 of 197 participants (8.1%) in the placebo group (adjusted OR, 1.44 [95% CI: 0.72 to 2.90]). Liver transaminase elevation occurred more commonly in the fostamatinib group (11.6%) than in the placebo group (5.5%) (adjusted OR, 2.27 [95% CI, 1.07-4.84]. The incidences of the other safety outcomes were similar between groups.

Safety results for the TRV-027 and TXA-127 trials:

The frequency of the safety events and outcomes were similar for both the TXA-127 or TRV-027 groups vs placebo.

Safety results for the fostamatinib trial:

Liver transaminase elevation occurred more commonly in the fostamatinib group (11.6%) than in the placebo group (5.5%) (adjusted OR, 2.27 [95% CI, 1.07-4.84]. The incidences of the other safety outcomes were similar between groups.

Conclusions: Among adults hospitalized with COVID-19 and hypoxemia, neither TRV-027, TXA-127, or Fostamatinib increased the number of oxygen-free days compared with placebo.

Date of the Report: 6/5/2024

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TABLE OF TABLES

4 DOCUMENT GUIDE

4.1 List of Abbreviations and Definitions of Term

Table 1 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ADR	Adverse drug reaction
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Ang(1-7)	Angiotensin 1-7
AST	Aspartate aminotransferase
Bili	Bilirubin
BP	Blood pressure
Crl	Confidence interval
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DAIDS	Division of AIDS
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
F/u	Follow-up
g/dL	Grams per deciliter
HFNC	High flow nasal canula
Hgb	Hemoglobin
HR	Heart rate
IRB	Institutional review board
ITT	Intention to treat
IMV	Invasive mechanical ventilation
LogR	Logistical regression
MAP	Mean arterial pressure
Mcl	Microliter
Mg	Milligrams
mITT	Modified intention to treat
NA	Not applicable
NAT	Nucleic Acid Test
NIV	Non-invasive mechanical ventilation
No.	Number
OFD	Oxygen-free days
Plat	Platelet
PO	Proportional odds
POLR	Proportional odds logistical regression
PSESE	Protocol-specified exempt serious event
RAAS	Renin-angiotensin aldosterone system

Abbreviation	Definition
Resp	Respiratory
RRT	Renal replacement therapy
SAE	Serious adverse event
SpO2	Saturation of peripheral oxygen
Temp	Temperature
Trop1c	Troponin-I (conventional)
Troptc	Troponin-T (conventional)
Tropth	Troponin-T (high-sensitivity)
Trop1h	Troponin-I (high-sensitivity)
ULN	Upper limit of normal
WHO	World Health Organization

4.2 Site and Participant ID Format

Each participant was assigned a unique identifier at enrollment consisting of a three-digit site number and four-digit participant number separated by a hyphen. The participant number represents the order in which participants were enrolled at each site. For example, participant ID "004-0008" represents the 8th participant enrolled at site "004". Sites located within the United States have a site identifier beginning with "0" and sites located outside the United States have a site identifier beginning with a "2". The site names, countries in which the sites are located, and the numbers of participants enrolled are listed in the table below.

Table 2 Site ID, Name, and Enrollments

Site ID	Site Name	Country	N[a]
001	Vanderbilt University Medical Center (VUMC)	United States	76
003	Cleveland Clinic Foundation	United States	14
004	Intermountain Healthcare	United States	23
006	Newton-Wellesley Hospital	United States	22
011	University of Colorado Denver	United States	59
013	University of Florida, Gainesville	United States	30
019	University of New Mexico Health Sciences Center	United States	67
020	University of Utah Health Sciences Center	United States	11
022	Virginia Commonwealth University (VCU)	United States	35
023	Beth Israel Deaconess Medical Center (BIDMC)	United States	11
036	Cleveland Clinic Foundation, Akron	United States	2
038	Alexian Brothers Medical Center/St. Alexius Medical Center	United States	1
040	Washington University	United States	53
041	Cleveland Clinic Fairview Hospital	United States	2
044	Baystate Health	United States	3

Site ID	Site Name	Country	N[a]
048	Massachusetts General Hospital (MGH)	United States	2
049	University of Nebraska Medical Center	United States	44
052	Columbia University Medical Center	United States	1
053	Brigham and Women's Hospital	United States	1
054	Cedars-Sinai Medical Center	United States	10
059	Yale University	United States	67
060	Denver Health Medical Center	United States	25
061	Dignity Health Research Institute	United States	31
064	Hennepin County Medical Center	United States	5
065	Johns Hopkins University	United States	11
066	Medical University of South Carolina (MUSC)	United States	4
067	Montefiore Medical Center, Albert Einstein College of Medicine	United States	14
068	Jack D. Weiler Hospital, Albert Einstein College of Medicine	United States	11
069	Oregon Health and Science University (OHSU)	United States	40
070	Ochsner Health/LSU	United States	3
071	Stanford	United States	23
072	Temple University	United States	10
075	University of Cincinnati	United States	26
078	University of Virginia (UVA)	United States	28
079	Wake Forest Baptist Health	United States	83
080	University of North Carolina (UNC)	United States	5
081	St. Alexius Medical Center	United States	2
082	Johns Hopkins Bayview Medical Center	United States	1
083	Grady Memorial Hospital/Emory Ponce de Leon CRS	United States	1
087	Emory St. Joseph Hospital	United States	1
088	Emory Johns Creek	United States	11
090	Harborview/University of Washington	United States	1
096	University of Texas, Houston	United States	1
201	Hospital Universitario Fundacion Alcorcon	Spain	1
203	Hospital Clinico San Carlos	Spain	4
204	Hospital Clinico Universitario Lozano Blesa	Spain	2
205	Hospital General Universitario de Elche	Spain	8
206	Hospital Universitario Vall dHebron (VHIR)	Spain	4
211	Hospital Federal dos Servidores do Estado	Brazil	1
212	University Hospital Bonn	Germany	1
215	University of Milan - ASST Ovest Milanese	Italy	1
216	San Raffaele Turro Hospital	Italy	1

Site ID	Site Name	Country	N[a]
220	Worthwhile Clinical Trials (WWCT Lakeview Hospital)	South Africa	2
222	Clinical HIV Research Unit - Helen Joseph Hospital (WITS CHRU)	South Africa	3

[a]Number of participants enrolled.

4.3 Organization of Multiple Trials

ACTIV-4 Host Tissue is a shared-placebo clinical trial platform consisting of three blinded, placebo-controlled trials of therapeutic approaches of host-tissue targeted therapies in hospitalized COVID-19 patients. The abbreviated CSR for each of the three trials are presented in one document. Within each subsection, where appropriate, information relating to each trial is presented separately using trial-specific headers (i.e., "TXA-127", "TRV-027", or "Fostamatinib"). Because some placebo participants contribute to more than one trial, listings that present data for individual participants are combined across trials. In these listing, each participant is identified by the trial (i.e., the study drug) and active/placebo assignment at randomization and, for placebo participants, the trials for which that participant was eligible, and thus was a member of the corresponding placebo comparator groups.

4.4 ex-US Version of the Abbreviated CSR

An ex-US version of the abbreviated CSR is identical to the combined (US and ex-US) abbreviated CSR except that listings of individual participants include only those participants enrolled ex-US (i.e., subject IDs beginning with "2").

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

Study Design and Randomization: ACTIV-4 Host Tissue is a shared-placebo clinical trial platform consisting of three blinded, placebo-controlled trials of therapeutic approaches of host-tissue targeted therapies in hospitalized COVID-19 patients. The three therapies tested were TRV-027, TXA-127, and Fostamatinib. During the randomization process, each participant was assigned to one of the three trials/therapies and either the active drug or a matching placebo. Statistical analyses were implemented separately for each trial. However, placebo participants were pooled across trials. Specifically, for each trial, the placebo comparator group consisted of all placebo participants that were eligible for that trial at the time of randomization. A participant is considered eligible for a trial if assignment to that arm was a possible outcome of randomization. Participants that decline to participate in any one or more trial prior to randomization will be treated as ineligible for those trials. The randomization process is designed to ensure balance in each active drug group versus the corresponding placebo comparator group.

Analysis Datasets: For each trial, the analysis datasets are defined in the listing below. Where not specified, summaries in this document are made using the Safety dataset.

Modified intention-to-treat (mITT) dataset: The mITT analysis dataset includes all randomized participants grouped by study arm and active/placebo assignment at randomization, regardless of subsequent compliance or protocol violations, with the following exceptions: 1. Participants who have not received the study drug assigned at randomization will be excluded. 2. Participants who were randomized and later found to be ineligible based on assessments initiated prior to randomization will be excluded. All statistical analyses will be implemented using mITT dataset unless otherwise explicitly specified in this statistical analysis plan.

Intention-to-treat (ITT) dataset: The ITT analysis dataset consists of all randomized participants grouped by study arm and active/placebo assignment at randomization regardless of subsequent compliance or protocol violations.

Safety dataset: The safety analysis dataset consists of all randomized participants grouped by study arm and active/placebo assignment at randomization regardless of subsequent compliance or protocol violations, with the following exceptions: Participants that were mistakenly administered an active medication when assigned to placebo, or vice versa, were grouped according to the medication administered.

Additional details of the platform and individual trials are described in the final IRB-approved protocol (version 4.0 included as a separate attachment).

9.1.1 Study Schematic

Please see schedule of events on page 28 of the final IRB-approved protocol (version 4.0 included as a separate attachment).

9.1.2 Amendments to the Original Protocol

Table 3 Protocol Revisions

Protocol version	Protocol Date	Key Changes
1.3	6/2/2021	Original IRB-approved protocol
1.6	9/20/2021	Added fostamatinib, including labs that will need to be collected in this arm, additional requirements for stopping criteria in the fostamatinib arm Added APN01 to the platform Updates to the PSESE section to align with FDA reporting guidelines Added text to allow patients to opt out of certain arms Updates to the statistical analysis plan

1.7	10/6/2021	Added details for measuring blood pressure at home in the fostamatinib arm, when applicable
1.8	12/17/2021	Removed APN01 from the platform (no participants were randomized to this trial) Changed final biospecimen collection to 2-36 hours after final inpatient study treatment
1.9	3/22/2022	Updates in the text to provide flexibility for including international sites Remove RAAS biomarkers that will not be analyzed
2.0	6/7/2022	Remove TRV-027 and TXA-127 from the platform Update to exclusion criteria #1 and #2 to provide clarification Revised fostamatinib appendix to clarify exclusions of concomitant use with strong CYP3A4 medications
3.0	9/16/2022	Minor changes to respond to international regulatory requests Updated text to clarify emergency unblinding
4.0	10/18/2022	Added definition of Adverse Events of Special Interest (AESIs)

9.8 Changes in the Conduct of the Study or Planned Analysis

Table 4 Statistical Analysis Plan Revisions

SAP Version	Date	Summary of Revisions:
1.0	2/14/22	Initial version
1.1	3/8/22	Simplified interim stopping rule Updated simulation results and decision thresholds at interim and final analyses Clarified purpose of AngioNECTAR Additional details about sensitivity analyses Summarized sample size reassessment process Additional details of final analysis procedure
1.2	7/28/22	Clarifications to address FDA comments Additional tipping point analysis to evaluate effect of partially observed outcomes on efficacy conclusion

		Additional supplemental appendices
1.3	3/2/22	Clarifications to address FDA comments
1.4	11/14/23	Clarifications to address FDA comments Additional sensitivity analysis to evaluate treatment efficacy if the proportional odds assumption is violated.

10 STUDY PATIENTS

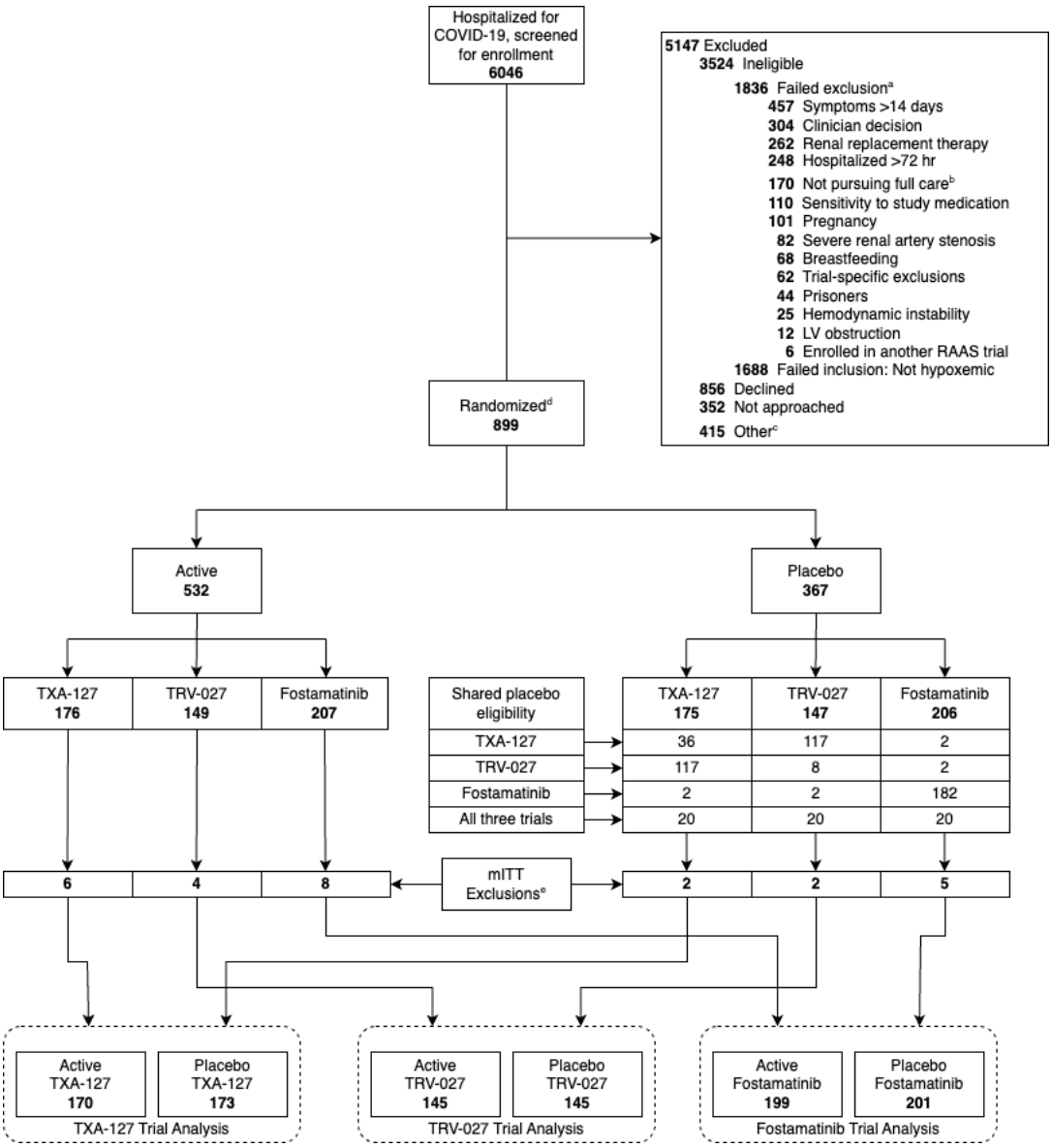
10.1 Disposition of Patients

The table below summarizes the disposition of all participants enrolled as part of the ACTIV-4 Host Tissue Platform organized by the trial and placebo/active assigned at randomization. Each participant was followed-up through day 90 unless the participant withdrew informed consent or was lost to follow-up. The CONSORT figure below gives the counts of active and placebo participants in the intention-to-treat (ITT) and modified intention-to-treat (mITT) datasets, accounting for placebo participants shared across the three trials. Two participants, 065-0001 and 061-0031 who were randomized to receive placebo TXA-127 and placebo Fostamatinib, respectively, and were eligible only for the trial to which they were randomized (i.e., not shared placebo participants), were inadvertently administered the active medication. Thus, for the safety datasets, these participants were grouped with participants assigned the active medication. In the Fostamatinib safety dataset, there are 208 active participants (vs 207 in the ITT dataset) and 205 placebo participants (vs 206 in the ITT dataset). In the TXA-127 safety dataset, there are 177 active participants (vs 176 in the ITT dataset) and 174 placebo participants (vs 175 in the ITT dataset). The TRV-027 safety dataset is identical to the TRV-027 ITT dataset. Unless otherwise specified, tabular summaries stratified by placebo/active group correspond to the safety dataset grouping.

Table 5 Disposition of Patients

Trial	**Fostamatinib**		**TRV-027**		**TXA-127**	
Randomized	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Number of participants	207	194	149	79	176	94
Disposition (%)						
Withdrawn day 0-27	8 (3.9)	5 (2.6)	3 (2.0)	1 (1.3)	8 (4.5)	2 (2.1)
Withdrawn day 28-90	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deceased day 0-27	22 (10.6)	14 (7.2)	29 (19.5)	6 (7.6)	23 (13.1)	16 (17.0)
Deceased day 28-90	5 (2.4)	8 (4.1)	5 (3.4)	6 (7.6)	6 (3.4)	3 (3.2)
LTFU 0-27	3 (1.4)	4 (2.1)	7 (4.7)	2 (2.5)	7 (4.0)	2 (2.1)
LTFU 28-59	7 (3.4)	3 (1.5)	3 (2.0)	1 (1.3)	5 (2.8)	1 (1.1)
LTFU 60-89	10 (4.8)	13 (6.7)	3 (2.0)	0 (0.0)	3 (1.7)	4 (4.3)
Completed day 90	152 (73.4)	147 (75.8)	99 (66.4)	63 (79.7)	124 (70.5)	66 (70.2)

Figure 1 Study CONSORT diagram



Footnotes:

a. The criteria were not mutually exclusive; some potential participants met multiple criteria for ineligibility.
b. The patient, clinical team, or both, was not pursuing full medical management (e.g., a do not intubate order).
c. Included (1) the patient was to be discharged from the hospital before the study procedures could be initiated, (2) the patient was enrolled in another trial, and (3) the patient's situation presented logistical challenges for trial enrollment.
d. Patients eligible for more than 1 trial were randomized with equal probability to a specific trial. Patients were randomized to active vs placebo in an *m*:1 ratio, with *m* representing the number of trials for which the patient was eligible. Patients randomized to placebo were included in the

placebo groups of each trial for which they were eligible. Patients randomized to receive an active drug contributed only to the trial they were randomized. Thus, patients randomized to receive active TXA-127 or active TRV-027 did not contribute to the fostamatinib trial, whereas patients assigned to placebo TXA-127 or TRV-027 and were eligible for the fostamatinib trial were included in the fostamatinib trial placebo groups. This design with a shared placebo group reduces the total number of patients who received placebo while retaining a statistically efficient 1:1 active vs placebo allocation for each trial.

e. Did not receive the randomized study drug or were randomized but did not meet the enrollment criteria.

12 SAFETY EVALUATION

This section presents a global summary of drug exposure, AEs, SAEs, AESIs, and PSESEs. Study drug exposure summaries are presented in section 12.1 using the mITT dataset. Adverse event summaries and listings are presented using the Safety dataset. Summaries of adverse events are presented in section 12.2. Summary of PSESEs are listed in section 12.3. Clinical laboratory data are presented in section 12.4. Vital sign data are presented in section 12.5. Safety conclusions are presented in section 12.6.

12.1 Extent of Drug Exposure

The tables below summarize the drug exposure for participants in the modified intention-to-treat (mITT) data set, and who received either the active medication or its placebo mimic.

- Error! Reference source not found.**TXA-127**

TXA-127 administered as 0.5 mg/kg intravenous over approximately 3 hours once daily for 5 days or until hospital discharge, whichever occurred first. To facilitate comparisons of study drug delivery, the table below shows patients in the modified intention-to-treat population who were randomized to receive active TXA-127 or the placebo mimic of the TXA-127. Some placebo participants in the TXA-127 trial received a placebo mimic of TRV-027 or Fostamatinib.

Table 6 TXA-127 Drug Exposure

	TXA-127 Active	TXA-127 Placebo
All patients		
Patient sample size, no.	170	92
Number of complete study drug doses delivered, no. (%)		
5 study drug doses	107 (62.9)	57 (62.0)
4 study drug doses	24 (14.1)	12 (13.0)
3 study drug doses	19 (11.2)	11 (12.0)
2 study drug doses	12 (7.1)	4 (4.4)
1 study drug doses	8 (4.7)	8 (8.7)
Patients alive and hospitalized ≥5 days (available for all 5 doses of study drug)		

Patient sample size, no.	121	62
Number of complete study drug doses delivered, no. (%)		
5 study drug doses	107 (88.4)	57 (91.9)
4 study drug doses	10 (8.3)	3 (4.8)
3 study drug doses	2 (1.7)	1 (1.6)
2 study drug doses	0 (0.0)	1 (1.6)
1 study drug doses	2 (1.7)	0 (0.0)

TRV-027

TRV-027 was administered as a continuous intravenous infusion at 12 mg/hour for 5 days (120 hours) or until hospital discharge, whichever occurred first. To facilitate comparisons of study drug delivery, the table below shows patients in the modified intention-to-treat population who were randomized to receive active TRV-027 or the placebo mimic of TRV-027. Some placebo participants in the TRV-027 trial received a placebo mimic of TXA-127 or Fostamatinib.

Table 7 TRV-027 Drug Exposure

	TRV-027 Active	TRV-027 Placebo
All patients		
Patient sample size, no.	145	79
Full dose of study drug received (12mg/hr for 120 hours = 1440 mg), no. (%)	93 (64.1)	51 (64.6)
Patients who did not receive a full dose of 120 hours of study drug delivery		
Patient sample size, no.	52	28
Reasons that full dose was not administered, no. (%)		
Hospital discharge/death	21 (40.4)	19 (67.9)
Adverse event	14 (25.0)	1 (3.6)
Other clinical event	7 (13.5)	6 (21.4)
Logistical barrier	10 (19.2)	2 (7.1)
Total dose administered (mg) among participants who did not receive the full dose (1440mg), median (IQR)	575.6 (261.7 - 953.0)	814.0 (473.0 - 1089.0)

Fostamatinib

Fostamatinib was administered as an oral medication twice daily for 14 days. To facilitate comparisons of study drug delivery, the table below shows patients in the modified intention-to-treat population who were randomized to the active Fostamatinib or the placebo mimic of Fostamatinib. Some placebo participants in the Fostamatinib trial received a placebo mimic of TXA-127 or TRV-027.

Table 8 Fostamatinib Drug Exposure

	Fostamatinib Active	Fostamatinib Placebo
All patients		
Patient sample size, no.	199	189
Full course of study drug received (28 pills) , no. (%)	57 (28.6)	59 (31.2)
Median (IQR) number of doses received	26 (12 – 28)	27 (11 – 28)

The table below summarizes all possible doses across participants who received either Fostamatinib or the placebo mimic of Fostamatinib, and the reasons for discontinuation of Fostamatinib.

Table 9 Fostamatinib Dose Detail and Reasons for Discontinuation

Dose status	Dose Detail	Reason for discontinuation	Combined Doses (N = 10864)	Placebo Doses (N = 5292)	Active Doses (N = 5572)
Taken			**7867**	**3850**	**4017**
	In-hospital		5059	2334	2725
	Outpatient		2808	1516	1292
Not taken			**2275**	**1116**	**1159**
	Death		199	107	92
	No reason given		399	162	237
	Permanent discontinuation [a]		*1360*	*706*	*654*
		AE/PSESE/ADR	*594*	*293*	*301*
		Logistical	*51*	*36*	*15*
		Patient refusal	*498*	*192*	*306*
		Other	*246*	*189*	*57*
		Clinical events (other than AE/PSESE)	*98*	*98*	*0*
	Temporary discontinuation [a]		317	141	176
		AE/PSESE	*120*	*35*	*85*
		Logistical	*76*	*47*	*29*
		Patient refusal	*39*	*11*	*28*
		Other	*109*	*65*	*44*
		Clinical events (other than AE/PSESE)	*72*	*55*	*17*
Uncertain due to loss to follow-up			**722**	**326**	**396**

[a] Discontinuation reasons are not mutually exclusive

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

Adverse event data were assessed continuously while hospitalized up to day 28 and on study days 1, 3, 7, 14, 21, 28 if those days occur after hospital discharge. Unless otherwise specified, summaries are cumulative from randomization to study day 28. For example, we report the count of adverse events that were reported within the follow-up period completed for each participant, up to study day 28. Table 10, 11, and 12 below summarize the number of subjects with at least one AEs, SAEs, and death for each trial.

TXA-127

Table 10 TXA-127 AEs, SAEs, and death

		Overall	Active	Placebo
n		351	177	174
Death (%)	No	289 (82.3)	146 (82.5)	143 (82.2)
	Yes	62 (17.7)	31 (17.5)	31 (17.8)
Death (%)	Alive	289 (82.3)	146 (82.5)	143 (82.2)
	Died after 7 days	50 (14.2)	25 (14.1)	25 (14.4)
	Died within 7 days	12 (3.4)	6 (3.4)	6 (3.4)
Any AE (%)	No	311 (88.6)	155 (87.6)	156 (89.7)
	Yes	40 (11.4)	22 (12.4)	18 (10.3)
Any SAE (%)	No	334 (95.2)	170 (96.0)	164 (94.3)
	Yes	17 (4.8)	7 (4.0)	10 (5.7)

TRV-027

Table 11 TRV-027 AEs, SAEs, and death

		Overall	Active	Placebo
n		296	149	147
Death (%)	No	236 (80.0)	115 (77.2)	122 (83.0)
	Yes	59 (20.0)	34 (22.8)	25 (17.0)
Death (%)	Alive	236 (80.0)	115 (77.2)	122 (83.0)
	Died after 7 days	47 (15.9)	26 (17.4)	21 (14.3)
	Died within 7 days	12 (4.1)	8 (5.4)	4 (2.7)
Any AE (%)	No	258 (87.5)	128 (85.9)	131 (89.1)
	Yes	37 (12.5)	21 (14.1)	16 (10.9)
Any SAE (%)	No	275 (93.2)	137 (91.9)	139 (94.6)
	Yes	20 (6.8)	12 (8.1)	8 (5.4)

Fostamatinib

Table 12 Fostamatinib AEs, SAEs, and death

		Overall	Active	Placebo
n		413	208	205
Death (%)	No	359 (86.9)	181 (87.0)	178 (86.8)
	Yes	54 (13.1)	27 (13.0)	27 (13.2)
Death (%)	Alive	359 (86.9)	181 (87.0)	178 (86.8)
	Died after 7 days	48 (11.6)	25 (12.0)	23 (11.2)
	Died within 7 days	6 (1.5)	2 (1.0)	4 (2.0)
Any AE (%)	No	312 (75.5)	153 (73.6)	159 (77.6)
	Yes	101 (24.5)	55 (26.4)	46 (22.4)
Any SAE (%)	No	343 (83.1)	172 (82.7)	171 (83.4)
	Yes	70 (16.9)	36 (17.3)	34 (16.6)

12.2.2 Summary of Serious Adverse Events by Organ System

The tables below summarize serious adverse events stratified by organ system for each of the three trials. The rows represent the number of each kind of adverse event recorded per participant.

TXA-127

Table 13 TXA-127 Adverse Events by Organ System

Characteristic	**N**	**Active**, N = 177[1]	**Placebo**, N = 174[1]	**Overall**, N = 351[1]
SAE classification - Cardiovascular	351			
0		175 (98.9%)	174 (100.0%)	349 (99.4%)
1		2 (1.13%)	0 (0%)	2 (0.57%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Respiratory	351			
0		176 (99.4%)	172 (98.9%)	348 (99.1%)
1		1 (0.56%)	1 (0.57%)	2 (0.57%)
2		0 (0%)	1 (0.57%)	1 (0.28%)

Characteristic	N	**Active**, N = 177[1]	**Placebo**, N = 174[1]	**Overall**, N = 351[1]
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Bleeding	351			
0		176 (99.4%)	173 (99.4%)	349 (99.4%)
1		1 (0.56%)	1 (0.57%)	2 (0.57%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Infection	351			
0		175 (98.9%)	168 (96.6%)	343 (97.7%)
1		2 (1.13%)	5 (2.87%)	7 (1.99%)
2		0 (0%)	1 (0.57%)	1 (0.28%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Thromboembolism	351			
0		176 (99.4%)	173 (99.4%)	349 (99.4%)
1		1 (0.56%)	1 (0.57%)	2 (0.57%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Gastrointestinal	351			
0		177 (100.0%)	173 (99.4%)	350 (99.7%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	1 (0.57%)	1 (0.28%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Liver injury	351			
0		177 (100.0%)	173 (99.4%)	350 (99.7%)
1		0 (0%)	0 (0%)	0 (0%)

Characteristic	N	**Active**, N = 177[1]	**Placebo**, N = 174[1]	**Overall**, N = 351[1]
2		0 (0%)	1 (0.57%)	1 (0.28%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Neurological	351			
0		176 (99.4%)	174 (100.0%)	350 (99.7%)
1		1 (0.56%)	0 (0%)	1 (0.28%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Pneumothorax or Pneumomediastinum	351			
0		177 (100.0%)	173 (99.4%)	350 (99.7%)
1		0 (0%)	1 (0.57%)	1 (0.28%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Renal	351			
0		177 (100.0%)	174 (100.0%)	351 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Hematological	351			
0		177 (100.0%)	174 (100.0%)	351 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Other	351			

Characteristic	N	**Active**, N = 177[1]	**Placebo**, N = 174[1]	**Overall**, N = 351[1]
0		177 (100.0%)	174 (100.0%)	351 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)

[1] n (%)

TRV-027

Table 14 TRV-027 Adverse Events by Organ System

Characteristic	N	**Active**, N = 149[1]	**Placebo**, N = 147[1]	**Overall**, N = 296[1]
SAE classification - Cardiovascular	296			
0		146 (98.0%)	147 (100.0%)	293 (99.0%)
1		3 (2.0%)	0 (0%)	3 (1.0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Respiratory	296			
0		146 (98.0%)	146 (99.3%)	292 (98.6%)
1		3 (2.0%)	1 (0.7%)	4 (1.4%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Bleeding	296			
0		149 (100.0%)	146 (99.3%)	295 (99.7%)
1		0 (0%)	1 (0.7%)	1 (0.3%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Infection	296			

Characteristic	N	**Active**, N = 149[1]	**Placebo**, N = 147[1]	**Overall**, N = 296[1]
0		146 (98.0%)	143 (97.3%)	289 (97.6%)
1		3 (2.0%)	4 (2.7%)	7 (2.4%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Thromboembolism	296			
0		148 (99.3%)	146 (99.3%)	294 (99.3%)
1		1 (0.7%)	1 (0.7%)	2 (0.7%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Gastrointestinal	296			
0		148 (99.3%)	146 (99.3%)	294 (99.3%)
1		1 (0.7%)	0 (0%)	1 (0.34%)
2		0 (0%)	1 (0.7%)	1 (0.34%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Liver injury	296			
0		149 (100.0%)	147 (100.0%)	296 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Neurological	296			
0		149 (100.0%)	147 (100.0%)	296 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)

Characteristic	N	**Active**, N = 149[1]	**Placebo**, N = 147[1]	**Overall**, N = 296[1]
SAE classification - Pneumothorax or Pneumomediastinum	296			
0		147 (98.7%)	146 (99.3%)	293 (99.0%)
1		1 (0.7%)	1 (0.7%)	2 (0.7%)
2		1 (0.7%)	0 (0%)	1 (0.3%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Renal	296			
0		149 (100.0%)	147 (100.0%)	296 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Hematological	296			
0		149 (100.0%)	147 (100.0%)	296 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Other	296			
0		147 (98.7%)	147 (100.0%)	294 (99.3%)
1		1 (0.67%)	0 (0%)	1 (0.34%)
2		1 (0.67%)	0 (0%)	1 (0.34%)
3 or more		0 (0%)	0 (0%)	0 (0%)

[1] n (%)

Fostamatinib

Table 15 Fostamatinib Adverse Events by Organ System

Characteristic	N	**Active**, N = 208[1]	**Placebo**, N = 205[1]	**Overall**, N = 413[1]
SAE classification - Cardiovascular	413			
0		206 (99.0%)	202 (98.5%)	408 (98.8%)
1		2 (1.0%)	3 (1.5%)	5 (1.2%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Respiratory	413			
0		200 (96.2%)	194 (94.6%)	394 (95.4%)
1		7 (3.37%)	10 (4.88%)	17 (4.1%)
2		1 (0.48%)	1 (0.49%)	2 (0.48%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Bleeding	413			
0		203 (97.6%)	203 (99.0%)	406 (98.3%)
1		5 (2.4%)	2 (1.0%)	7 (1.7%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Infection	413			
0		202 (97.1%)	195 (95.1%)	397 (96.1%)
1		6 (2.88%)	10 (4.88%)	16 (3.87%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Thromboembolism	413			
0		207 (99.5%)	203 (99.0%)	410 (99.3%)
1		1 (0.5%)	2 (1.0%)	3 (0.7%)

Characteristic	N	**Active**, N = 208[1]	**Placebo**, N = 205[1]	**Overall**, N = 413[1]
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Gastrointestinal	413			
0		201 (96.6%)	200 (97.6%)	401 (97.1%)
1		6 (2.9%)	4 (2.0%)	10 (2.4%)
2		1 (0.5%)	1 (0.5%)	2 (0.5%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Liver injury	413			
0		206 (99.0%)	201 (98.0%)	407 (98.5%)
1		2 (1.0%)	4 (2.0%)	6 (1.5%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Neurological	413			
0		205 (98.6%)	203 (99.0%)	408 (98.8%)
1		3 (1.4%)	2 (1.0%)	5 (1.2%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Pneumothorax or Pneumomediastinum	413			
0		208 (100.0%)	205 (100.0%)	413 (100.0%)
1		0 (0%)	0 (0%)	0 (0%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Renal	413			
0		207 (99.5%)	205 (100.0%)	412 (99.8%)
1		1 (0.5%)	0 (0%)	1 (0.2%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)

Characteristic	N	**Active**, N = 208[1]	**Placebo**, N = 205[1]	**Overall**, N = 413[1]
SAE classification - Hematological	413			
0		207 (99.5%)	205 (100.0%)	412 (99.8%)
1		1 (0.5%)	0 (0%)	1 (0.2%)
2		0 (0%)	0 (0%)	0 (0%)
3 or more		0 (0%)	0 (0%)	0 (0%)
SAE classification - Other	413			
0		201 (96.6%)	201 (98.0%)	402 (97.3%)
1		6 (2.88%)	3 (1.46%)	9 (2.18%)
2		1 (0.48%)	0 (0%)	1 (0.24%)
3 or more		0 (0%)	1 (0.49%)	1 (0.24%)

[1] n (%)

12.2.3 Summary of Adverse Events by Severity and Relatedness to Study Drug

12.2.3.1 Summary of Adverse Events by Severity

TXA-127

Table 16 TXA-127 Adverse Events by Severity

	Per-person Count/Value	Overall	Active	Placebo
n		351	177	174
Grade 1 AE (%)	0	346 (98.6)	173 (97.7)	173 (99.4)
	1	4 (1.1)	3 (1.7)	1 (0.6)
	5	1 (0.3)	1 (0.6)	0 (0.0)
Grade 2 AE (%)	0	343 (97.7)	172 (97.2)	171 (98.3)
	1	7 (2.0)	4 (2.3)	3 (1.7)
	2	1 (0.3)	1 (0.6)	0 (0.0)
Grade 3 AE (%)	0	327 (93.2)	164 (92.7)	163 (93.7)

	1	16 (4.6)	10 (5.6)	6 (3.4)
	2	4 (1.1)	1 (0.6)	3 (1.7)
	3	2 (0.6)	0 (0.0)	2 (1.1)
	4	2 (0.6)	2 (1.1)	0 (0.0)
Grade 4 AE (%)	0	343 (97.7)	174 (98.3)	169 (97.1)
	1	7 (2.0)	3 (1.7)	4 (2.3)
	3	1 (0.3)	0 (0.0)	1 (0.6)
Grade 5 (Event Resulting in death) AE (%)	0	345 (98.3)	174 (98.3)	171 (98.3)
	1	5 (1.4)	2 (1.1)	3 (1.7)
	2	1 (0.3)	1 (0.6)	0 (0.0)

TRV-027

Table 17 TRV-027 Adverse Events by Severity

	Per-person Count/Value	Overall	Active	Placebo
n		296	149	147
Grade 1 AE (%)	0	293 (99.0)	147 (98.7)	146 (99.3)
	1	3 (1.0)	2 (1.3)	1 (0.7)
Grade 2 AE (%)	0	292 (98.6)	148 (99.3)	144 (98.0)
	1	3 (1.0)	0 (0.0)	3 (2.0)
	2	1 (0.3)	1 (0.7)	0 (0.0)
Grade 3 AE (%)	0	281 (94.9)	142 (95.3)	139 (94.6)
	1	13 (4.4)	7 (4.7)	6 (4.1)
	2	1 (0.3)	0 (0.0)	1 (0.7)
	3	1 (0.3)	0 (0.0)	1 (0.7)
Grade 4 AE (%)	0	281 (94.9)	138 (92.6)	143 (97.3)
	1	12 (4.1)	8 (5.4)	4 (2.7)
	2	3 (1.0)	3 (2.0)	0 (0.0)
Grade 5 (Event Resulting in death) AE (%)	0	289 (97.6)	144 (96.6)	145 (98.6)

	1	7 (2.4)	5 (3.4)	2 (1.4)

Fostamatinib

Table 18 Fostamatinib Adverse Events by Severity

	Per-person Count/Value	Overall	Active	Placebo
n		413	208	205
Grade 1 AE (%)	0	395 (95.6)	195 (93.8)	200 (97.6)
	1	13 (3.1)	10 (4.8)	3 (1.5)
	2	3 (0.7)	2 (1.0)	1 (0.5)
	4	1 (0.2)	1 (0.5)	0 (0.0)
	6	1 (0.2)	0 (0.0)	1 (0.5)
Grade 2 AE (%)	0	389 (94.2)	197 (94.7)	192 (93.7)
	1	20 (4.8)	9 (4.3)	11 (5.4)
	2	3 (0.7)	2 (1.0)	1 (0.5)
	5	1 (0.2)	0 (0.0)	1 (0.5)
Grade 3 AE (%)	0	364 (88.1)	178 (85.6)	186 (90.7)
	1	38 (9.2)	23 (11.1)	15 (7.3)
	2	7 (1.7)	4 (1.9)	3 (1.5)
	3	3 (0.7)	3 (1.4)	0 (0.0)
	4	1 (0.2)	0 (0.0)	1 (0.5)
Grade 4 AE (%)	0	387 (93.7)	194 (93.3)	193 (94.1)
	1	20 (4.8)	11 (5.3)	9 (4.4)
	2	6 (1.5)	3 (1.4)	3 (1.5)
Grade 5 (Event Resulting in death) AE (%)	0	402 (97.3)	205 (98.6)	197 (96.1)

1	11 (2.7)	3 (1.4)	8 (3.9)

12.2.3.2 Summary of Adverse Events by Relatedness to Study Drug

The tables below summarize the relatedness for all adverse events.

TXA-127

Table 19 TXA-127 Relationship of Adverse Events to Study Drug

		Overall	Active	Placebo
# adverse events		73	41	32
relationship (%)	Definitely Related	1 (1.4)	1 (2.4)	0 (0.0)
	Possibly Related	11 (15.1)	10 (24.4)	1 (3.1)
	Probably or Possibly Related	1 (1.4)	0 (0.0)	1 (3.1)
	Probably Not Related	6 (8.2)	3 (7.3)	3 (9.4)
	Definitely Not Related	52 (71.2)	27 (65.9)	25 (78.1)
	Uncertain Relationship	2 (2.7)	0 (0.0)	2 (6.2)

TRV-027

Table 20 TRV-027 Relationship of Adverse Events to Study Drug

		Overall	Active	Placebo
# adverse events		51	30	21
relationship (%)	Possibly Related	8 (15.7)	7 (23.3)	1 (4.8)
	Probably or Possibly Related	2 (3.9)	1 (3.3)	1 (4.8)
	Probably Not Related	8 (15.7)	5 (16.7)	3 (14.3)
	Definitely Not Related	31 (60.8)	17 (56.7)	14 (66.7)
	Uncertain Relationship	2 (3.9)	0 (0.0)	2 (9.5)

Fostamatinib

Table 21 Fostamatinib Relationship of Adverse Events to Study Drug

		Overall	Active	Placebo
# adverse events		168	91	77
relationship (%)	Definitely Related	0 (0.0)	0 (0.0)	0 (0.0)
	Possibly Related	0 (0.0)	0 (0.0)	0 (0.0)
	Probably or Possibly Related	32 (19.0)	24 (26.4)	8 (10.4)
	Probably Not Related	77 (45.8)	40 (44.0)	37 (48.1)
	Definitely Not Related	56 (33.3)	25 (27.5)	31 (40.3)
	Uncertain Relationship	3 (1.8)	2 (2.2)	1 (1.3)

12.2.3.3 Severity of Adverse Events Related to Study Drug

The tables below summarize the DAIDS severity grading of adverse events marked as "Definitely Related", "Possibly Related", or "Probably or Possibly Related".

TXA-127

Table 22 TXA-127 Severity of Adverse Events Related to Study Drug

	Severity	Overall	Active	Placebo
n		13	11	2
DAIDS Grade (%)	Grade 1	6 (46.2)	6 (54.5)	0 (0.0)
	Grade 2	5 (38.5)	4 (36.4)	1 (50.0)
	Grade 3	1 (7.7)	1 (9.1)	0 (0.0)
	Grade 4	1 (7.7)	0 (0.0)	1 (50.0)

TRV-027

Table 23 TRV-027 Severity of Adverse Events Related to Study Drug

	Severity	Overall	Active	Placebo
n		10	8	2
DAIDS Grade (%)	Grade 1	1 (10.0)	1 (12.5)	0 (0.0)
	Grade 2	3 (30.0)	2 (25.0)	1 (50.0)
	Grade 4	6 (60.0)	5 (62.5)	1 (50.0)

Fostamatinib

Table 24 Fostamatinib Severity of Adverse Events Related to Study Drug

	Severity	Overall	Active	Placebo
n		32	24	8
DAIDS Grade (%)	Grade 1	9 (28.1)	9 (37.5)	0 (0.0)
	Grade 2	11 (34.4)	7 (29.2)	4 (50.0)
	Grade 3	10 (31.2)	7 (29.2)	3 (37.5)
	Grade 4	2 (6.2)	1 (4.2)	1 (12.5)

12.3 Protocol Specified Exempt Serious Events (PSESEs)

Outcomes of acute respiratory infection, COVID-19, and critical illness through study day 60 were systematically collected as Protocol-specified exempt serious events

(PSESEs). PSESEs were exempt from adverse event reporting unless: 1) the event is determined to be Serious and Definitely or Possibly Related to the study drug or study procedures; or 2) the event is determined to be Unexpected and Definitely or Possibly Related to the study drug or study procedures. PSESEs were reviewed regularly (unblinded, by treatment arm) by the DSMB. The table below lists all PSESEs for all participants enrolled as part of the ACTIV 4 Host Tissue platform, the study day on which the event occurred, and the type of event. For participants that received a placebo, the "Eligibility" field lists the trials for which the participant was eligible. For example, a placebo participant with eligibility "TXA-TRV-Fos" was eligible for all three trials and thus would be part of the placebo group for all three trials.

Certain types of PSESEs were identified and reported by the site coordinator on the basis of clinical data, whereas other types of PSESEs were identified (by the data coordinating center) by examining routinely collected (i.e., daily, closest to 8am) clinical laboratory data. The latter PSESEs were detected by comparing laboratory values with the following thresholds:

ALT > 102U/L for Men, ALT > 72U/L for Women (3x ULN)
ALT > 136U/L for Men, ALT > 96U/L for Women (3x ULN)
AST > 96U/L for Men, AST > 78U/L for Women (4x ULN)
AST > 128U/L for Men, AST > 104U/L for Women (4x ULN)
Bilirubin ≥ 2.4 mg/dL
ALC < 1000 cells/mcl
ANC < 500 cells/mcl
Hgb < 7g/dL for Men, Hgb < 6.5g/dL for Women
Platelets < 100 G/L
High-sensitivity Troponin I ("trophi") > 30 ng/L
Conventional Troponin I ("tropci") > 0.03 ng/mL
High-sensitivity Troponin T ("tropht") > 14 ng/L
Conventional Troponin T ("tropct") > 0.01 ng/mL

Some types of PSESEs were identified by both site coordinator report and by examining laboratory data, including thrombocytopenia, lymphopenia, anemia, neutropenia, elevations in alanine aminotransferase, elevations in aspartate aminotransferase, and acute kidney injury. In the individual listing, PSESEs identified using laboratory data refer to the specific thresholds listed above (e.g., "ALC <1000"), whereas PSESEs reported by the site coordinator refer to a condition (e.g., "lymphopenia").

The individual listing of PSESEs is attached as a separate document due to its size.

12.3.1 Analysis and Discussion of Safety Outcomes, Deaths, and PSESEs

TXA-127 and TRV-027[1]:

The frequency of safety outcomes, protocol-specified exempt serious events and adverse events was similar between the active group and placebo group in both the TXA-127 and

TRV-027 trials. The tables below present safety dataset summaries of PSESEs through day 60 stratified by group for both trials.

Analysis of pre-specified safety outcomes in the TXA-127 mITT cohort

Pre-specified safety outcome[c]	TXA-127 (n = 170)	Placebo (n=173)	Unadjusted absolute difference (95% CI)[a]	aOR (95% CI)[b]
Hypotension through day 7, no. (%)	19 (11.2)	21 (12.1)	-1.0 (-7.7, 5.8)	0.66 (0.31 - 1.38)
New renal replacement therapy through day 28, no. (%)	11 (6.5)	12 (6.9)	-0.5 (-5.8, 4.9)	0.75 (0.31 - 1.84)
Allergic reaction through day 7, no. (%)	3 (0)	0 (0)	--	--

Footnotes:

a. Binomial distribution with improper (flat) beta prior was used for each binary outcome.
b. aOR = adjusted Odds Ratio. Odds ratios were calculated using multivariable logistic regression adjusting for age group, sex, and baseline WHO COVID-19 clinical progression scale. (OR <1.0 is direction of fewer safety events in the active group).
c. All safety outcomes were based on clinician assessment during routine follow-up.

Analysis of pre-specified safety outcomes in the TRV-027 mITT cohort

Pre-specified safety outcome[c]	TRV-027 (n=145)	Placebo (n=145)	Unadjusted absolute difference (95% CI)[a]	aOR (95% CI)[b]
Hypotension through day 7, no. (%)	21 (14.5)	16 (11.0)	3.5 (-4.2, 11.1)	1.04 (0.48 - 2.25)
New renal replacement therapy through day 28, no. (%)	9 (6.2)	11 (7.6)	-1.4 (-7.3, 4.4)	0.59 (0.22 - 1.55)
Allergic reaction through day 7, no. (%)	0 (0)	0 (0)	--	--

Footnotes:

a. Binomial distribution with improper beta prior was used for each binary outcome.
b. aOR = adjusted Odds Ratio. Odds ratios were calculated using multivariable logistic regression adjusting for age group, sex, and baseline WHO COVID-19 clinical progression scale. (OR <1.0 is direction of fewer safety events in the active group).
c. All safety outcomes were based on clinician assessment during routine follow-up.

Table 25 TXA-127 Summary of PSESEs to Day 60

	Overall	Active	Placebo
	351	177	174
Seizure = Yes (%)	2 (0.6)	1 (0.6)	1 (0.6)
Stroke = Yes (%)	5 (1.4)	5 (2.8)	0 (0.0)

	Overall	Active	Placebo
Hypotension = Yes (%)	63 (17.9)	32 (18.1)	31 (17.8)
Atrial or ventricular arrhythmia event = Yes (%)	28 (8.0)	18 (10.2)	10 (5.7)
Cardiomyopathy event = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest event = Yes (%)	12 (3.4)	6 (3.4)	6 (3.4)
Myocardial injury event = Yes (%)	4 (1.1)	1 (0.6)	3 (1.7)
Acute coronary syndrome = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)
High-sensitivity Troponin I > 30 ng/L = Yes (%)	1 (0.3)	1 (0.6)	0 (0.0)
Conventional Troponin I > 0.03 ng/mL = Yes (%)	12 (3.4)	4 (2.3)	8 (4.6)
High-sensitivity Troponin T > 14 ng/L = Yes (%)	1 (0.3)	1 (0.6)	0 (0.0)
Conventional Troponin T > 0.01 ng/mL = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)
Combined abnormal Troponin = Yes (%)	14 (4.0)	6 (3.4)	8 (4.6)
Hypoxemia requiring supplemental oxygen = Yes (%)	17 (4.8)	9 (5.1)	8 (4.6)
Acute respiratory distress syndrome = Yes (%)	36 (10.3)	16 (9.0)	20 (11.5)
Non-invasive ventilation = Yes (%)	53 (15.1)	26 (14.7)	27 (15.5)
Invasive mechanical ventilation = Yes (%)	78 (22.2)	40 (22.6)	38 (21.8)
ECMO = Yes (%)	5 (1.4)	2 (1.1)	3 (1.7)
Elevation in alanine aminotransferase = Yes (%)	12 (3.4)	7 (4.0)	5 (2.9)
ALT > 102U/L for Men and > 72U/L for Women = Yes (%)	80 (22.8)	50 (28.2)	30 (17.2)
Reported ALT elevation or ALT > 102U/L for Men and > 72U/L for Women = Yes (%)	85 (24.2)	53 (29.9)	32 (18.4)
Number of measures that ALT > 102U/L for Men and > 72U/L for Women (%)			
0	271 (77.2)	127 (71.8)	144 (82.8)
1	22 (6.3)	13 (7.3)	9 (5.2)
2	13 (3.7)	9 (5.1)	4 (2.3)
3 or more	45 (12.8)	28 (15.8)	17 (9.8)
ALT > 136U/L for Men and > 96U/L for Women = Yes (%)	56 (16.0)	37 (20.9)	19 (10.9)
Reported ALT elevation or ALT > 136U/L for Men and > 96U/L for Women = Yes (%)	63 (17.9)	41 (23.2)	22 (12.6)
Number of measures that ALT > 136U/L for Men and > 96U/L for Women (%)			
0	295 (84.0)	140 (79.1)	155 (89.1)
1	24 (6.8)	18 (10.2)	6 (3.4)
2	10 (2.8)	7 (4.0)	3 (1.7)
3 or more	22 (6.3)	12 (6.8)	10 (5.7)
Number of measured ALT per participant (%)			
0	63 (17.9)	33 (18.6)	30 (17.2)
1	43 (12.3)	21 (11.9)	22 (12.6)
2	34 (9.7)	17 (9.6)	17 (9.8)
3 or more	211 (60.1)	106 (59.9)	105 (60.3)
ALT > 5x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	15 (4.3)	11 (6.2)	4 (2.3)
ALT > 10x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	2 (0.6)	1 (0.6)	1 (0.6)
Elevation in aspartate aminotransferase = Yes (%)	6 (1.7)	1 (0.6)	5 (2.9)
AST > 96U/L for Men and > 78U/L for Women = Yes (%)	49 (14.0)	24 (13.6)	25 (14.4)
Reported AST elevation or AST > 96U/L for Men and > 78U/L for Women = Yes (%)	53 (15.1)	25 (14.1)	28 (16.1)

	Overall	Active	Placebo
Number of measures that AST > 96U/L for Men and > 78U/L for Women (%)			
0	302 (86.0)	153 (86.4)	149 (85.6)
1	19 (5.4)	9 (5.1)	10 (5.7)
2	10 (2.8)	5 (2.8)	5 (2.9)
3 or more	20 (5.7)	10 (5.6)	10 (5.7)
AST > 128U/L for Men and > 104U/L for Women = Yes (%)	32 (9.1)	17 (9.6)	15 (8.6)
Reported AST elevation or AST > 128U/L for Men and > 104U/L for Women = Yes (%)	36 (10.3)	18 (10.2)	18 (10.3)
Number of measures that AST > 128U/L for Men and > 104U/L for Women (%)			
0	319 (90.9)	160 (90.4)	159 (91.4)
1	16 (4.6)	11 (6.2)	5 (2.9)
2	6 (1.7)	1 (0.6)	5 (2.9)
3 or more	10 (2.8)	5 (2.8)	5 (2.9)
Number of measured AST per participant (%)			
0	64 (18.2)	33 (18.6)	31 (17.8)
1	44 (12.5)	22 (12.4)	22 (12.6)
2	32 (9.1)	16 (9.0)	16 (9.2)
3 or more	211 (60.1)	106 (59.9)	105 (60.3)
AST > 5x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	4 (1.1)	2 (1.1)	2 (1.1)
AST > 10x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	2 (0.6)	1 (0.6)	1 (0.6)
Bilirubin 2.4 mg/dL or higher = Yes (%)	20 (5.7)	11 (6.2)	9 (5.2)
Number of measure that bilirubin 2.4 mg/dL or higher (%)			
0	331 (94.3)	166 (93.8)	165 (94.8)
1	10 (2.8)	5 (2.8)	5 (2.9)
2	5 (1.4)	3 (1.7)	2 (1.1)
3 or more	5 (1.4)	3 (1.7)	2 (1.1)
Number of measured bilirubin per participant (%)			
0	63 (17.9)	33 (18.6)	30 (17.2)
1	42 (12.0)	21 (11.9)	21 (12.1)
2	36 (10.3)	18 (10.2)	18 (10.3)
3 or more	210 (59.8)	105 (59.3)	105 (60.3)
Acute pancreatitis = Yes (%)	1 (0.3)	0 (0.0)	1 (0.6)
Acute kidney injury = Yes (%)	5 (1.4)	2 (1.1)	3 (1.7)
KDIGO AKI Stage 1 = Yes (%)	69 (19.7)	36 (20.3)	33 (19.0)
KDIGO AKI Stage 2 = Yes (%)	42 (12.0)	22 (12.4)	20 (11.5)
Reported AKI or KDIGO AKI stage I = Yes (%)	70 (19.9)	36 (20.3)	34 (19.5)
Reported AKI or KDIGO AKI stage II = Yes (%)	44 (12.5)	22 (12.4)	22 (12.6)
KDIGO AKI Stage 1 within 7 days = Yes (%)	48 (13.7)	27 (15.3)	21 (12.1)
KDIGO AKI Stage 2 within 7 days = Yes (%)	22 (6.3)	14 (7.9)	8 (4.6)
Symptomatic hypoglycemia = Yes (%)	1 (0.3)	1 (0.6)	0 (0.0)
Lymphopenia = Yes (%)	4 (1.1)	2 (1.1)	2 (1.1)
ALC < 1000 cells/mcl = Yes (%)	130 (37.0)	64 (36.2)	66 (37.9)
Reported Lymphopenia or ALC < 1000 cells/mcl = Yes (%)	133 (37.9)	66 (37.3)	67 (38.5)
Number of measured ALC per participant (%)			

	Overall	Active	Placebo
0	179 (51.0)	93 (52.5)	86 (49.4)
1	30 (8.5)	19 (10.7)	11 (6.3)
2	19 (5.4)	9 (5.1)	10 (5.7)
3 or more	123 (35.0)	56 (31.6)	67 (38.5)
Neutropenia = Yes (%)	1 (0.3)	0 (0.0)	1 (0.6)
ANC < 500 cells/mcl = Yes (%)	10 (2.8)	4 (2.3)	6 (3.4)
Reported Neutropenia or ANC < 500 cells/mcl = Yes (%)	11 (3.1)	4 (2.3)	7 (4.0)
Number of measured ANC per participant (%)			
0	181 (51.6)	94 (53.1)	87 (50.0)
1	29 (8.3)	18 (10.2)	11 (6.3)
2	19 (5.4)	9 (5.1)	10 (5.7)
3 or more	122 (34.8)	56 (31.6)	66 (37.9)
Anemia = Yes (%)	4 (1.1)	1 (0.6)	3 (1.7)
Hgb < 7g/dL for Men and < 6.5g/dL for Women = Yes (%)	15 (4.3)	6 (3.4)	9 (5.2)
Reported Anemia or Hgb < 7g/dL for Men and < 6.5g/dL for Women = Yes (%)	19 (5.4)	7 (4.0)	12 (6.9)
Thrombocytopenia = Yes (%)	2 (0.6)	0 (0.0)	2 (1.1)
Platelets < 100 G/L = Yes (%)	43 (12.3)	19 (10.7)	24 (13.8)
Reported Thrombocytopenia or Platelets < 100 G/L = Yes (%)	43 (12.3)	19 (10.7)	24 (13.8)
Venous thromboembolism = Yes (%)	26 (7.4)	13 (7.3)	13 (7.5)
Severe dermatologic reaction = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)

Table 26 TRV-027 Summary of PSESEs to Day 60

	Overall	Active	Placebo
n	296	149	147
Seizure = Yes (%)	3 (1.0)	2 (1.3)	1 (0.7)
Stroke = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension = Yes (%)	58 (19.6)	33 (22.1)	25 (17.0)
Atrial or ventricular arrhythmia event = Yes (%)	15 (5.1)	8 (5.4)	7 (4.8)
Cardiomyopathy event = Yes (%)	1 (0.3)	1 (0.7)	0 (0.0)
Cardiac arrest event = Yes (%)	12 (4.1)	7 (4.7)	5 (3.4)
Myocardial injury event = Yes (%)	2 (0.7)	0 (0.0)	2 (1.4)
Acute coronary syndrome = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)
High-sensitivity Troponin I > 30 ng/L = Yes (%)	1 (0.3)	1 (0.7)	0 (0.0)
Conventional Troponin I > 0.03 ng/mL = Yes (%)	8 (2.7)	2 (1.3)	6 (4.1)
High-sensitivity Troponin T > 14 ng/L = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)
Conventional Troponin T > 0.01 ng/mL = Yes (%)	1 (0.3)	1 (0.7)	0 (0.0)
Combined abnormal Troponin = Yes (%)	10 (3.4)	4 (2.7)	6 (4.1)
Hypoxemia requiring supplemental oxygen = Yes (%)	12 (4.1)	4 (2.7)	8 (5.4)
Acute respiratory distress syndrome = Yes (%)	30 (10.1)	14 (9.4)	16 (10.9)
Non-invasive ventilation = Yes (%)	45 (15.2)	24 (16.1)	21 (14.3)
Invasive mechanical ventilation = Yes (%)	70 (23.6)	39 (26.2)	31 (21.1)
ECMO = Yes (%)	6 (2.0)	3 (2.0)	3 (2.0)
Elevation in alanine aminotransferase = Yes (%)	12 (4.1)	7 (4.7)	5 (3.4)
ALT > 102U/L for Men and > 72U/L for Women = Yes (%)	74 (25.0)	49 (32.9)	25 (17.0)

	Overall	Active	Placebo
Reported ALT elevation or ALT > 102U/L for Men and > 72U/L for Women = Yes (%)	78 (26.4)	51 (34.2)	27 (18.4)
Number of measures that ALT > 102U/L for Men and > 72U/L for Women (%)			
0	222 (75.0)	100 (67.1)	122 (83.0)
1	22 (7.4)	13 (8.7)	9 (6.1)
2	12 (4.1)	8 (5.4)	4 (2.7)
3 or more	40 (13.5)	28 (18.8)	12 (8.2)
ALT > 136U/L for Men and > 96U/L for Women = Yes (%)	49 (16.6)	35 (23.5)	14 (9.5)
Reported ALT elevation or ALT > 136U/L for Men and > 96U/L for Women = Yes (%)	55 (18.6)	38 (25.5)	17 (11.6)
Number of measures that ALT > 136U/L for Men and > 96U/L for Women (%)			
0	247 (83.4)	114 (76.5)	133 (90.5)
1	16 (5.4)	10 (6.7)	6 (4.1)
2	6 (2.0)	5 (3.4)	1 (0.7)
3 or more	27 (9.1)	20 (13.4)	7 (4.8)
Number of measured ALT per participant (%)			
0	51 (17.2)	22 (14.8)	29 (19.7)
1	38 (12.8)	21 (14.1)	17 (11.6)
2	37 (12.5)	22 (14.8)	15 (10.2)
3 or more	170 (57.4)	84 (56.4)	86 (58.5)
ALT > 5x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	16 (5.4)	15 (10.1)	1 (0.7)
ALT > 10x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	6 (2.0)	6 (4.0)	0 (0.0)
Elevation in aspartate aminotransferase = Yes (%)	10 (3.4)	5 (3.4)	5 (3.4)
AST > 96U/L for Men and > 78U/L for Women = Yes (%)	55 (18.6)	35 (23.5)	20 (13.6)
Reported AST elevation or AST > 96U/L for Men and > 78U/L for Women = Yes (%)	60 (20.3)	37 (24.8)	23 (15.6)
Number of measures that AST > 96U/L for Men and > 78U/L for Women (%)			
0	241 (81.4)	114 (76.5)	127 (86.4)
1	24 (8.1)	16 (10.7)	8 (5.4)
2	9 (3.0)	5 (3.4)	4 (2.7)
3 or more	22 (7.4)	14 (9.4)	8 (5.4)
AST > 128U/L for Men and > 104U/L for Women = Yes (%)	35 (11.8)	24 (16.1)	11 (7.5)
Reported AST elevation or AST > 128U/L for Men and > 104U/L for Women = Yes (%)	40 (13.5)	26 (17.4)	14 (9.5)
Number of measures that AST > 128U/L for Men and > 104U/L for Women (%)			
0	261 (88.2)	125 (83.9)	136 (92.5)
1	15 (5.1)	11 (7.4)	4 (2.7)
2	9 (3.0)	5 (3.4)	4 (2.7)
3 or more	11 (3.7)	8 (5.4)	3 (2.0)
Number of measured AST per participant (%)			
0	51 (17.2)	21 (14.1)	30 (20.4)
1	40 (13.5)	23 (15.4)	17 (11.6)
2	36 (12.2)	22 (14.8)	14 (9.5)

	Overall	Active	Placebo
3 or more	169 (57.1)	83 (55.7)	86 (58.5)
AST > 5x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	7 (2.4)	6 (4.0)	1 (0.7)
AST > 10x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	6 (2.0)	5 (3.4)	1 (0.7)
Bilirubin 2.4 mg/dL or higher = Yes (%)	14 (4.7)	6 (4.0)	8 (5.4)
Number of measure that bilirubin 2.4 mg/dL or higher (%)			
0	282 (95.3)	143 (96.0)	139 (94.6)
1	8 (2.7)	3 (2.0)	5 (3.4)
2	2 (0.7)	0 (0.0)	2 (1.4)
3 or more	4 (1.4)	3 (2.0)	1 (0.7)
Number of measured bilirubin per participant (%)			
0	51 (17.2)	22 (14.8)	29 (19.7)
1	38 (12.8)	21 (14.1)	17 (11.6)
2	37 (12.5)	22 (14.8)	15 (10.2)
3 or more	170 (57.4)	84 (56.4)	86 (58.5)
Acute pancreatitis = Yes (%)	2 (0.7)	1 (0.7)	1 (0.7)
Acute kidney injury = Yes (%)	7 (2.4)	4 (2.7)	3 (2.0)
KDIGO AKI Stage 1 = Yes (%)	63 (21.3)	36 (24.2)	27 (18.4)
KDIGO AKI Stage 2 = Yes (%)	38 (12.8)	20 (13.4)	18 (12.2)
Reported AKI or KDIGO AKI stage I = Yes (%)	65 (22.0)	37 (24.8)	28 (19.0)
Reported AKI or KDIGO AKI stage II = Yes (%)	42 (14.2)	22 (14.8)	20 (13.6)
KDIGO AKI Stage 1 within 7 days = Yes (%)	37 (12.5)	22 (14.8)	15 (10.2)
KDIGO AKI Stage 2 within 7 days = Yes (%)	15 (5.1)	8 (5.4)	7 (4.8)
Symptomatic hypoglycemia = Yes (%)	1 (0.3)	1 (0.7)	0 (0.0)
Lymphopenia = Yes (%)	7 (2.4)	5 (3.4)	2 (1.4)
ALC < 1000 cells/mcl = Yes (%)	106 (35.8)	44 (29.5)	62 (42.2)
Reported Lymphopenia or ALC < 1000 cells/mcl = Yes (%)	109 (36.8)	46 (30.9)	63 (42.9)
Number of measured ALC per participant (%)			
0	156 (52.7)	85 (57.0)	70 (48.3)
1	20 (6.8)	11 (7.4)	9 (6.1)
2	19 (6.4)	12 (8.1)	7 (4.8)
3 or more	101 (34.1)	41 (27.5)	60 (40.8)
Neutropenia = Yes (%)	1 (0.3)	0 (0.0)	1 (0.7)
ANC < 500 cells/mcl = Yes (%)	9 (3.0)	3 (2.0)	6 (4.1)
Reported Neutropenia or ANC < 500 cells/mcl = Yes (%)	10 (3.4)	3 (2.0)	7 (4.8)
Number of measured ANC per participant (%)			
0	157 (53.0)	85 (57.0)	72 (49.0)
1	21 (7.1)	12 (8.1)	9 (6.1)
2	18 (6.1)	11 (7.4)	7 (4.8)
3 or more	100 (33.8)	41 (27.5)	59 (40.1)
Anemia = Yes (%)	7 (2.4)	4 (2.7)	3 (2.0)
Hgb < 7g/dL for Men and < 6.5g/dL for Women = Yes (%)	11 (3.7)	6 (4.0)	5 (3.4)
Reported Anemia or Hgb < 7g/dL for Men and < 6.5g/dL for Women = Yes (%)	18 (6.1)	10 (6.7)	8 (5.4)
Thrombocytopenia = Yes (%)	8 (2.7)	5 (3.4)	3 (2.0)
Platelets < 100 G/L = Yes (%)	39 (13.2)	17 (11.4)	22 (15.0)
Reported Thrombocytopenia or Platelets < 100 G/L = Yes (%)	41 (13.9)	18 (12.1)	23 (15.6)

	Overall	Active	Placebo
Venous thromboembolism = Yes (%)	17 (5.7)	5 (3.4)	12 (8.2)
Severe dermatologic reaction = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)

Fostamatinib

In the mITT (primary analysis) dataset, the proportion of participants who experienced an AST >128 U/L (men) or 104 U/L (women) was greater in the fostamatinib group (11.6%) than in the placebo group (5.5%) (adjusted OR, 2.28; 95% CI, 1.07-4.84). The proportion of patients in each group who experienced an ALT >136 U/L for men or 96 U/L for women was similar (7.04% vs 6.97%; aOR, 0.98; 95% CI, 0.45-2.14). In the mITT dataset, six participants in the fostamatinib group and four in the placebo group experienced the adverse event of special interest of AST or ALT elevation >5x the larger of the local laboratory upper limit of normal or baseline value. Among the six patients receiving fostamatinib who experienced an adverse event of special interest, there was no evidence of subsequent hepatic failure during follow-up. The frequency of other safety outcomes, PSESEs and serious adverse events was similar between the fostamatinib and placebo groups. The tables below present safety dataset summaries of PSESEs through day 60 stratified by group for the Fostamatinib trial.

Analysis of pre-specified safety outcomes in the Fostamatinib mITT cohort

Pre-specified safety outcome[c]	Fostamatinib (n=199)	Placebo (n=201)	Unadjusted absolute difference (95% CI)[a]	aOR (95% CI)[b]
Hypertension through day 28, no. (%)	24 (12.1)	19 (9.45)	2.6 (-3.4 - 8.7)	0.75 (0.39 - 1.43)
ANC < 500 cells/mcl through day 28, no. (%)	17 (8.54)	9 (4.48)	4.1 (-0.7 - 9.0)	2.01 (0.86 - 4.67)
ALT > 136 U/L for men, >ALT > 96 U/L for women through day 28, no. (%)	14 (7.04)	14 (6.97)	0.1 (-4.9 - 5.1)	0.98 (0.45 - 2.14)
AST > 128 U/L for men, >104 U/L for women through day 28, no. (%)	23 (11.6)	11 (5.47)	6.1 (0.7 - 11.6)	2.28 (1.07 - 4.84)

Footnotes:

a. Binomial distribution with improper beta prior was used for each binary outcome.
b. aOR = adjusted Odds Ratio. Odds ratios were calculated using the following regression techniques with co-variable adjustment for age group, sex, and baseline WHO COVID-19 clinical progression ordinal scale: all safety outcomes—multivariable logistic regression (OR <1.0 is direction of fewer safety events in the active group).
c. All safety outcomes were based on clinician assessment during routine follow-up.

Table 27 Fostamatinib Summary of PSESEs to Day 60

	Overall	Active	Placebo
n	413	208	205
Seizure = Yes (%)	2 (0.5)	1 (0.5)	1 (0.5)
Stroke = Yes (%)	1 (0.2)	0 (0.0)	1 (0.5)
Hypertension = Yes (%)	43 (10.4)	24 (11.5)	19 (9.3)
Hypotension = Yes (%)	45 (10.9)	27 (13.0)	18 (8.8)
Atrial or ventricular arrhythmia event = Yes (%)	26 (6.3)	17 (8.2)	9 (4.4)
Cardiomyopathy event = Yes (%)	2 (0.5)	2 (1.0)	0 (0.0)
Cardiac arrest event = Yes (%)	5 (1.2)	2 (1.0)	3 (1.5)
Myocardial injury event = Yes (%)	1 (0.2)	0 (0.0)	1 (0.5)
Acute coronary syndrome = Yes (%)	1 (0.2)	0 (0.0)	1 (0.5)
High-sensitivity Troponin I > 30 ng/L = Yes (%)	11 (2.7)	4 (1.9)	7 (3.4)
Conventional Troponin I > 0.03 ng/mL = Yes (%)	15 (3.6)	8 (3.8)	7 (3.4)
High-sensitivity Troponin T > 14 ng/L = Yes (%)	12 (2.9)	5 (2.4)	7 (3.4)
Conventional Troponin T > 0.01 ng/mL = Yes (%)	3 (0.7)	1 (0.5)	2 (1.0)
Combined abnormal Troponin = Yes (%)	34 (8.2)	16 (7.7)	18 (8.8)
Hypoxemia requiring supplemental oxygen = Yes (%)	26 (6.3)	16 (7.7)	10 (4.9)
Acute respiratory distress syndrome = Yes (%)	15 (3.6)	9 (4.3)	6 (2.9)
Non-invasive ventilation = Yes (%)	41 (9.9)	21 (10.1)	20 (9.8)
Invasive mechanical ventilation = Yes (%)	50 (12.1)	27 (13.0)	23 (11.2)
ECMO = Yes (%)	2 (0.5)	0 (0.0)	2 (1.0)
Elevation in alanine aminotransferase = Yes (%)	14 (3.4)	6 (2.9)	8 (3.9)
ALT > 102U/L for Men and > 72U/L for Women = Yes (%)	47 (11.4)	26 (12.5)	21 (10.2)
Reported ALT elevation or ALT > 102U/L for Men and > 72U/L for Women = Yes (%)	52 (12.6)	28 (13.5)	24 (11.7)
Number of measures that ALT > 102U/L for Men and > 72U/L for Women (%)			
0	366 (88.6)	182 (87.5)	184 (89.8)
1	15 (3.6)	9 (4.3)	6 (2.9)
2	5 (1.2)	1 (0.5)	4 (2.0)
3 or more	27 (6.5)	16 (7.7)	11 (5.4)
ALT > 136U/L for Men and > 96U/L for Women = Yes (%)	30 (7.3)	15 (7.2)	15 (7.3)
Reported ALT elevation or ALT > 136U/L for Men and > 96U/L for Women = Yes (%)	38 (9.2)	20 (9.6)	18 (8.8)
Number of measures that ALT > 136U/L for Men and > 96U/L for Women (%)			
0	383 (92.7)	193 (92.8)	190 (92.7)
1	11 (2.7)	5 (2.4)	6 (2.9)
2	3 (0.7)	1 (0.5)	2 (1.0)
3 or more	16 (3.9)	9 (4.3)	7 (3.4)
Number of measured ALT per participant (%)			
0	23 (5.6)	10 (4.8)	13 (6.3)
1	66 (16.0)	34 (16.3)	32 (15.6)
2	56 (13.6)	27 (13.0)	29 (14.1)
3 or more	268 (64.9)	137 (65.9)	131 (63.9)
ALT > 5x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	15 (3.6)	8 (3.8)	7 (3.4)

	Overall	Active	Placebo
ALT > 10x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	4 (1.0)	1 (0.5)	3 (1.5)
Elevation in aspartate aminotransferase = Yes (%)	21 (5.1)	12 (5.8)	9 (4.4)
AST > 96U/L for Men and > 78U/L for Women = Yes (%)	50 (12.1)	31 (14.9)	19 (9.3)
Reported AST elevation or AST > 96U/L for Men and > 78U/L for Women = Yes (%)	58 (14.0)	35 (16.8)	23 (11.2)
Number of measures that AST > 96U/L for Men and > 78U/L for Women (%)			
0	363 (87.9)	177 (85.1)	186 (90.7)
1	18 (4.4)	11 (5.3)	7 (3.4)
2	8 (1.9)	5 (2.4)	3 (1.5)
3 or more	24 (5.8)	15 (7.2)	9 (4.4)
AST > 128U/L for Men and > 104U/L for Women = Yes (%)	36 (8.7)	24 (11.5)	12 (5.9)
Reported AST elevation or AST > 128U/L for Men and > 104U/L for Women = Yes (%)	44 (10.7)	28 (13.5)	16 (7.8)
Number of measures that AST > 128U/L for Men and > 104U/L for Women (%)			
0	377 (91.3)	184 (88.5)	193 (94.1)
1	14 (3.4)	12 (5.8)	2 (1.0)
2	5 (1.2)	2 (1.0)	3 (1.5)
3 or more	17 (4.1)	10 (4.8)	7 (3.4)
Number of measured AST per participant (%)			
0	23 (5.6)	10 (4.8)	13 (6.3)
1	67 (16.2)	35 (16.8)	32 (15.6)
2	56 (13.6)	27 (13.0)	29 (14.1)
3 or more	267 (64.6)	136 (65.4)	131 (63.9)
AST > 5x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	13 (3.1)	8 (3.8)	5 (2.4)
AST > 10x the larger of ULN or baseline (ULN if no baseline) = Yes (%)	4 (1.0)	1 (0.5)	3 (1.5)
Bilirubin 2.4 mg/dL or higher = Yes (%)	19 (4.6)	15 (7.2)	4 (2.0)
Number of measure that bilirubin 2.4 mg/dL or higher (%)			
0	394 (95.4)	193 (92.8)	201 (98.0)
1	5 (1.2)	5 (2.4)	0 (0.0)
2	5 (1.2)	4 (1.9)	1 (0.5)
3 or more	9 (2.2)	6 (2.9)	3 (1.5)
Number of measured bilirubin per participant (%)			
0	26 (6.3)	11 (5.3)	15 (7.3)
1	67 (16.2)	34 (16.3)	33 (16.1)
2	59 (14.3)	30 (14.4)	29 (14.1)
3 or more	261 (63.2)	133 (63.9)	128 (62.4)
Acute pancreatitis = Yes (%)	1 (0.2)	0 (0.0)	1 (0.5)
Acute kidney injury = Yes (%)	9 (2.2)	4 (1.9)	5 (2.4)
KDIGO AKI Stage 1 = Yes (%)	70 (16.9)	40 (19.2)	30 (14.6)
KDIGO AKI Stage 2 = Yes (%)	25 (6.1)	14 (6.7)	11 (5.4)
Reported AKI or KDIGO AKI stage I = Yes (%)	75 (18.2)	42 (20.2)	33 (16.1)
Reported AKI or KDIGO AKI stage II = Yes (%)	33 (8.0)	18 (8.7)	15 (7.3)
KDIGO AKI Stage 1 within 7 days = Yes (%)	53 (12.8)	30 (14.4)	23 (11.2)
KDIGO AKI Stage 2 within 7 days = Yes (%)	13 (3.1)	7 (3.4)	6 (2.9)

	Overall	Active	Placebo
Symptomatic hypoglycemia = Yes (%)	1 (0.2)	1 (0.5)	0 (0.0)
Lymphopenia = Yes (%)	3 (0.7)	2 (1.0)	1 (0.5)
ALC < 1000 cells/mcl = Yes (%)	231 (55.9)	112 (53.8)	119 (58.0)
Reported Lymphopenia or ALC < 1000 cells/mcl = Yes (%)	231 (55.9)	112 (53.8)	119 (58.0)
Number of measured ALC per participant (%)			
0	54 (13.1)	25 (12.0)	29 (14.1)
1	67 (16.2)	36 (17.3)	31 (15.1)
2	52 (12.6)	26 (12.5)	26 (12.7)
3 or more	240 (58.1)	121 (58.2)	119 (58.0)
Neutropenia = Yes (%)	5 (1.2)	4 (1.9)	1 (0.5)
ANC < 500 cells/mcl = Yes (%)	26 (6.3)	17 (8.2)	9 (4.4)
Reported Neutropenia or ANC < 500 cells/mcl = Yes (%)	31 (7.5)	21 (10.1)	10 (4.9)
Number of measured ANC per participant (%)			
0	30 (7.3)	12 (5.8)	18 (8.8)
1	68 (16.5)	36 (17.3)	32 (15.6)
2	55 (13.3)	27 (13.0)	28 (13.7)
3 or more	260 (63.0)	133 (63.9)	127 (62.0)
Anemia = Yes (%)	25 (6.1)	16 (7.7)	9 (4.4)
Hgb < 7g/dL for Men and < 6.5g/dL for Women = Yes (%)	18 (4.4)	12 (5.8)	6 (2.9)
Reported Anemia or Hgb < 7g/dL for Men and < 6.5g/dL for Women = Yes (%)	39 (9.4)	26 (12.5)	13 (6.3)
Thrombocytopenia = Yes (%)	11 (2.7)	5 (2.4)	6 (2.9)
Platelets < 100 G/L = Yes (%)	58 (14.0)	34 (16.3)	24 (11.7)
Reported Thrombocytopenia or Platelets < 100 G/L = Yes (%)	64 (15.5)	37 (17.8)	27 (13.2)
Venous thromboembolism = Yes (%)	13 (3.1)	4 (1.9)	9 (4.4)
Severe dermatologic reaction = Yes (%)	0 (0.0)	0 (0.0)	0 (0.0)

12.4 Clinical Laboratory Evaluation

12.4.1 Summaries of Laboratory Measurements by Study Day

Individual abnormal laboratory values were recorded as PSESEs. Clinical laboratory values are summarized in the tables below by study day including the median [IQR] values and the percent of participants with an abnormal value defined using the thresholds listed below:

ALT > 102U/L for Men, ALT > 72U/L for Women
AST > 96U/L for Men, AST > 78U/L for Women
Bilirubin ≥ 2.4 mg/dL
ALC < 1000 cells/mcl
ANC < 500 cells/mcl
Hgb < 7g/dL for Men, Hgb < 6.5g/dL for Women
Platelets < 100 G/L
High-sensitivity Troponin I > 30 ng/L
Conventional Troponin I > 0.03 ng/mL
High-sensitivity Troponin T > 14 ng/L

Conventional Troponin T > 0.01 ng/mL

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Table 28 TXA-127 Laboratory Values Over Time

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALT	0	134	33 [19, 53]	16 (11.9%)	140	30.5 [18, 51]	8 (5.7%)
ALT	1	115	31 [22, 61]	16 (13.9%)	120	29.5 [17, 51.5]	7 (5.8%)
ALT	2	114	31 [21, 60]	15 (13.2%)	114	32 [18, 55]	14 (12.3%)
ALT	3	96	35 [20, 77.75]	21 (21.9%)	97	32 [21, 68]	14 (14.4%)
ALT	4	81	40 [22, 76]	18 (22.2%)	78	37 [21, 61]	14 (17.9%)
ALT	5	72	38 [24.75, 67.25]	9 (12.5%)	67	36 [19, 64.5]	10 (14.9%)
ALT	6	55	37 [23.5, 56.5]	7 (12.7%)	52	43 [23.5, 71.75]	9 (17.3%)
ALT	7	49	45 [31, 77]	10 (20.4%)	48	34 [22.75, 67.25]	8 (16.7%)
ALT	8	38	40 [20.25, 81.5]	9 (23.7%)	41	37 [21, 67]	3 (7.3%)
ALT	9	35	50 [28.5, 89.5]	8 (22.9%)	40	41.5 [21.75, 64.75]	4 (10%)
ALT	10	31	40 [26, 97]	8 (25.8%)	36	40 [24.25, 60.75]	5 (13.9%)
ALT	11	28	53.5 [30, 88.5]	7 (25%)	30	37 [22, 56]	4 (13.3%)
ALT	12	24	47.5 [23.75, 70.25]	3 (12.5%)	29	47 [32, 73]	2 (6.9%)
ALT	13	24	50 [26.5, 72.75]	2 (8.3%)	24	41.5 [27.25, 61.25]	4 (16.7%)
ALT	14	17	63 [27, 82]	3 (17.6%)	18	38.5 [24, 78.75]	3 (16.7%)
ALT	15	19	62 [32, 99]	5 (26.3%)	21	38 [24, 47]	1 (4.8%)
ALT	16	13	71 [54, 126]	4 (30.8%)	19	35 [19.5, 54.5]	2 (10.5%)
ALT	17	15	50 [41.5, 99.5]	4 (26.7%)	17	33 [24, 42]	2 (11.8%)
ALT	18	14	56 [48.25, 97.75]	5 (35.7%)	12	25.5 [17.25, 55.5]	1 (8.3%)
ALT	19	14	58 [52.25, 89.5]	3 (21.4%)	12	35.5 [21.25, 42.5]	1 (8.3%)
ALT	20	15	60 [38, 107.5]	4 (26.7%)	11	38 [13.5, 46.5]	1 (9.1%)
ALT	21	11	78 [49.5, 105.5]	4 (36.4%)	13	32 [14, 43]	0 (0%)
ALT	22	11	71 [48, 94]	2 (18.2%)	12	26.5 [13, 47.25]	0 (0%)
ALT	23	10	69.5 [47.75, 91.5]	1 (10%)	10	29.5 [19.75, 50.25]	0 (0%)
ALT	24	11	51 [39.5, 89.5]	3 (27.3%)	10	31 [24.75, 49.25]	0 (0%)
ALT	25	7	66 [30, 130]	2 (28.6%)	8	34 [18, 62]	0 (0%)
ALT	26	7	55 [39, 79]	2 (28.6%)	7	38 [32, 75]	1 (14.3%)
ALT	27	6	57.5 [38.25, 91]	2 (33.3%)	9	23 [18, 40]	1 (11.1%)
ALT	28	8	39 [24.5, 99]	3 (37.5%)	5	25 [23, 73]	1 (20%)
AST	0	133	45 [33, 66]	14 (10.5%)	138	38 [25, 52]	14 (10.1%)
AST	1	114	40 [28, 57.75]	12 (10.5%)	119	36 [24.5, 58.5]	8 (6.7%)
AST	2	114	35 [24.25, 50]	7 (6.1%)	113	37 [24, 52]	10 (8.8%)
AST	3	96	38 [24.75, 52.25]	8 (8.3%)	97	35 [21, 47]	8 (8.2%)
AST	4	81	32 [24, 55]	4 (4.9%)	78	32 [22, 49]	6 (7.7%)
AST	5	71	30 [20.5, 47.5]	1 (1.4%)	67	29 [21, 44.5]	6 (9%)
AST	6	55	26 [18.5, 44]	2 (3.6%)	51	31 [22, 42]	3 (5.9%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
AST	7	49	31 [19, 50]	2 (4.1%)	48	28.5 [19, 50.5]	5 (10.4%)
AST	8	38	32.5 [21, 53.25]	2 (5.3%)	41	32 [20, 56]	4 (9.8%)
AST	9	35	29 [22.5, 51.5]	2 (5.7%)	40	26.5 [19.5, 48.5]	3 (7.5%)
AST	10	31	34 [25, 41]	2 (6.5%)	35	27 [19.5, 57]	1 (2.9%)
AST	11	28	31 [26.5, 58.5]	1 (3.6%)	30	29 [21.75, 60]	1 (3.3%)
AST	12	24	28.5 [23.5, 41.75]	1 (4.2%)	29	35 [26, 62]	0 (0%)
AST	13	24	29 [23.75, 43]	1 (4.2%)	24	36 [25.25, 52.25]	1 (4.2%)
AST	14	17	36 [23, 67]	1 (5.9%)	18	36 [24.5, 53.5]	1 (5.6%)
AST	15	19	27 [22.5, 71]	3 (15.8%)	21	33 [22, 42]	1 (4.8%)
AST	16	13	47 [26, 69]	3 (23.1%)	19	31 [19.5, 44]	1 (5.3%)
AST	17	15	36 [25.5, 55]	2 (13.3%)	17	29 [26, 41]	2 (11.8%)
AST	18	14	36.5 [27.5, 68.75]	2 (14.3%)	12	27.5 [19.75, 38]	1 (8.3%)
AST	19	14	44 [29.5, 61.25]	3 (21.4%)	12	32 [24.5, 39.75]	0 (0%)
AST	20	15	47 [30.5, 74]	2 (13.3%)	11	28 [20, 40.5]	0 (0%)
AST	21	11	54 [36, 87.5]	3 (27.3%)	13	27 [24, 44]	0 (0%)
AST	22	11	52 [43, 69]	2 (18.2%)	12	33 [23.75, 40.5]	0 (0%)
AST	23	10	57.5 [36.75, 70]	2 (20%)	10	28 [21.25, 51]	0 (0%)
AST	24	11	47 [28.5, 57.5]	1 (9.1%)	10	33.5 [25.75, 59.5]	0 (0%)
AST	25	7	41 [30, 66]	1 (14.3%)	8	30 [21.75, 50.75]	1 (12.5%)
AST	26	7	44 [28, 55.5]	1 (14.3%)	7	42 [25, 66.5]	1 (14.3%)
AST	27	6	45.5 [34.5, 52.75]	1 (16.7%)	9	28 [25, 43]	1 (11.1%)
AST	28	8	39.5 [25.75, 92.5]	1 (12.5%)	5	33 [23, 37]	1 (20%)
Bili	0	136	0.5 [0.4, 0.7]	5 (3.7%)	140	0.5 [0.4, 0.6]	4 (2.9%)
Bili	1	115	0.5 [0.4, 0.7]	1 (0.9%)	121	0.4 [0.3, 0.6]	1 (0.8%)
Bili	2	112	0.5 [0.4, 0.7]	3 (2.7%)	112	0.5 [0.4, 0.7]	3 (2.7%)
Bili	3	95	0.5 [0.4, 0.7]	2 (2.1%)	98	0.5 [0.4, 0.7]	1 (1%)
Bili	4	77	0.6 [0.4, 0.8]	0 (0%)	78	0.55 [0.4, 0.8]	1 (1.3%)
Bili	5	70	0.6 [0.4, 0.7]	1 (1.4%)	68	0.6 [0.4, 0.8]	3 (4.4%)
Bili	6	54	0.6 [0.4, 0.8]	1 (1.9%)	52	0.6 [0.475, 0.825]	2 (3.8%)
Bili	7	49	0.6 [0.4, 0.8]	2 (4.1%)	48	0.6 [0.475, 0.8]	1 (2.1%)
Bili	8	38	0.5 [0.4, 0.8]	1 (2.6%)	40	0.55 [0.4, 0.725]	0 (0%)
Bili	9	35	0.6 [0.45, 0.95]	1 (2.9%)	41	0.6 [0.5, 0.9]	1 (2.4%)
Bili	10	31	0.6 [0.4, 0.8]	1 (3.2%)	36	0.6 [0.5, 0.9]	1 (2.8%)
Bili	11	28	0.65 [0.4, 0.95]	1 (3.6%)	30	0.6 [0.4, 0.975]	1 (3.3%)
Bili	12	24	0.8 [0.5, 1]	1 (4.2%)	29	0.5 [0.4, 0.7]	1 (3.4%)
Bili	13	23	0.6 [0.45, 0.9]	1 (4.3%)	24	0.55 [0.4, 0.725]	1 (4.2%)
Bili	14	17	0.7 [0.6, 1]	2 (11.8%)	18	0.6 [0.425, 0.7]	1 (5.6%)
Bili	15	19	0.7 [0.5, 1]	3 (15.8%)	21	0.5 [0.5, 0.8]	2 (9.5%)
Bili	16	13	0.7 [0.5, 1.1]	3 (23.1%)	19	0.5 [0.4, 0.6]	1 (5.3%)
Bili	17	15	0.6 [0.45, 1.05]	3 (20%)	17	0.5 [0.4, 0.7]	0 (0%)
Bili	18	14	0.8 [0.45, 1.125]	2 (14.3%)	12	0.6 [0.45, 0.7]	0 (0%)
Bili	19	13	0.9 [0.5, 1.2]	1 (7.7%)	12	0.45 [0.3, 0.55]	0 (0%)
Bili	20	15	0.8 [0.6, 1.2]	1 (6.7%)	11	0.4 [0.35, 0.5]	0 (0%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Bili	21	11	0.8 [0.55, 1.1]	1 (9.1%)	13	0.6 [0.4, 0.9]	0 (0%)
Bili	22	11	0.6 [0.5, 0.9]	1 (9.1%)	12	0.5 [0.4, 0.625]	0 (0%)
Bili	23	10	0.7 [0.525, 0.9]	1 (10%)	10	0.45 [0.325, 0.675]	0 (0%)
Bili	24	11	0.5 [0.45, 0.7]	1 (9.1%)	10	0.55 [0.4, 0.675]	0 (0%)
Bili	25	7	0.8 [0.45, 0.95]	1 (14.3%)	8	0.5 [0.375, 0.675]	1 (12.5%)
Bili	26	7	0.8 [0.45, 1]	1 (14.3%)	7	0.7 [0.55, 1.45]	1 (14.3%)
Bili	27	6	1 [0.85, 1.45]	1 (16.7%)	9	0.5 [0.3, 1]	0 (0%)
Bili	28	8	0.6 [0.35, 1.075]	1 (12.5%)	5	0.3 [0.2, 1.2]	0 (0%)
Hgb	0	160	13.2 [12.175, 14.625]	0 (0%)	161	13.2 [12, 14.5]	2 (1.2%)
Hgb	1	149	13.1 [11.9, 14.4]	0 (0%)	144	13.2 [11.975, 14]	0 (0%)
Hgb	2	137	13.1 [11.9, 14.1]	0 (0%)	132	13.05 [11.9, 14.1]	1 (0.8%)
Hgb	3	126	13.1 [12.025, 14.7]	0 (0%)	117	13.2 [11.4, 14.3]	0 (0%)
Hgb	4	113	13 [12, 14.4]	0 (0%)	101	13 [11.3, 14.2]	0 (0%)
Hgb	5	102	13.25 [11.8, 14.675]	0 (0%)	91	13 [11.55, 14.2]	0 (0%)
Hgb	6	91	13.4 [11.85, 14.3]	0 (0%)	82	12.95 [11.425, 14]	0 (0%)
Hgb	7	83	13 [11.55, 14.15]	0 (0%)	70	12.6 [10.875, 13.7]	1 (1.4%)
Hgb	8	72	12.45 [11.275, 14.125]	0 (0%)	57	12.7 [10.8, 13.6]	1 (1.8%)
Hgb	9	57	12.4 [10.9, 13.7]	0 (0%)	51	12.6 [10.2, 13.95]	1 (2%)
Hgb	10	54	12.35 [10.55, 13.375]	0 (0%)	48	12.15 [10.1, 14.125]	0 (0%)
Hgb	11	50	12.1 [10.5, 13.275]	0 (0%)	46	11.6 [9.775, 13.2]	0 (0%)
Hgb	12	41	11.5 [10, 13.2]	2 (4.9%)	41	11.2 [9.8, 13.3]	2 (4.9%)
Hgb	13	42	11.7 [10.025, 12.775]	0 (0%)	37	10.8 [8.9, 12.8]	1 (2.7%)
Hgb	14	37	11.2 [10.1, 12.9]	0 (0%)	30	11.15 [9.15, 12.775]	0 (0%)
Hgb	15	33	11 [9.7, 12.4]	1 (3%)	33	10.7 [9, 12.4]	1 (3%)
Hgb	16	25	10.8 [8.9, 11.8]	0 (0%)	31	11 [8.7, 12.4]	1 (3.2%)
Hgb	17	30	10.55 [9.625, 11.6]	0 (0%)	29	10.6 [8.4, 11.9]	0 (0%)
Hgb	18	29	10.2 [8.9, 11.8]	1 (3.4%)	23	10.2 [8, 12.2]	0 (0%)
Hgb	19	24	9.95 [8.75, 11.925]	0 (0%)	25	10 [8.9, 11.2]	0 (0%)
Hgb	20	25	9.9 [8.7, 11.1]	1 (4%)	24	9.55 [8.375, 12.05]	0 (0%)
Hgb	21	20	9.75 [8.1, 10.6]	0 (0%)	20	9 [8, 10.55]	0 (0%)
Hgb	22	21	9.1 [8.1, 9.7]	0 (0%)	19	8.8 [7.85, 10.4]	0 (0%)
Hgb	23	19	9 [8.5, 11.15]	0 (0%)	19	9.2 [8.05, 10]	0 (0%)
Hgb	24	17	9 [8.7, 10.2]	1 (5.9%)	19	9.6 [8.55, 10.4]	1 (5.3%)
Hgb	25	15	9.6 [8.95, 11.05]	0 (0%)	18	9.4 [8.225, 10.725]	1 (5.6%)
Hgb	26	16	9.1 [8.775, 11]	0 (0%)	14	9.75 [8.325, 11.225]	0 (0%)
Hgb	27	13	8.6 [7.8, 9.6]	1 (7.7%)	16	9.1 [8.475, 11.45]	1 (6.2%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Hgb	28	13	9.3 [7.7, 11]	0 (0%)	14	9.05 [8.2, 9.925]	0 (0%)
Plat	0	161	224 [154, 306]	11 (6.8%)	161	231 [161, 285]	9 (5.6%)
Plat	1	150	247.5 [182.25, 327.75]	7 (4.7%)	145	250 [178, 338]	5 (3.4%)
Plat	2	137	260 [189, 376]	6 (4.4%)	133	277 [193, 345]	7 (5.3%)
Plat	3	126	279 [194.75, 375]	6 (4.8%)	118	284.5 [213.5, 366.5]	6 (5.1%)
Plat	4	113	289 [186, 366]	8 (7.1%)	101	282 [211, 375]	8 (7.9%)
Plat	5	102	300 [234.25, 391.5]	3 (2.9%)	92	313.5 [205.75, 396.5]	8 (8.7%)
Plat	6	91	292 [240, 391]	3 (3.3%)	82	303.5 [195, 401.25]	9 (11%)
Plat	7	83	308 [222.5, 398.5]	3 (3.6%)	70	305.5 [192.25, 452.5]	6 (8.6%)
Plat	8	72	302.5 [231.25, 397.75]	3 (4.2%)	57	276 [192, 449]	5 (8.8%)
Plat	9	57	293 [223, 358]	3 (5.3%)	51	269 [186.5, 434]	4 (7.8%)
Plat	10	53	269 [211, 336]	3 (5.7%)	47	290 [188, 458]	4 (8.5%)
Plat	11	50	261 [190.25, 327.5]	3 (6%)	46	269 [152, 426.75]	6 (13%)
Plat	12	40	239.5 [210.25, 303]	3 (7.5%)	41	264 [156, 387]	7 (17.1%)
Plat	13	42	229.5 [157.25, 300.75]	5 (11.9%)	37	251 [154, 299]	7 (18.9%)
Plat	14	37	220 [176, 307]	2 (5.4%)	31	205 [146, 306.5]	5 (16.1%)
Plat	15	33	211 [150, 285]	2 (6.1%)	32	212 [132.75, 283.75]	6 (18.8%)
Plat	16	25	204 [158, 268]	1 (4%)	31	207 [123.5, 272.5]	7 (22.6%)
Plat	17	30	190.5 [134.75, 263.25]	3 (10%)	29	190 [90, 269]	8 (27.6%)
Plat	18	29	200 [114, 282]	4 (13.8%)	23	168 [98.5, 281.5]	6 (26.1%)
Plat	19	24	214.5 [123.75, 283]	3 (12.5%)	24	206.5 [150.25, 295.75]	4 (16.7%)
Plat	20	25	192 [116, 282]	5 (20%)	24	202 [123.75, 299.5]	5 (20.8%)
Plat	21	20	199 [114.75, 283.75]	3 (15%)	20	188.5 [128, 279.5]	3 (15%)
Plat	22	21	203 [124, 292]	2 (9.5%)	19	178 [127, 278]	3 (15.8%)
Plat	23	18	195.5 [139.75, 297.5]	1 (5.6%)	19	203 [155.5, 281]	3 (15.8%)
Plat	24	17	205 [117, 270]	1 (5.9%)	19	213 [132, 292.5]	4 (21.1%)
Plat	25	15	236 [169.5, 317]	1 (6.7%)	18	253 [174.25, 299.5]	3 (16.7%)
Plat	26	16	241 [142, 309]	1 (6.2%)	14	258 [189.75, 309]	2 (14.3%)
Plat	27	12	221.5 [122.5, 323]	1 (8.3%)	16	283 [214.25, 315.25]	2 (12.5%)
Plat	28	13	202 [137, 271]	2 (15.4%)	14	259 [228.25, 429.25]	3 (21.4%)
ALC	0	78	665.04 [348, 1058.5]	55 (70.5%)	84	737.635 [493.935, 1175.325]	57 (67.9%)
ALC	1	54	705.3 [449.625, 1263.27]	35 (64.8%)	61	790.4 [423, 1152.8]	40 (65.6%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALC	2	48	703.43 [403.2, 1148.55]	33 (68.8%)	60	731.65 [462.75, 1362.965]	38 (63.3%)
ALC	3	40	880.12 [482.5, 1287.3]	24 (60%)	56	965.46 [545.1625, 1362]	31 (55.4%)
ALC	4	43	864.24 [470.525, 1434.845]	23 (53.5%)	49	1121.45 [511.2, 1655.4]	23 (46.9%)
ALC	5	36	899.34 [554.85, 1355.55]	19 (52.8%)	41	864 [486, 1566]	25 (61%)
ALC	6	32	903.65 [358.475, 1428.35]	19 (59.4%)	34	741 [364.7, 1450]	22 (64.7%)
ALC	7	27	846.3 [416.85, 1386.42]	15 (55.6%)	32	615.72 [331.175, 1689.545]	21 (65.6%)
ALC	8	28	1252 [434.1, 1741.125]	13 (46.4%)	29	655.5 [450, 1612]	17 (58.6%)
ALC	9	22	857.4 [376.825, 1335.525]	12 (54.5%)	27	576 [400, 889.75]	21 (77.8%)
ALC	10	22	1038.1 [417.2, 1651.155]	11 (50%)	24	760 [571.44, 1264.15]	16 (66.7%)
ALC	11	19	937.2 [532.275, 1532.84]	12 (63.2%)	22	750.4 [506.04, 1538.675]	15 (68.2%)
ALC	12	14	955.7 [360.575, 1685]	9 (64.3%)	20	950.545 [531.825, 1567.8]	11 (55%)
ALC	13	15	866.4 [525.895, 1073.5]	10 (66.7%)	18	911 [609.1275, 1739.1325]	10 (55.6%)
ALC	14	13	812.7 [720, 1124.7]	9 (69.2%)	11	684 [475.305, 1602]	7 (63.6%)
ALC	15	12	908.1 [816.35, 1095]	8 (66.7%)	11	680 [528.6, 1746]	6 (54.5%)
ALC	16	7	1445.76 [823.6, 2049.75]	2 (28.6%)	15	1505.1 [591, 1758.65]	7 (46.7%)
ALC	17	10	891.15 [593.8, 1315.65]	5 (50%)	14	1057.7 [688.5, 1740.425]	6 (42.9%)
ALC	18	9	684 [655.5, 1091.4]	5 (55.6%)	11	1231.2 [1014.5, 1497.76]	3 (27.3%)
ALC	19	6	1169.3 [929.8, 1202.85]	2 (33.3%)	12	1598.16 [1406.25, 1749.5725]	2 (16.7%)
ALC	20	7	1007 [732.25, 1452.3]	3 (42.9%)	11	1732.5 [946.4, 2195.9]	4 (36.4%)
ALC	21	7	1067.6 [876.7, 1591.3]	3 (42.9%)	8	1162.31 [657.5, 1380.6]	3 (37.5%)
ALC	22	8	1161.9 [740.175, 1761.15]	4 (50%)	7	997.5 [544, 1489.35]	4 (57.1%)
ALC	23	5	1016.4 [1010, 1317.6]	1 (20%)	5	728 [265.5, 846.3]	4 (80%)
ALC	24	3	561 [478.25, 1208.45]	2 (66.7%)	6	1299.8 [1004.95, 1582.95]	2 (33.3%)
ALC	25	7	570.4 [329.7, 1551.4]	4 (57.1%)	9	1516.8 [1065.16, 1666]	2 (22.2%)
ALC	26	5	490 [448, 863.5]	4 (80%)	7	1095 [741.5, 1742]	2 (28.6%)
ALC	27	2	387.9 [257.85, 517.95]	2 (100%)	7	2009.14 [1181.2, 2335.8]	2 (28.6%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALC	28	3	480 [340.2, 838.4]	2 (66.7%)	6	927.6 [718.3, 1747.625]	3 (50%)
ANC	0	77	5010.3 [3015.5, 7568]	1 (1.3%)	81	5431.5 [3076, 8832]	3 (3.7%)
ANC	1	53	5889.24 [3431.6, 8325.9]	1 (1.9%)	60	6113.2 [4524.08, 8921.55]	0 (0%)
ANC	2	48	5966.1 [3503.799, 7838.9875]	1 (2.1%)	59	6996.6 [4758.4, 9087.7]	2 (3.4%)
ANC	3	39	6316.3 [3970.7, 7665.01]	0 (0%)	55	6557 [4158.72, 8340]	4 (7.3%)
ANC	4	43	6545 [4834.49, 9338.54]	1 (2.3%)	49	7917 [5576, 10030.2]	2 (4.1%)
ANC	5	35	7327 [5031, 10061.95]	1 (2.9%)	41	7656 [4503, 10735]	2 (4.9%)
ANC	6	32	6861.1 [4084.7575, 9322.8]	0 (0%)	33	9473.8 [5568, 12848]	1 (3%)
ANC	7	27	7309.8 [4779.28, 11215]	0 (0%)	31	10225.8 [6515.85, 13648.5]	1 (3.2%)
ANC	8	28	7969.055 [4211.685, 12590.675]	0 (0%)	27	10416 [7074.25, 15671.7]	1 (3.7%)
ANC	9	22	7884 [5353.86, 11025.85]	0 (0%)	26	10195.25 [8771.9, 15374.46]	0 (0%)
ANC	10	22	6225.315 [3856.9125, 10274.625]	1 (4.5%)	24	9943.2 [8073.65, 15956.9]	0 (0%)
ANC	11	19	7524 [5225.3, 11216.65]	0 (0%)	21	9270 [5629.5, 11232]	0 (0%)
ANC	12	14	8706 [5054.1, 10712]	1 (7.1%)	20	8339.7 [6895, 10653.8]	0 (0%)
ANC	13	15	9167.4 [5326.716, 14464.325]	0 (0%)	18	7348.7 [5280.6525, 9579.725]	2 (11.1%)
ANC	14	13	7695 [5085.3, 9867.9]	0 (0%)	11	6640 [4632.3, 8461.5]	0 (0%)
ANC	15	12	10579.7 [4407.825, 12436.2]	0 (0%)	10	6537.75 [4556.9, 8129.775]	0 (0%)
ANC	16	7	11260.6 [5059.62, 19575.6]	0 (0%)	14	7176.3 [4407.7, 11795.375]	0 (0%)
ANC	17	9	6302 [4321.5, 11583]	0 (0%)	13	6966 [4365.9, 11502.4]	0 (0%)
ANC	18	9	4560 [3136.5, 7106]	1 (11.1%)	10	6583.25 [4563.25, 8721.2]	0 (0%)
ANC	19	6	6260 [4970.05, 7516.8]	0 (0%)	11	6918.5 [4491.5, 10215.105]	0 (0%)
ANC	20	6	5841.65 [4226.875, 7254.6]	0 (0%)	10	6628.4 [4128, 9047.65]	0 (0%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ANC	21	6	4760.4 [3653.25, 8268.45]	0 (0%)	7	6497 [5157.9, 8407.75]	0 (0%)
ANC	22	7	4035.6 [3485.95, 6699.1]	0 (0%)	6	7225.5 [5229, 8946]	0 (0%)
ANC	23	4	4306.75 [3905.45, 5926.875]	0 (0%)	4	8340.15 [7541.775, 9175.7]	0 (0%)
ANC	24	3	4182 [4017.25, 6492.35]	0 (0%)	5	10132 [10070.8, 10427.6]	0 (0%)
ANC	25	7	5842.2 [4519.4, 10934]	0 (0%)	8	10128.4 [7741, 11268.715]	0 (0%)
ANC	26	5	4386 [3773, 9688]	0 (0%)	5	8536 [8450, 10332]	0 (0%)
ANC	27	2	7813.3 [5166.65, 10459.95]	0 (0%)	5	10567.2 [8792, 10828.02]	0 (0%)
ANC	28	3	4399.6 [3431.8, 9973.65]	0 (0%)	5	10336 [10010.64, 10935]	0 (0%)
Trop1c	0	12	0.0285 [0.01, 0.10125]	6 (50%)	12	0.025 [0.017, 0.0575]	4 (33.3%)
Trop1c	1	2	0.0445 [0.03225, 0.05675]	1 (50%)	3	0.02 [0.0185, 0.03]	1 (33.3%)
Trop1c	2	0	-	-	2	0.0485 [0.03275, 0.06425]	1 (50%)
Trop1c	3	0	-	-	2	0.06 [0.06, 0.06]	2 (100%)
Trop1c	4	0	-	-	2	0.34 [0.19, 0.49]	2 (100%)
Trop1c	5	0	-	-	2	1.955 [0.9925, 2.9175]	1 (50%)
Trop1c	6	0	-	-	2	0.515 [0.2625, 0.7675]	1 (50%)
Trop1c	7	1	0.08 [0.08, 0.08]	1 (100%)	1	0.98 [0.98, 0.98]	1 (100%)
Trop1c	8	0	-	-	1	0.17 [0.17, 0.17]	1 (100%)
Trop1c	9	1	0.02 [0.02, 0.02]	0 (0%)	2	0.0985 [0.05775, 0.13925]	1 (50%)
Trop1c	10	0	-	-	1	0.12 [0.12, 0.12]	1 (100%)
Trop1c	11	0	-	-	2	0.04 [0.03, 0.05]	1 (50%)
Trop1c	12	0	-	-	0	-	-
Trop1c	13	1	0.21 [0.21, 0.21]	1 (100%)	2	0.0161 [0.01565, 0.01655]	0 (0%)
Trop1c	14	0	-	-	1	0.076 [0.076, 0.076]	1 (100%)
Trop1c	15	1	0.01 [0.01, 0.01]	0 (0%)	1	0.069 [0.069, 0.069]	1 (100%)
Trop1c	16	0	-	-	0	-	-
Trop1c	17	0	-	-	0	-	-
Trop1c	18	0	-	-	1	0.077 [0.077, 0.077]	1 (100%)
Trop1c	19	0	-	-	0	-	-
Trop1c	20	0	-	-	0	-	-
Trop1c	21	0	-	-	0	-	-
Trop1c	22	0	-	-	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Trop1c	23	0	-	-	0	-	-
Trop1c	24	0	-	-	0	-	-
Trop1c	25	0	-	-	0	-	-
Trop1c	26	0	-	-	0	-	-
Trop1c	27	3	0.01 [0.005, 0.03]	1 (33.3%)	0	-	-
Trop1c	28	1	0 [0, 0]	0 (0%)	0	-	-
Tropth	0	4	7 [4.5025, 14.5]	1 (25%)	0	-	-
Tropth	1	1	17 [17, 17]	1 (100%)	0	-	-
Tropth	2	0	-	-	1	6 [6, 6]	0 (0%)
Tropth	3	1	18 [18, 18]	1 (100%)	0	-	-
Tropth	4	0	-	-	1	11 [11, 11]	0 (0%)
Tropth	5	0	-	-	0	-	-
Tropth	6	0	-	-	0	-	-
Tropth	7	0	-	-	0	-	-
Tropth	8	0	-	-	0	-	-
Tropth	9	0	-	-	0	-	-
Tropth	10	0	-	-	0	-	-
Tropth	11	0	-	-	0	-	-
Tropth	12	0	-	-	0	-	-
Tropth	13	0	-	-	0	-	-
Tropth	14	0	-	-	0	-	-
Tropth	15	0	-	-	0	-	-
Tropth	16	0	-	-	0	-	-
Tropth	17	0	-	-	0	-	-
Tropth	18	0	-	-	0	-	-
Tropth	19	0	-	-	0	-	-
Tropth	20	0	-	-	0	-	-
Tropth	21	0	-	-	0	-	-
Tropth	22	0	-	-	0	-	-
Tropth	23	0	-	-	0	-	-
Tropth	24	0	-	-	0	-	-
Tropth	25	0	-	-	0	-	-
Tropth	26	0	-	-	0	-	-
Tropth	27	0	-	-	0	-	-
Tropth	28	0	-	-	0	-	-
Trop1h	0	13	16 [10, 18]	2 (15.4%)	6	8 [6.5, 9.5]	0 (0%)
Trop1h	1	3	13 [8.5, 16]	0 (0%)	1	4 [4, 4]	0 (0%)
Trop1h	2	0	-	-	0	-	-
Trop1h	3	0	-	-	0	-	-
Trop1h	4	0	-	-	0	-	-
Trop1h	5	0	-	-	0	-	-
Trop1h	6	0	-	-	0	-	-
Trop1h	7	0	-	-	0	-	-
Trop1h	8	1	6 [6, 6]	0 (0%)	0	-	-
Trop1h	9	0	-	-	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Trop1h	10	1	26 [26, 26]	0 (0%)	0	-	-
Trop1h	11	0	-	-	0	-	-
Trop1h	12	0	-	-	0	-	-
Trop1h	13	0	-	-	0	-	-
Trop1h	14	0	-	-	0	-	-
Trop1h	15	0	-	-	0	-	-
Trop1h	16	0	-	-	0	-	-
Trop1h	17	0	-	-	0	-	-
Trop1h	18	0	-	-	0	-	-
Trop1h	19	1	44 [44, 44]	1 (100%)	0	-	-
Trop1h	20	1	28 [28, 28]	0 (0%)	0	-	-
Trop1h	21	0	-	-	0	-	-
Trop1h	22	1	13 [13, 13]	0 (0%)	0	-	-
Trop1h	23	0	-	-	0	-	-
Trop1h	24	0	-	-	0	-	-
Trop1h	25	0	-	-	0	-	-
Trop1h	26	0	-	-	0	-	-
Trop1h	27	1	32 [32, 32]	1 (100%)	0	-	-
Trop1h	28	0	-	-	0	-	-
Troptc	0	0	-	-	0	-	-
Troptc	1	0	-	-	0	-	-
Troptc	2	0	-	-	0	-	-
Troptc	3	0	-	-	0	-	-
Troptc	4	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Troptc	5	0	-	-	0	-	-
Troptc	6	0	-	-	0	-	-
Troptc	7	0	-	-	0	-	-
Troptc	8	0	-	-	0	-	-
Troptc	9	0	-	-	0	-	-
Troptc	10	0	-	-	0	-	-
Troptc	11	0	-	-	0	-	-
Troptc	12	0	-	-	0	-	-
Troptc	13	0	-	-	0	-	-
Troptc	14	0	-	-	0	-	-
Troptc	15	0	-	-	0	-	-
Troptc	16	0	-	-	0	-	-
Troptc	17	0	-	-	0	-	-
Troptc	18	0	-	-	0	-	-
Troptc	19	0	-	-	0	-	-
Troptc	20	0	-	-	0	-	-
Troptc	21	0	-	-	0	-	-
Troptc	22	0	-	-	0	-	-
Troptc	23	0	-	-	0	-	-
Troptc	24	0	-	-	0	-	-
Troptc	25	0	-	-	0	-	-
Troptc	26	0	-	-	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Troptc	27	0	-	-	0	-	-
Troptc	28	0	-	-	0	-	-

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Table 29 TRV-027 Laboratory Values Over Time

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALT	0	118	37.5 [22, 72]	18 (15.3%)	118	31 [18.25, 52]	9 (7.6%)
ALT	1	100	38 [24.25, 72.25]	18 (18%)	96	30 [17, 51.5]	6 (6.2%)
ALT	2	87	43 [27, 81.5]	19 (21.8%)	90	32 [19, 56.75]	12 (13.3%)
ALT	3	78	53.5 [25.25, 98.25]	21 (26.9%)	79	32 [22, 67]	12 (15.2%)
ALT	4	70	56.5 [23.5, 100]	20 (28.6%)	65	41 [23, 61]	11 (16.9%)
ALT	5	49	46 [25, 100]	12 (24.5%)	53	42 [21, 63]	7 (13.2%)
ALT	6	42	53 [27.25, 85.75]	9 (21.4%)	38	43.5 [28, 80]	7 (18.4%)
ALT	7	37	50 [28, 92]	8 (21.6%)	36	36.5 [23, 67.25]	5 (13.9%)
ALT	8	32	49 [31.25, 99.5]	9 (28.1%)	34	40 [20.25, 64.75]	1 (2.9%)
ALT	9	31	54 [39.5, 115.5]	10 (32.3%)	32	37.5 [21.75, 61.5]	2 (6.2%)
ALT	10	27	56 [34.5, 97]	7 (25.9%)	30	40 [27, 57.25]	3 (10%)
ALT	11	24	61.5 [37.75, 79]	7 (29.2%)	25	37 [25, 53]	2 (8%)
ALT	12	20	66.5 [41.5, 93.5]	7 (35%)	25	47 [32, 73]	2 (8%)
ALT	13	20	58 [35.25, 83.75]	5 (25%)	21	40 [28, 59]	4 (19%)
ALT	14	17	51 [30, 78]	6 (35.3%)	16	38.5 [23.5, 82.25]	3 (18.8%)
ALT	15	18	58.5 [27.5, 79]	5 (27.8%)	17	35 [24, 47]	1 (5.9%)
ALT	16	13	55 [38, 108]	6 (46.2%)	16	34.5 [17, 41.25]	1 (6.2%)
ALT	17	11	29 [20.5, 70]	2 (18.2%)	15	31 [24, 40.5]	1 (6.7%)
ALT	18	11	47 [26, 62]	1 (9.1%)	10	24.5 [13.75, 36.5]	0 (0%)
ALT	19	10	56.5 [23.25, 69.5]	2 (20%)	11	34 [19.5, 41]	0 (0%)
ALT	20	5	31 [16, 48]	0 (0%)	10	31 [11.75, 45.25]	0 (0%)
ALT	21	8	23 [15.5, 49.25]	1 (12.5%)	12	27 [13.5, 42.25]	0 (0%)
ALT	22	5	25 [18, 30]	0 (0%)	10	19.5 [13, 42]	0 (0%)
ALT	23	5	23 [22, 61]	1 (20%)	9	27 [19, 48]	0 (0%)
ALT	24	6	39 [21.75, 52.5]	0 (0%)	9	32 [24, 54]	0 (0%)
ALT	25	6	32.5 [22, 49.75]	0 (0%)	8	34 [18, 62]	0 (0%)
ALT	26	7	44 [22, 80.5]	2 (28.6%)	7	38 [32, 75]	1 (14.3%)
ALT	27	6	37 [25.5, 87.5]	2 (33.3%)	9	23 [18, 40]	1 (11.1%)
ALT	28	7	43 [38, 69]	2 (28.6%)	5	25 [23, 73]	1 (20%)
AST	0	117	53 [33, 82]	23 (19.7%)	116	37 [25, 52.25]	13 (11.2%)
AST	1	99	48 [31.5, 69.5]	13 (13.1%)	95	36 [23.5, 52.5]	6 (6.3%)
AST	2	87	44 [29.5, 64]	9 (10.3%)	89	36 [22, 52]	8 (9%)
AST	3	78	40 [29.5, 67.75]	10 (12.8%)	79	35 [21, 49.5]	6 (7.6%)
AST	4	70	37.5 [25.25, 62.25]	6 (8.6%)	65	33 [23, 52]	5 (7.7%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
AST	5	49	37 [25, 50]	6 (12.2%)	53	33 [21, 46]	5 (9.4%)
AST	6	42	38 [25, 53.5]	5 (11.9%)	37	33 [22, 51]	3 (8.1%)
AST	7	37	39 [22, 46]	3 (8.1%)	36	30.5 [18.75, 49.25]	4 (11.1%)
AST	8	32	36 [24, 52]	3 (9.4%)	34	32.5 [19.25, 51.75]	3 (8.8%)
AST	9	31	37 [28.5, 60.5]	3 (9.7%)	32	25 [19.5, 43.25]	2 (6.2%)
AST	10	27	35 [29, 64]	5 (18.5%)	29	27 [19, 55]	1 (3.4%)
AST	11	24	33 [26, 51.5]	3 (12.5%)	25	28 [21, 58]	1 (4%)
AST	12	20	33.5 [25.25, 55]	2 (10%)	25	35 [28, 62]	0 (0%)
AST	13	20	29 [23.5, 44.25]	2 (10%)	21	35 [23, 51]	1 (4.8%)
AST	14	17	31 [21, 46]	2 (11.8%)	16	36 [22.5, 51.75]	1 (6.2%)
AST	15	18	32 [23, 48]	1 (5.6%)	17	31 [22, 37]	1 (5.9%)
AST	16	13	27 [22, 47]	1 (7.7%)	16	28 [17.25, 36.75]	0 (0%)
AST	17	11	22 [20, 26]	1 (9.1%)	15	28 [25.5, 40.5]	1 (6.7%)
AST	18	11	23 [23, 26]	1 (9.1%)	10	23.5 [19.25, 33.25]	0 (0%)
AST	19	10	27.5 [23.5, 32]	0 (0%)	11	30 [24, 36]	0 (0%)
AST	20	5	25 [24, 25]	0 (0%)	10	26 [20, 35.25]	0 (0%)
AST	21	8	30.5 [17, 40.5]	0 (0%)	12	26.5 [23.75, 35.75]	0 (0%)
AST	22	5	34 [26, 42]	0 (0%)	10	31 [23.25, 38.5]	0 (0%)
AST	23	5	45 [33, 90]	2 (40%)	9	25 [20, 39]	0 (0%)
AST	24	6	35.5 [28.5, 49.25]	1 (16.7%)	9	29 [25, 61]	0 (0%)
AST	25	6	40.5 [30.25, 55.25]	1 (16.7%)	8	30 [21.75, 50.75]	1 (12.5%)
AST	26	7	50 [32.5, 107]	2 (28.6%)	7	42 [25, 66.5]	1 (14.3%)
AST	27	6	48.5 [36.25, 135.75]	2 (33.3%)	9	28 [25, 43]	1 (11.1%)
AST	28	7	66 [34.5, 101.5]	2 (28.6%)	5	33 [23, 37]	1 (20%)
Bili	0	120	0.5 [0.3, 0.7]	2 (1.7%)	119	0.4 [0.4, 0.6]	3 (2.5%)
Bili	1	101	0.5 [0.3, 0.6]	0 (0%)	95	0.4 [0.3, 0.5]	0 (0%)
Bili	2	87	0.5 [0.4, 0.7]	3 (3.4%)	88	0.5 [0.3, 0.6]	2 (2.3%)
Bili	3	78	0.5 [0.4, 0.7]	1 (1.3%)	80	0.5 [0.3, 0.6]	0 (0%)
Bili	4	69	0.5 [0.4, 0.7]	1 (1.4%)	64	0.5 [0.4, 0.7]	0 (0%)
Bili	5	48	0.5 [0.4, 0.725]	1 (2.1%)	54	0.55 [0.4, 0.775]	2 (3.7%)
Bili	6	41	0.5 [0.4, 0.7]	1 (2.4%)	38	0.5 [0.4, 0.8]	1 (2.6%)
Bili	7	37	0.6 [0.4, 0.8]	0 (0%)	36	0.5 [0.4, 0.725]	0 (0%)
Bili	8	32	0.6 [0.375, 0.825]	1 (3.1%)	34	0.5 [0.4, 0.7]	0 (0%)
Bili	9	31	0.6 [0.4, 0.75]	0 (0%)	33	0.6 [0.5, 0.9]	0 (0%)
Bili	10	27	0.7 [0.5, 1.05]	0 (0%)	30	0.5 [0.425, 0.7]	0 (0%)
Bili	11	23	0.6 [0.45, 1.05]	1 (4.3%)	25	0.6 [0.4, 0.8]	0 (0%)
Bili	12	20	0.7 [0.4, 1.1]	1 (5%)	25	0.5 [0.4, 0.7]	1 (4%)
Bili	13	21	0.6 [0.4, 0.8]	0 (0%)	21	0.5 [0.4, 0.7]	1 (4.8%)
Bili	14	17	0.5 [0.3, 0.7]	0 (0%)	16	0.6 [0.375, 0.725]	1 (6.2%)
Bili	15	18	0.5 [0.325, 0.8]	1 (5.6%)	17	0.5 [0.4, 0.8]	2 (11.8%)
Bili	16	13	0.4 [0.3, 0.6]	0 (0%)	16	0.5 [0.4, 0.6]	1 (6.2%)
Bili	17	11	0.4 [0.3, 0.6]	0 (0%)	15	0.5 [0.4, 0.7]	0 (0%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Bili	18	11	0.4 [0.3, 0.65]	0 (0%)	10	0.6 [0.525, 0.675]	0 (0%)
Bili	19	10	0.5 [0.425, 1.075]	0 (0%)	11	0.4 [0.3, 0.6]	0 (0%)
Bili	20	5	0.5 [0.3, 1]	0 (0%)	10	0.4 [0.325, 0.5]	0 (0%)
Bili	21	8	0.55 [0.375, 0.8]	0 (0%)	12	0.6 [0.4, 0.925]	0 (0%)
Bili	22	5	0.8 [0.5, 1]	1 (20%)	10	0.55 [0.4, 0.675]	0 (0%)
Bili	23	5	2 [0.8, 2]	1 (20%)	9	0.5 [0.3, 0.7]	0 (0%)
Bili	24	6	0.65 [0.45, 0.775]	0 (0%)	9	0.6 [0.4, 0.7]	0 (0%)
Bili	25	6	0.8 [0.475, 1.8]	1 (16.7%)	8	0.5 [0.375, 0.675]	1 (12.5%)
Bili	26	7	1.4 [0.65, 1.75]	1 (14.3%)	7	0.7 [0.55, 1.45]	1 (14.3%)
Bili	27	6	1.15 [0.65, 1.65]	1 (16.7%)	9	0.5 [0.3, 1]	0 (0%)
Bili	28	7	0.9 [0.5, 1.5]	1 (14.3%)	5	0.3 [0.2, 1.2]	0 (0%)
Hgb	0	141	13.4 [12, 14.7]	0 (0%)	138	13.2 [12.125, 14.475]	1 (0.7%)
Hgb	1	120	13 [11.675, 14.2]	0 (0%)	122	13.2 [12, 14]	0 (0%)
Hgb	2	108	12.7 [11.275, 14.125]	1 (0.9%)	109	13.1 [12, 14.1]	0 (0%)
Hgb	3	99	12.9 [11.5, 14.2]	0 (0%)	97	13.2 [12, 14.5]	0 (0%)
Hgb	4	93	13 [11.1, 14.3]	0 (0%)	83	13 [11.95, 14.2]	0 (0%)
Hgb	5	77	12.5 [10.8, 14]	0 (0%)	75	13 [11.6, 14.2]	0 (0%)
Hgb	6	67	12.3 [10.8, 14.15]	1 (1.5%)	66	13.05 [11.425, 14]	0 (0%)
Hgb	7	65	12.7 [10.5, 13.9]	0 (0%)	55	12.6 [11.35, 13.7]	0 (0%)
Hgb	8	59	12.5 [10.3, 14]	0 (0%)	48	12.75 [10.8, 13.525]	0 (0%)
Hgb	9	55	12.5 [10.2, 13.65]	0 (0%)	42	12.7 [10.6, 13.975]	0 (0%)
Hgb	10	44	11.8 [10.075, 13.9]	0 (0%)	41	12.2 [10.2, 14.1]	0 (0%)
Hgb	11	43	12 [9.6, 13.95]	2 (4.7%)	38	11.6 [10.125, 13.1]	0 (0%)
Hgb	12	36	11.4 [9.35, 13.575]	0 (0%)	35	11.2 [10.15, 13.25]	1 (2.9%)
Hgb	13	33	11.1 [8.9, 14.3]	1 (3%)	31	10.7 [9.7, 12.75]	1 (3.2%)
Hgb	14	33	10.8 [8.8, 13.4]	0 (0%)	26	11.15 [8.775, 12.35]	0 (0%)
Hgb	15	30	10.4 [8.3, 12.4]	0 (0%)	27	10.7 [9.15, 12.15]	1 (3.7%)
Hgb	16	27	10.3 [9, 11.55]	0 (0%)	25	11 [9.2, 12.7]	0 (0%)
Hgb	17	24	9.5 [8.55, 11.4]	0 (0%)	24	10.7 [8.7, 12.05]	0 (0%)
Hgb	18	24	9.55 [8.575, 11.325]	0 (0%)	20	10.3 [8, 12.35]	0 (0%)
Hgb	19	22	9.25 [8.3, 11.3]	0 (0%)	22	10.15 [9, 11.15]	0 (0%)
Hgb	20	18	9.3 [8.125, 11.325]	1 (5.6%)	21	10.1 [8.5, 12]	0 (0%)
Hgb	21	17	9.7 [8.2, 11.3]	0 (0%)	17	9.1 [8.1, 10.5]	0 (0%)
Hgb	22	17	8.8 [7.7, 11.2]	0 (0%)	16	8.85 [8.05, 10.2]	0 (0%)
Hgb	23	16	9.1 [7.675, 10.9]	0 (0%)	17	8.7 [8, 10.1]	0 (0%)
Hgb	24	15	9 [8.15, 10.05]	0 (0%)	17	9.6 [8.4, 10.2]	1 (5.9%)
Hgb	25	13	8.9 [8.1, 10.6]	0 (0%)	17	9.6 [8.1, 10.9]	1 (5.9%)
Hgb	26	12	8.8 [8.125, 9.75]	2 (16.7%)	12	9.75 [8.2, 10.5]	0 (0%)
Hgb	27	12	9.7 [8.75, 10.675]	0 (0%)	15	9.3 [8.35, 11.6]	1 (6.7%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Hgb	28	11	9.2 [8.5, 10.05]	0 (0%)	13	9 [8.1, 10.1]	0 (0%)
Plat	0	140	210 [169, 283.25]	6 (4.3%)	137	231 [165, 287]	7 (5.1%)
Plat	1	120	247.5 [195, 318.75]	5 (4.2%)	123	246 [175.5, 338]	4 (3.3%)
Plat	2	107	262 [201, 343]	4 (3.7%)	110	278 [188.25, 344.25]	6 (5.5%)
Plat	3	98	269.5 [198.5, 337.75]	5 (5.1%)	99	285 [199.5, 366]	5 (5.1%)
Plat	4	93	300 [227, 364]	4 (4.3%)	82	299.5 [205, 373.5]	6 (7.3%)
Plat	5	77	298 [222, 375]	4 (5.2%)	76	316 [190, 396.5]	7 (9.2%)
Plat	6	66	329.5 [252.25, 384.75]	2 (3%)	66	297 [176.75, 399]	8 (12.1%)
Plat	7	64	322 [222.25, 379.5]	3 (4.7%)	55	293 [184.5, 453.5]	5 (9.1%)
Plat	8	58	323.5 [235.5, 376.5]	2 (3.4%)	48	270.5 [169.25, 455.5]	5 (10.4%)
Plat	9	55	286 [201.5, 355.5]	3 (5.5%)	42	271.5 [173.25, 428.75]	4 (9.5%)
Plat	10	42	273.5 [200.5, 332]	3 (7.1%)	41	290 [172, 461]	4 (9.8%)
Plat	11	42	251 [192, 321.5]	5 (11.9%)	38	274 [131.25, 429]	6 (15.8%)
Plat	12	35	276 [187.5, 312]	3 (8.6%)	35	275 [133, 395]	8 (22.9%)
Plat	13	33	252 [219, 293]	4 (12.1%)	31	248 [122, 301]	8 (25.8%)
Plat	14	33	248 [194, 308]	5 (15.2%)	26	204 [138, 316.75]	5 (19.2%)
Plat	15	30	233.5 [173, 285.25]	4 (13.3%)	26	244 [128.25, 293.25]	5 (19.2%)
Plat	16	27	234 [181.5, 259]	3 (11.1%)	25	207 [91, 285]	7 (28%)
Plat	17	24	229.5 [146.25, 313.75]	4 (16.7%)	24	185 [75, 273.25]	8 (33.3%)
Plat	18	24	228 [163.75, 274.5]	3 (12.5%)	20	184 [77.5, 281.25]	6 (30%)
Plat	19	22	221 [149.25, 275.75]	3 (13.6%)	21	206 [136, 289]	4 (19%)
Plat	20	18	225 [169.25, 307]	2 (11.1%)	21	204 [111, 299]	5 (23.8%)
Plat	21	17	234 [193, 312]	2 (11.8%)	17	186 [122, 277]	3 (17.6%)
Plat	22	17	268 [185, 335]	2 (11.8%)	16	176.5 [109.75, 280.25]	3 (18.8%)
Plat	23	16	206 [143, 303.75]	3 (18.8%)	17	175 [144, 283]	3 (17.6%)
Plat	24	15	251 [159.5, 354]	3 (20%)	17	213 [113, 297]	4 (23.5%)
Plat	25	13	267 [64, 389]	5 (38.5%)	17	251 [159, 307]	3 (17.6%)
Plat	26	12	237.5 [71.5, 387]	4 (33.3%)	12	258 [166.75, 313.5]	2 (16.7%)
Plat	27	12	344 [179, 541]	2 (16.7%)	15	280 [206.5, 316.5]	2 (13.3%)
Plat	28	11	297 [135, 500]	2 (18.2%)	13	258 [225, 459]	3 (23.1%)
ALC	0	61	623.7 [318, 1009.2]	45 (73.8%)	70	737.635 [503.525, 1170.925]	49 (70%)
ALC	1	46	832.2 [506.65, 1304.925]	26 (56.5%)	51	753.27 [421.645, 1049.9]	36 (70.6%)
ALC	2	39	852.6 [385.4, 1494]	22 (56.4%)	51	702 [435.5, 1103.24]	35 (68.6%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALC	3	32	753.45 [368.5, 1412.1]	19 (59.4%)	51	971.52 [570.8, 1364.4]	28 (54.9%)
ALC	4	33	864 [412.3, 1142.6]	20 (60.6%)	44	1087.075 [630.9375, 1621.65]	21 (47.7%)
ALC	5	30	872.3 [592.35, 1192.92]	17 (56.7%)	36	765.75 [462, 1296.83]	24 (66.7%)
ALC	6	26	962.925 [625.95, 1520.35]	14 (53.8%)	29	735 [363.6, 1056.16]	21 (72.4%)
ALC	7	25	887.03 [394, 1348.5]	13 (52%)	26	537 [337.14, 1641.33]	18 (69.2%)
ALC	8	24	1340.1 [629.42, 1748.93]	10 (41.7%)	27	655.5 [423.6, 1545.17]	17 (63%)
ALC	9	23	1166 [595.85, 1682]	11 (47.8%)	25	566.4 [332, 960.5]	19 (76%)
ALC	10	17	1365 [971.1, 1741.32]	5 (29.4%)	22	760.5 [555.12, 1424.05]	14 (63.6%)
ALC	11	17	1326.92 [732.29, 2030]	6 (35.3%)	19	780.8 [504, 1570.3]	12 (63.2%)
ALC	12	16	1302.94 [741.75, 1653.1]	7 (43.8%)	19	976 [596, 1645.2]	10 (52.6%)
ALC	13	14	1294.475 [791.44, 1654.8525]	6 (42.9%)	17	952 [580.17, 1763.91]	9 (52.9%)
ALC	14	17	1242.6 [823.2, 1828.64]	6 (35.3%)	11	684 [475.305, 1602]	7 (63.6%)
ALC	15	18	1151.8 [921.3, 1480.9]	6 (33.3%)	10	1051 [496.8, 1784.4]	5 (50%)
ALC	16	15	1085 [794.8, 1644.585]	6 (40%)	14	1537.925 [677.25, 1802.725]	6 (42.9%)
ALC	17	11	960 [689.4, 1571.95]	6 (54.5%)	13	1096.2 [648, 1794.1]	5 (38.5%)
ALC	18	13	1192.8 [632.4, 1742.7]	6 (46.2%)	10	1311.6 [1020.25, 1523.68]	3 (30%)
ALC	19	12	1298.9 [721.35, 1995.84]	5 (41.7%)	11	1606.32 [1348.65, 1768.715]	2 (18.2%)
ALC	20	10	1683.15 [796.95, 2184.775]	3 (30%)	10	1733.9 [1010.1, 2241.95]	3 (30%)
ALC	21	7	1479 [964.05, 1661.5]	2 (28.6%)	7	1266.82 [869.9, 1419.6]	2 (28.6%)
ALC	22	8	1684.42 [916.775, 2091]	3 (37.5%)	6	1230.75 [822.375, 1502.025]	3 (50%)
ALC	23	10	1346.93 [1292, 1897.35]	2 (20%)	4	787.15 [612.375, 1106.475]	3 (75%)
ALC	24	9	1269 [823.2, 1884.8]	4 (44.4%)	6	1299.8 [1004.95, 1582.95]	2 (33.3%)
ALC	25	8	1123.7 [456, 1892.7825]	4 (50%)	9	1516.8 [1065.16, 1666]	2 (22.2%)
ALC	26	6	788.4 [581.7, 1499.175]	4 (66.7%)	7	1095 [741.5, 1742]	2 (28.6%)
ALC	27	6	1203 [433.5, 1841.5575]	3 (50%)	7	2009.14 [1181.2, 2335.8]	2 (28.6%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALC	28	5	1287 [651.9, 1784.7]	2 (40%)	6	927.6 [718.3, 1747.625]	3 (50%)
ANC	0	59	5288.87 [3610, 8156.69]	4 (6.8%)	69	5846.6 [3306.7, 8832]	2 (2.9%)
ANC	1	47	7242 [3980.75, 8954.4]	2 (4.3%)	50	6113.2 [4622.705, 8729.2]	0 (0%)
ANC	2	38	8152.45 [6670.625, 9361]	1 (2.6%)	50	7014.3 [5268.305, 9140.64]	2 (4%)
ANC	3	32	7996 [6285.3, 9936.2]	0 (0%)	50	6533.465 [4286, 8317.5]	4 (8%)
ANC	4	34	7443.06 [5005.2, 10602.65]	1 (2.9%)	44	8552.4 [5995.66, 10682.425]	2 (4.5%)
ANC	5	30	9578.5 [5722.5, 12775.5]	0 (0%)	36	7668.48 [4753.725, 10781.25]	2 (5.6%)
ANC	6	27	11162.27 [6352.35, 12739.35]	0 (0%)	27	10162.5 [7045.55, 13728.84]	1 (3.7%)
ANC	7	25	9609.6 [6867.6, 14804.6]	1 (4%)	25	10683.6 [8010, 13824]	1 (4%)
ANC	8	23	9476 [7198.45, 13008.99]	1 (4.3%)	25	10912 [8786, 15521]	1 (4%)
ANC	9	23	11104.4 [6861.65, 13909.48]	1 (4.3%)	24	10195.25 [8795.7, 15224.82]	0 (0%)
ANC	10	17	13626.9 [8403.48, 15292.8]	0 (0%)	22	9943.2 [8164.65, 14800.3]	0 (0%)
ANC	11	17	13210.2 [10534.12, 18816]	0 (0%)	18	9271.115 [6287, 11101.5]	0 (0%)
ANC	12	16	12010.32 [7574.175, 17244.5625]	0 (0%)	19	8829.8 [7151.95, 10200]	0 (0%)
ANC	13	14	12847.02 [9446.425, 14252.8]	0 (0%)	17	7641 [5585.01, 9794]	2 (11.8%)
ANC	14	17	10920 [7241.83, 13725.9]	0 (0%)	11	6640 [4632.3, 8461.5]	0 (0%)
ANC	15	18	9975.9 [7372.545, 12352.2]	1 (5.6%)	9	6660 [4760, 8142.7]	0 (0%)
ANC	16	15	9500.4 [6124.465, 13398]	0 (0%)	13	7436.6 [4498, 12240]	0 (0%)
ANC	17	11	7509.6 [5133, 10417.96]	0 (0%)	12	8623.8 [5518.875, 11974.8]	0 (0%)
ANC	18	12	5898.09 [4503.1, 9413.64]	1 (8.3%)	9	6630 [5992, 8857.8]	0 (0%)
ANC	19	12	4710.5 [3513.4, 8459.25]	0 (0%)	10	7226.55 [4552.5, 10390.1925]	0 (0%)
ANC	20	10	6220.2 [5441.16, 8771.175]	0 (0%)	9	7360 [4248, 9295]	0 (0%)
ANC	21	7	6982.8 [3664.55, 8968.4]	0 (0%)	6	6843.1 [4893.75, 8611.625]	0 (0%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ANC	22	7	8585.4 [6380.8, 9734]	0 (0%)	5	8700 [5751, 9028]	0 (0%)
ANC	23	10	7149.78 [4082.475, 8263.75]	0 (0%)	3	7798.7 [7284.85, 8340.15]	0 (0%)
ANC	24	8	7913.8 [7096.95, 8582.28]	0 (0%)	5	10132 [10070.8, 10427.6]	0 (0%)
ANC	25	7	7366 [5804.1, 8517.7]	0 (0%)	8	10128.4 [7741, 11268.715]	0 (0%)
ANC	26	6	8100 [6689.25, 11422.5525]	0 (0%)	5	8536 [8450, 10332]	0 (0%)
ANC	27	6	8738 [7281, 11460.4675]	0 (0%)	5	10567.2 [8792, 10828.02]	0 (0%)
ANC	28	5	10139.74 [6996, 10462.2]	0 (0%)	5	10336 [10010.64, 10935]	0 (0%)
Trop1c	0	10	0.0135 [0.0025, 0.01925]	1 (10%)	10	0.025 [0.017, 0.045]	3 (30%)
Trop1c	1	0	-	-	2	0.0285 [0.02275, 0.03425]	1 (50%)
Trop1c	2	0	-	-	2	0.0485 [0.03275, 0.06425]	1 (50%)
Trop1c	3	0	-	-	2	0.06 [0.06, 0.06]	2 (100%)
Trop1c	4	0	-	-	2	0.34 [0.19, 0.49]	2 (100%)
Trop1c	5	0	-	-	2	1.955 [0.9925, 2.9175]	1 (50%)
Trop1c	6	0	-	-	0	-	-
Trop1c	7	1	0.02 [0.02, 0.02]	0 (0%)	1	0.98 [0.98, 0.98]	1 (100%)
Trop1c	8	0	-	-	1	0.17 [0.17, 0.17]	1 (100%)
Trop1c	9	0	-	-	2	0.0985 [0.05775, 0.13925]	1 (50%)
Trop1c	10	0	-	-	1	0.12 [0.12, 0.12]	1 (100%)
Trop1c	11	0	-	-	2	0.04 [0.03, 0.05]	1 (50%)
Trop1c	12	1	0.02 [0.02, 0.02]	0 (0%)	0	-	-
Trop1c	13	0	-	-	2	0.0161 [0.01565, 0.01655]	0 (0%)
Trop1c	14	0	-	-	1	0.076 [0.076, 0.076]	1 (100%)
Trop1c	15	0	-	-	1	0.069 [0.069, 0.069]	1 (100%)
Trop1c	16	0	-	-	0	-	-
Trop1c	17	0	-	-	0	-	-
Trop1c	18	0	-	-	0	-	-
Trop1c	19	0	-	-	0	-	-
Trop1c	20	0	-	-	0	-	-
Trop1c	21	0	-	-	0	-	-
Trop1c	22	0	-	-	0	-	-
Trop1c	23	0	-	-	0	-	-
Trop1c	24	1	99.9 [99.9, 99.9]	1 (100%)	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Trop1c	25	2	41.7 [24.5, 58.9]	2 (100%)	0	-	-
Trop1c	26	0	-	-	0	-	-
Trop1c	27	0	-	-	0	-	-
Trop1c	28	0	-	-	0	-	-
Tropth	0	2	3.005 [1.5075, 4.5025]	0 (0%)	0	-	-
Tropth	1	0	-	-	0	-	-
Tropth	2	0	-	-	1	6 [6, 6]	0 (0%)
Tropth	3	0	-	-	0	-	-
Tropth	4	0	-	-	1	11 [11, 11]	0 (0%)
Tropth	5	0	-	-	0	-	-
Tropth	6	0	-	-	0	-	-
Tropth	7	0	-	-	0	-	-
Tropth	8	0	-	-	0	-	-
Tropth	9	0	-	-	0	-	-
Tropth	10	0	-	-	0	-	-
Tropth	11	0	-	-	0	-	-
Tropth	12	0	-	-	0	-	-
Tropth	13	0	-	-	0	-	-
Tropth	14	0	-	-	0	-	-
Tropth	15	0	-	-	0	-	-
Tropth	16	0	-	-	0	-	-
Tropth	17	0	-	-	0	-	-
Tropth	18	0	-	-	0	-	-
Tropth	19	0	-	-	0	-	-
Tropth	20	0	-	-	0	-	-
Tropth	21	0	-	-	0	-	-
Tropth	22	0	-	-	0	-	-
Tropth	23	0	-	-	0	-	-
Tropth	24	0	-	-	0	-	-
Tropth	25	0	-	-	0	-	-
Tropth	26	0	-	-	0	-	-
Tropth	27	0	-	-	0	-	-
Tropth	28	0	-	-	0	-	-
Trop1h	0	3	11 [8, 11]	0 (0%)	6	7 [6, 18.5]	0 (0%)
Trop1h	1	0	-	-	1	4 [4, 4]	0 (0%)
Trop1h	2	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Trop1h	3	0	-	-	0	-	-
Trop1h	4	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Trop1h	5	0	-	-	0	-	-
Trop1h	6	0	-	-	0	-	-
Trop1h	7	0	-	-	0	-	-
Trop1h	8	0	-	-	0	-	-
Trop1h	9	0	-	-	0	-	-
Trop1h	10	0	-	-	0	-	-
Trop1h	11	0	-	-	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Trop1h	12	0	-	-	0	-	-
Trop1h	13	0	-	-	0	-	-
Trop1h	14	0	-	-	0	-	-
Trop1h	15	1	9736 [9736, 9736]	1 (100%)	0	-	-
Trop1h	16	1	14831 [14831, 14831]	1 (100%)	0	-	-
Trop1h	17	0	-	-	0	-	-
Trop1h	18	0	-	-	0	-	-
Trop1h	19	1	4 [4, 4]	0 (0%)	0	-	-
Trop1h	20	0	-	-	0	-	-
Trop1h	21	0	-	-	0	-	-
Trop1h	22	0	-	-	0	-	-
Trop1h	23	0	-	-	0	-	-
Trop1h	24	0	-	-	0	-	-
Trop1h	25	0	-	-	0	-	-
Trop1h	26	0	-	-	0	-	-
Trop1h	27	0	-	-	0	-	-
Trop1h	28	0	-	-	0	-	-
Troptc	0	0	-	-	0	-	-
Troptc	1	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Troptc	2	0	-	-	0	-	-
Troptc	3	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Troptc	4	0	-	-	0	-	-
Troptc	5	0	-	-	0	-	-
Troptc	6	2	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Troptc	7	0	-	-	0	-	-
Troptc	8	0	-	-	0	-	-
Troptc	9	0	-	-	0	-	-
Troptc	10	0	-	-	0	-	-
Troptc	11	0	-	-	0	-	-
Troptc	12	1	0.04 [0.04, 0.04]	1 (100%)	0	-	-
Troptc	13	1	0.03 [0.03, 0.03]	1 (100%)	0	-	-
Troptc	14	1	0.05 [0.05, 0.05]	1 (100%)	0	-	-
Troptc	15	0	-	-	0	-	-
Troptc	16	0	-	-	0	-	-
Troptc	17	1	0.11 [0.11, 0.11]	1 (100%)	0	-	-
Troptc	18	1	0.09 [0.09, 0.09]	1 (100%)	0	-	-
Troptc	19	0	-	-	0	-	-
Troptc	20	0	-	-	0	-	-
Troptc	21	0	-	-	0	-	-
Troptc	22	1	0.09 [0.09, 0.09]	1 (100%)	0	-	-
Troptc	23	0	-	-	0	-	-
Troptc	24	0	-	-	0	-	-
Troptc	25	0	-	-	0	-	-
Troptc	26	0	-	-	0	-	-
Troptc	27	0	-	-	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Troptc	28	0	-	-	0	-	-

Fostamatinib

Table 30 Fostamatinib Laboratory Values Over Time

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALT	0	204	19 [14, 29]	4 (2%)	198	20 [15, 33.75]	7 (3.5%)
ALT	1	195	21 [14, 31.5]	7 (3.6%)	187	21 [14, 34]	3 (1.6%)
ALT	2	163	23 [15, 32.5]	6 (3.7%)	153	23 [14, 35]	7 (4.6%)
ALT	3	134	23.5 [16, 41]	8 (6%)	128	28 [16, 39]	8 (6.2%)
ALT	4	113	26 [18, 43]	8 (7.1%)	106	30.5 [18, 51.75]	7 (6.6%)
ALT	5	89	26 [17, 45]	10 (11.2%)	84	33 [19.75, 55]	10 (11.9%)
ALT	6	82	27.5 [17.25, 52]	10 (12.2%)	66	38 [20.5, 54.25]	7 (10.6%)
ALT	7	74	27.5 [17, 55.5]	8 (10.8%)	59	32 [21, 45]	4 (6.8%)
ALT	8	58	30 [18.25, 53.75]	6 (10.3%)	49	31 [21, 42]	2 (4.1%)
ALT	9	54	27.5 [17.5, 48.75]	4 (7.4%)	41	29 [22, 41]	4 (9.8%)
ALT	10	45	34 [18, 57]	5 (11.1%)	38	28.5 [19.25, 40.75]	3 (7.9%)
ALT	11	44	28.5 [19.75, 41.25]	4 (9.1%)	31	25 [20, 44]	2 (6.5%)
ALT	12	38	31.5 [21, 48.25]	6 (15.8%)	23	30 [20, 45]	2 (8.7%)
ALT	13	38	28 [19.25, 45.75]	7 (18.4%)	20	23 [18, 48.75]	2 (10%)
ALT	14	32	27 [20, 38.25]	3 (9.4%)	16	23 [16.75, 36.25]	1 (6.2%)
ALT	15	16	34 [19.5, 48.25]	2 (12.5%)	13	35 [15, 41]	0 (0%)
ALT	16	15	40 [22.5, 48]	2 (13.3%)	11	33 [14, 37.5]	0 (0%)
ALT	17	12	28.5 [17.25, 43]	1 (8.3%)	11	29 [15.5, 39]	1 (9.1%)
ALT	18	10	33.5 [12.25, 51]	1 (10%)	8	18.5 [10.75, 33.25]	1 (12.5%)
ALT	19	10	23 [10.75, 48]	1 (10%)	7	24 [15.5, 39.5]	1 (14.3%)
ALT	20	10	26.5 [14.25, 49]	1 (10%)	8	21.5 [12.25, 44.25]	1 (12.5%)
ALT	21	8	36.5 [16.75, 75.75]	2 (25%)	7	15 [11, 21]	1 (14.3%)
ALT	22	9	21 [12, 53]	1 (11.1%)	6	15.5 [12, 19.75]	1 (16.7%)
ALT	23	8	23.5 [15.75, 53.25]	2 (25%)	5	22 [15, 59]	1 (20%)
ALT	24	7	17 [13.5, 113.5]	2 (28.6%)	6	21.5 [18.25, 48.75]	1 (16.7%)
ALT	25	7	28 [15, 37]	1 (14.3%)	3	21 [16, 99]	1 (33.3%)
ALT	26	5	17 [11, 49]	1 (20%)	3	35 [26, 105.5]	1 (33.3%)
ALT	27	6	19 [12.75, 29]	1 (16.7%)	5	23 [23, 75]	1 (20%)
ALT	28	6	46 [21.75, 70.25]	1 (16.7%)	5	21 [10, 23]	1 (20%)
AST	0	202	27.5 [19.25, 40]	8 (4%)	198	27.5 [18, 45]	10 (5.1%)
AST	1	194	27 [20, 40]	8 (4.1%)	186	25 [17.25, 39.75]	4 (2.2%)
AST	2	160	30 [19, 44.5]	9 (5.6%)	153	26 [17, 40]	4 (2.6%)
AST	3	134	28 [20.25, 46]	9 (6.7%)	127	26 [18.5, 39]	3 (2.4%)
AST	4	113	28 [20, 41]	7 (6.2%)	106	28 [19.25, 40.75]	4 (3.8%)
AST	5	89	30 [22, 49]	8 (9%)	83	28 [20, 43]	7 (8.4%)
AST	6	82	33 [21.25, 51.75]	9 (11%)	66	30 [18.75, 44.5]	3 (4.5%)
AST	7	73	33 [24, 47]	6 (8.2%)	58	26 [19, 39.5]	2 (3.4%)
AST	8	59	35 [24.5, 48.5]	3 (5.1%)	49	25 [16, 37]	3 (6.1%)
AST	9	54	35 [24.5, 48]	4 (7.4%)	41	25 [18, 35]	5 (12.2%)
AST	10	45	38 [26, 49]	5 (11.1%)	38	26 [16, 38]	3 (7.9%)
AST	11	44	36 [26.75, 58]	7 (15.9%)	31	24 [16, 38]	1 (3.2%)
AST	12	38	44.5 [24, 62.75]	6 (15.8%)	23	30 [16.5, 45.5]	0 (0%)
AST	13	38	36.5 [27.25, 59.25]	5 (13.2%)	20	29 [22.5, 42.5]	0 (0%)
AST	14	32	36.5 [28, 47.75]	4 (12.5%)	15	25 [21.5, 37.5]	1 (6.7%)
AST	15	16	35 [26.5, 58.75]	2 (12.5%)	13	32 [22, 38]	1 (7.7%)
AST	16	15	35 [26, 65.5]	1 (6.7%)	11	24 [18, 45.5]	0 (0%)
AST	17	13	35 [23, 55]	1 (7.7%)	10	34.5 [23.5, 49]	0 (0%)
AST	18	10	34 [26.25, 49.5]	1 (10%)	8	22 [18.75, 41.25]	0 (0%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
AST	19	10	30 [20, 62.25]	1 (10%)	7	34 [25, 43]	0 (0%)
AST	20	10	31 [17.75, 68.5]	2 (20%)	8	27 [20.75, 48.5]	0 (0%)
AST	21	8	35 [18, 106.25]	2 (25%)	7	24 [18, 39]	0 (0%)
AST	22	9	27 [18, 126]	3 (33.3%)	6	25 [20.75, 40.5]	0 (0%)
AST	23	8	32 [15.5, 85.75]	2 (25%)	4	35 [22.25, 58.75]	0 (0%)
AST	24	7	42 [18.5, 139.5]	2 (28.6%)	6	40.5 [23, 67]	1 (16.7%)
AST	25	7	31 [21.5, 55]	1 (14.3%)	3	34 [28, 64.5]	1 (33.3%)
AST	26	5	41 [15, 92]	1 (20%)	3	42 [36, 65]	1 (33.3%)
AST	27	6	27.5 [17, 53]	1 (16.7%)	5	40 [28, 51]	1 (20%)
AST	28	6	66 [40.75, 109.25]	2 (33.3%)	5	37 [26, 47]	1 (20%)
Bili	0	200	0.4 [0.3, 0.6]	2 (1%)	193	0.4 [0.3, 0.6]	2 (1%)
Bili	1	192	0.4 [0.3, 0.5]	2 (1%)	183	0.4 [0.3, 0.5]	2 (1.1%)
Bili	2	159	0.4 [0.3, 0.6]	2 (1.3%)	149	0.4 [0.3, 0.5]	2 (1.3%)
Bili	3	132	0.405 [0.3, 0.7]	1 (0.8%)	125	0.4 [0.3, 0.5]	1 (0.8%)
Bili	4	112	0.5 [0.3, 0.815]	4 (3.6%)	105	0.4 [0.3, 0.6]	2 (1.9%)
Bili	5	89	0.6 [0.3, 0.8]	1 (1.1%)	83	0.409269 [0.3, 0.7]	2 (2.4%)
Bili	6	79	0.6 [0.32, 0.8]	1 (1.3%)	65	0.6 [0.4, 0.8]	2 (3.1%)
Bili	7	72	0.6 [0.4, 0.9]	4 (5.6%)	57	0.5 [0.3, 0.8]	1 (1.8%)
Bili	8	58	0.6 [0.4, 1.075]	3 (5.2%)	48	0.55 [0.3, 0.8]	1 (2.1%)
Bili	9	54	0.75 [0.4, 1.1]	3 (5.6%)	40	0.6 [0.4, 0.9]	0 (0%)
Bili	10	45	0.83 [0.5, 1.1]	2 (4.4%)	37	0.5 [0.4, 0.8]	0 (0%)
Bili	11	43	0.7 [0.45, 1.15]	3 (7%)	30	0.6 [0.4, 0.775]	0 (0%)
Bili	12	39	0.7 [0.4, 1.25]	4 (10.3%)	22	0.6 [0.5, 0.7]	0 (0%)
Bili	13	37	0.79 [0.4, 1.1]	5 (13.5%)	19	0.5 [0.3, 0.7]	0 (0%)
Bili	14	32	0.625 [0.475, 1.1]	2 (6.2%)	15	0.5 [0.4, 0.8]	0 (0%)
Bili	15	16	0.7 [0.475, 1.1]	1 (6.2%)	13	0.7 [0.5, 0.8]	0 (0%)
Bili	16	15	0.7 [0.4, 0.95]	1 (6.7%)	11	0.8 [0.45, 0.8]	0 (0%)
Bili	17	13	0.7 [0.3, 1]	1 (7.7%)	10	0.65 [0.425, 0.775]	0 (0%)
Bili	18	10	0.7 [0.45, 1.125]	1 (10%)	8	0.6 [0.475, 0.825]	0 (0%)
Bili	19	10	0.55 [0.325, 1.65]	2 (20%)	7	0.7 [0.45, 1]	0 (0%)
Bili	20	10	0.8 [0.425, 1.625]	2 (20%)	8	0.45 [0.3, 0.775]	0 (0%)
Bili	21	8	0.85 [0.375, 1.725]	1 (12.5%)	7	0.4 [0.3929411, 0.95]	0 (0%)
Bili	22	9	0.8 [0.2, 1.3]	1 (11.1%)	6	0.55 [0.425, 1.05]	0 (0%)
Bili	23	8	0.65 [0.45, 0.925]	0 (0%)	5	0.6 [0.5, 1.3]	0 (0%)
Bili	24	7	0.7 [0.35, 1]	0 (0%)	6	0.75 [0.625, 1.025]	0 (0%)
Bili	25	7	0.7 [0.45, 0.75]	0 (0%)	3	0.6 [0.4, 0.8]	0 (0%)
Bili	26	5	0.4 [0.4, 0.8]	0 (0%)	3	0.7 [0.45, 0.95]	0 (0%)
Bili	27	6	0.4 [0.325, 0.55]	0 (0%)	5	0.4 [0.3, 0.8]	0 (0%)
Bili	28	6	0.6 [0.45, 0.75]	0 (0%)	5	0.8 [0.3566487, 1.3]	0 (0%)
Hgb	0	206	12.15 [10.4, 13.675]	1 (0.5%)	204	12.5 [10.975, 13.825]	2 (1%)
Hgb	1	194	12 [9.925, 13.375]	0 (0%)	189	12.3 [10.8, 13.4]	2 (1.1%)
Hgb	2	163	12.1 [9.85, 13.55]	0 (0%)	157	12.5 [10.8, 13.7]	0 (0%)
Hgb	3	136	11.8 [9.875, 13.725]	0 (0%)	132	12.25 [10.575, 13.725]	1 (0.8%)
Hgb	4	115	12 [10.1, 14.3]	1 (0.9%)	110	12.45 [10.425, 13.6]	1 (0.9%)
Hgb	5	92	12.3 [10.075, 14.05]	2 (2.2%)	87	12.1 [10.15, 13.4]	0 (0%)
Hgb	6	85	11.7 [9.5, 14.5]	1 (1.2%)	70	11.8 [10.025, 13.375]	0 (0%)
Hgb	7	79	11.4 [9.2, 14.5]	2 (2.5%)	63	12.1 [9.85, 13.35]	1 (1.6%)
Hgb	8	64	11.45 [9.35, 13.475]	0 (0%)	53	11.7 [9.9, 13.2]	0 (0%)
Hgb	9	59	11.2 [9.25, 13.75]	0 (0%)	43	11.6 [9.85, 12.9]	0 (0%)
Hgb	10	51	10.7 [8.6, 13.5]	0 (0%)	43	11.8 [9.9, 12.8]	0 (0%)
Hgb	11	50	10.3 [8.175, 12.95]	1 (2%)	37	10.8 [9.3, 12.9]	0 (0%)
Hgb	12	41	10 [8.1, 12.3]	1 (2.4%)	30	10.25 [8.875, 12.425]	0 (0%)
Hgb	13	40	10.15 [8.275, 12.65]	2 (5%)	25	10 [8.7, 11.2]	0 (0%)
Hgb	14	37	9.2 [7.9, 12.5]	0 (0%)	23	10 [7.95, 10.75]	1 (4.3%)
Hgb	15	24	8.4 [7.6, 12.3]	0 (0%)	19	9.6 [7.7, 10.8]	1 (5.3%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Hgb	16	23	8.6 [7.45, 11.35]	0 (0%)	16	10.1 [8.275, 11.8]	0 (0%)
Hgb	17	23	8.2 [7.75, 9.95]	2 (8.7%)	19	9.5 [8.25, 11.3]	0 (0%)
Hgb	18	20	8.1 [7.8, 10.275]	0 (0%)	13	9.7 [8, 12.3]	1 (7.7%)
Hgb	19	19	8.4 [8, 9.8]	0 (0%)	13	9.6 [7.8, 10.8]	0 (0%)
Hgb	20	18	8.3 [7.9, 10.175]	0 (0%)	13	9.3 [8.6, 10.5]	0 (0%)
Hgb	21	17	8.6 [8, 9.5]	1 (5.9%)	12	9.05 [8.35, 9.75]	0 (0%)
Hgb	22	15	8 [7.85, 9.4]	0 (0%)	9	8.9 [8.1, 9.6]	0 (0%)
Hgb	23	12	8.2 [8, 8.7]	0 (0%)	9	8.7 [8.4, 9.5]	0 (0%)
Hgb	24	12	8.4 [8.125, 8.925]	0 (0%)	9	9.2 [8.8, 9.7]	0 (0%)
Hgb	25	11	8.6 [7.85, 9.3]	0 (0%)	10	9.25 [8.95, 10.15]	0 (0%)
Hgb	26	8	7.75 [7.5, 8.55]	0 (0%)	8	9 [8.65, 9.5]	0 (0%)
Hgb	27	9	7.9 [7.1, 8]	2 (22.2%)	9	8.6 [7.9, 9.3]	0 (0%)
Hgb	28	9	7.5 [7.2, 7.5]	1 (11.1%)	10	8.65 [8.175, 9.15]	0 (0%)
Plat	0	206	210 [148.75, 261]	18 (8.7%)	200	214 [158, 280]	15 (7.5%)
Plat	1	194	218.5 [150, 275.5]	15 (7.7%)	187	230 [182, 292.5]	10 (5.3%)
Plat	2	163	245 [170, 314.5]	8 (4.9%)	156	236 [182.75, 298.5]	9 (5.8%)
Plat	3	136	269.5 [180.75, 317.25]	8 (5.9%)	131	240 [175.5, 305.5]	7 (5.3%)
Plat	4	115	267 [198, 340]	8 (7%)	109	249 [202, 326]	5 (4.6%)
Plat	5	92	249 [185.75, 360.5]	7 (7.6%)	86	260.5 [199.5, 330.5]	3 (3.5%)
Plat	6	84	271 [156.75, 361.25]	6 (7.1%)	70	256 [176.25, 336.75]	2 (2.9%)
Plat	7	79	261 [167.5, 365.5]	9 (11.4%)	61	264 [193, 328]	1 (1.6%)
Plat	8	64	259 [155.75, 368.75]	6 (9.4%)	52	242 [179.75, 310.5]	3 (5.8%)
Plat	9	59	260 [157, 425.5]	6 (10.2%)	42	224 [146.25, 293.25]	1 (2.4%)
Plat	10	50	238 [132.75, 405.75]	7 (14%)	42	220 [136.25, 301.25]	4 (9.5%)
Plat	11	50	221 [131.75, 346.5]	7 (14%)	36	238.5 [140.25, 277.25]	2 (5.6%)
Plat	12	41	217 [111, 342]	8 (19.5%)	29	226 [137, 273]	3 (10.3%)
Plat	13	41	224 [138, 369]	6 (14.6%)	24	234 [133.25, 277.75]	3 (12.5%)
Plat	14	37	201 [112, 283]	8 (21.6%)	23	195 [132.5, 260]	4 (17.4%)
Plat	15	24	203.5 [111.5, 269.25]	4 (16.7%)	19	187 [118, 279]	3 (15.8%)
Plat	16	23	193 [91.5, 264.5]	6 (26.1%)	16	197 [106, 256.75]	4 (25%)
Plat	17	23	175 [101.5, 273]	5 (21.7%)	19	179 [129.5, 235.5]	4 (21.1%)
Plat	18	20	166 [105, 256.75]	5 (25%)	13	137 [80, 211]	5 (38.5%)
Plat	19	19	152 [85, 232.5]	5 (26.3%)	13	152 [93, 284]	5 (38.5%)
Plat	20	18	156 [79.5, 218.5]	6 (33.3%)	13	131 [89, 189]	4 (30.8%)
Plat	21	17	134 [79, 215]	7 (41.2%)	12	148.5 [111.5, 206.75]	3 (25%)
Plat	22	15	152 [78.5, 210]	5 (33.3%)	9	128 [106, 184]	2 (22.2%)
Plat	23	12	137.5 [109, 197.75]	2 (16.7%)	9	126 [76, 267]	3 (33.3%)
Plat	24	12	124.5 [113.25, 256.75]	3 (25%)	9	135 [78, 288]	3 (33.3%)
Plat	25	11	195 [143.5, 239.5]	2 (18.2%)	10	223 [99, 304.75]	3 (30%)
Plat	26	8	211 [167.25, 246.25]	1 (12.5%)	8	214 [78.75, 339.75]	3 (37.5%)
Plat	27	9	193 [145, 235]	1 (11.1%)	9	257 [86, 280]	3 (33.3%)
Plat	28	9	200 [124, 208]	2 (22.2%)	10	272.5 [112.75, 334.5]	3 (30%)
ALC	0	181	646.8 [423, 1209.71]	122 (67.4%)	181	707.46 [424, 1085]	130 (71.8%)
ALC	1	175	1038.5 [600.95, 1690.9]	85 (48.6%)	165	819 [504, 1241]	97 (58.8%)
ALC	2	144	1105 [611.6, 1940.9975]	65 (45.1%)	138	803.25 [422.6, 1323.59]	87 (63%)
ALC	3	118	1182 [671.4, 1893.6]	45 (38.1%)	114	828 [436.825, 1463.625]	63 (55.3%)
ALC	4	103	1132.5 [780, 2029.25]	44 (42.7%)	93	844.2 [401.7, 1786.4]	51 (54.8%)
ALC	5	82	1102.4 [564.45, 1903.4775]	38 (46.3%)	72	777.75 [384.35, 1770.145]	40 (55.6%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ALC	6	72	1100.6 [615.015, 2170.95]	33 (45.8%)	55	734.4 [408.35, 1378.2]	33 (60%)
ALC	7	68	1029.22 [496, 1408.6]	33 (48.5%)	51	700 [394.3, 1481.2]	29 (56.9%)
ALC	8	55	948.6 [433.2, 1540.35]	30 (54.5%)	46	717.16 [454.54, 1505.85]	28 (60.9%)
ALC	9	51	871.2 [354.89, 1565.15]	28 (54.9%)	37	749.7 [321.3, 1236]	27 (73%)
ALC	10	39	1098.9 [429.05, 1877.48]	16 (41%)	34	777.95 [433.545, 1510.56]	21 (61.8%)
ALC	11	40	935.09 [495.435, 1791.525]	22 (55%)	28	734.6 [480.35, 1840]	19 (67.9%)
ALC	12	34	944.43 [625.3475, 2018.625]	18 (52.9%)	23	717.6 [455.3, 983.6]	18 (78.3%)
ALC	13	33	876 [474, 1687.2]	17 (51.5%)	19	774 [606, 971.65]	15 (78.9%)
ALC	14	30	786.5 [297.75, 1324.3]	17 (56.7%)	17	619.2 [276.8, 1068.2]	12 (70.6%)
ALC	15	15	654 [209.95, 1021.5]	11 (73.3%)	12	523.6 [389.45, 1011.3]	9 (75%)
ALC	16	13	475.8 [144, 881.1]	10 (76.9%)	11	509.53 [230.6, 677.1]	9 (81.8%)
ALC	17	12	577.6 [208.275, 740]	10 (83.3%)	10	344.5 [236, 787.475]	8 (80%)
ALC	18	13	554.4 [118.4, 888.1]	11 (84.6%)	8	346.15 [172.95, 1114.51]	6 (75%)
ALC	19	13	504 [125.4, 984]	10 (76.9%)	9	376.3 [249.6, 1152]	6 (66.7%)
ALC	20	10	578.75 [360, 1098.6]	7 (70%)	8	481.215 [368.05, 696]	7 (87.5%)
ALC	21	12	424.6 [123.7425, 766.425]	10 (83.3%)	8	342 [208.875, 552.49]	8 (100%)
ALC	22	8	705.75 [187.76, 1297.8]	4 (50%)	7	322.4 [268.65, 390.05]	7 (100%)
ALC	23	8	732.95 [433.235, 1576.325]	5 (62.5%)	5	319.6 [265.5, 442.39]	5 (100%)
ALC	24	7	640.5 [386.98, 1157]	5 (71.4%)	6	526.5 [303.45, 695.1]	6 (100%)
ALC	25	5	990.6 [180.36, 2592]	3 (60%)	8	453.35 [283.95, 596.4]	7 (87.5%)
ALC	26	4	1001.6 [667.665, 1446.6]	2 (50%)	7	350.72 [284.4, 654.3]	6 (85.7%)
ALC	27	5	884.4 [842.8, 996.8]	4 (80%)	6	314.9 [165.165, 702.55]	5 (83.3%)
ALC	28	4	652.35 [497.35, 699.25]	4 (100%)	6	393.45 [217.7325, 528.225]	5 (83.3%)
ANC	0	195	4972.8 [3067.4, 8639.5]	8 (4.1%)	192	5435.115 [3390.3975, 8730]	7 (3.6%)
ANC	1	187	5260.2 [3086.86, 8688.55]	8 (4.3%)	175	6059 [4127.5, 8633.905]	3 (1.7%)
ANC	2	155	5544 [3318.75, 8622.7]	6 (3.9%)	148	6724.4 [4219.82, 8519.13]	3 (2%)
ANC	3	128	5607.7 [3068.925, 9126.7]	6 (4.7%)	121	6272 [4340.7, 8671.5]	6 (5%)
ANC	4	111	5658.4 [3480.2, 9232.36]	6 (5.4%)	98	6388.77 [4625.955, 9107.675]	4 (4.1%)
ANC	5	88	6601.8 [4022.9775, 9672.25]	3 (3.4%)	75	7265.3 [4557.45, 10499.67]	3 (4%)
ANC	6	78	6391.2 [4264.0875, 9309.375]	0 (0%)	57	6873 [4757.85, 9975]	1 (1.8%)
ANC	7	73	6167.04 [4785.48, 8882.1]	2 (2.7%)	55	7140 [4271.3, 10980.9]	1 (1.8%)
ANC	8	58	7387.95 [4955.55, 12061.35]	1 (1.7%)	46	7800.25 [5207.76, 14435.08]	0 (0%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
ANC	9	54	7477.35 [5495.025, 11104.55]	3 (5.6%)	37	9794 [5662, 13800.6]	0 (0%)
ANC	10	41	7526.4 [4651.24, 10294.3]	2 (4.9%)	36	8731.86 [5526.4, 11101.525]	0 (0%)
ANC	11	42	6682.445 [4116, 10492.515]	1 (2.4%)	29	8874 [5670, 10837.5]	0 (0%)
ANC	12	35	6487.6 [3674.7, 10508.7]	2 (5.7%)	25	7764.4 [6749, 9982.8]	0 (0%)
ANC	13	34	5919.99 [4108.455, 11920]	0 (0%)	20	7884.6 [6521.8, 10648.05]	0 (0%)
ANC	14	30	5006.55 [3519.375, 8529.91]	0 (0%)	18	7790.2 [5739.75, 10990.4]	0 (0%)
ANC	15	15	6640 [3931.9, 8265.6]	0 (0%)	11	7392 [3842.6, 7903.17]	1 (9.1%)
ANC	16	13	7402.8 [4180.5, 10374]	0 (0%)	10	7431.1 [3203.325, 8911.68]	1 (10%)
ANC	17	12	5180.8 [4131.75, 10245.06]	0 (0%)	10	4165.45 [3410.275, 7496.02]	1 (10%)
ANC	18	12	6906.05 [3382.425, 9925.05]	0 (0%)	7	5531.4 [3541.35, 6972.07]	0 (0%)
ANC	19	12	6538.8 [3921.05, 11629.995]	1 (8.3%)	8	4987.575 [4205.3, 6165.875]	0 (0%)
ANC	20	9	5356.8 [3939.6, 6510]	0 (0%)	7	4680.5 [4336.6, 6989.425]	0 (0%)
ANC	21	11	5102.7 [2607, 6378.65]	1 (9.1%)	8	4507 [3305.8175, 6447.9425]	0 (0%)
ANC	22	8	4399.875 [2408.7, 7011.9825]	0 (0%)	6	4339.25 [3402.75, 4954.15]	0 (0%)
ANC	23	7	6398.7 [2421.55, 7754.89]	0 (0%)	4	4111.355 [3833.7, 4395.9075]	0 (0%)
ANC	24	6	6778.8 [3591.9, 8387.73]	0 (0%)	5	3520.3 [3366, 3553.2]	1 (20%)
ANC	25	5	8787.54 [2538, 10896.6]	0 (0%)	7	3604.8 [3102.675, 5437.5]	1 (14.3%)
ANC	26	4	9197.09 [6497.11, 11157.075]	0 (0%)	6	4338.4 [2896.4, 4593.75]	0 (0%)
ANC	27	5	11577.6 [1748, 11676.8]	0 (0%)	5	3390.2 [2907, 4623]	1 (20%)
ANC	28	5	6090.9 [5700, 11717.3]	0 (0%)	6	2644.51 [1979.555, 4692.6]	1 (16.7%)
Trop1c	0	22	0.0135 [0.01, 0.0375]	6 (27.3%)	20	0.0185 [0.01, 0.03]	4 (20%)
Trop1c	1	6	0.035 [0.01, 0.0975]	3 (50%)	3	0.01 [0.01, 0.02]	0 (0%)
Trop1c	2	5	0.03 [0.01, 0.05]	2 (40%)	5	0.02 [0.01, 0.07]	2 (40%)
Trop1c	3	2	0.015 [0.0125, 0.0175]	0 (0%)	4	0.01 [0.01, 0.0225]	1 (25%)
Trop1c	4	2	0.01 [0.01, 0.01]	0 (0%)	1	0.01 [0.01, 0.01]	0 (0%)
Trop1c	5	3	0.02 [0.015, 0.06]	1 (33.3%)	3	0.04 [0.025, 4.52]	2 (66.7%)
Trop1c	6	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Trop1c	7	1	0.01 [0.01, 0.01]	0 (0%)	2	38.755 [19.3825, 58.1275]	1 (50%)
Trop1c	8	0	-	-	0	-	-
Trop1c	9	2	0.06085 [0.031275, 0.090425]	1 (50%)	1	0.017 [0.017, 0.017]	0 (0%)
Trop1c	10	1	0.131 [0.131, 0.131]	1 (100%)	0	-	-
Trop1c	11	1	0.102 [0.102, 0.102]	1 (100%)	1	0.06 [0.06, 0.06]	1 (100%)
Trop1c	12	1	0.04 [0.04, 0.04]	1 (100%)	0	-	-

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Trop1c	13	1	0.04 [0.04, 0.04]	1 (100%)	1	0.0152 [0.0152, 0.0152]	0 (0%)
Trop1c	14	0	-	-	2	0.043 [0.0265, 0.0595]	1 (50%)
Trop1c	15	0	-	-	1	0.069 [0.069, 0.069]	1 (100%)
Trop1c	16	0	-	-	0	-	-
Trop1c	17	0	-	-	0	-	-
Trop1c	18	0	-	-	0	-	-
Trop1c	19	0	-	-	0	-	-
Trop1c	20	0	-	-	0	-	-
Trop1c	21	0	-	-	0	-	-
Trop1c	22	0	-	-	0	-	-
Trop1c	23	0	-	-	0	-	-
Trop1c	24	0	-	-	0	-	-
Trop1c	25	0	-	-	0	-	-
Trop1c	26	0	-	-	0	-	-
Trop1c	27	0	-	-	0	-	-
Trop1c	28	0	-	-	0	-	-
Tropth	0	8	39.5 [19.95, 84.25]	6 (75%)	3	93 [52.5, 111.5]	2 (66.7%)
Tropth	1	1	20 [20, 20]	1 (100%)	2	19 [16.5, 21.5]	1 (50%)
Tropth	2	2	41.5 [28.75, 54.25]	2 (100%)	1	106 [106, 106]	1 (100%)
Tropth	3	0	-	-	0	-	-
Tropth	4	2	32.5 [22.25, 42.75]	1 (50%)	1	82 [82, 82]	1 (100%)
Tropth	5	0	-	-	1	215 [215, 215]	1 (100%)
Tropth	6	0	-	-	1	66 [66, 66]	1 (100%)
Tropth	7	0	-	-	0	-	-
Tropth	8	0	-	-	1	103 [103, 103]	1 (100%)
Tropth	9	0	-	-	2	147 [126, 168]	2 (100%)
Tropth	10	0	-	-	0	-	-
Tropth	11	0	-	-	0	-	-
Tropth	12	0	-	-	0	-	-
Tropth	13	0	-	-	0	-	-
Tropth	14	0	-	-	0	-	-
Tropth	15	0	-	-	0	-	-
Tropth	16	0	-	-	0	-	-
Tropth	17	0	-	-	0	-	-
Tropth	18	0	-	-	0	-	-
Tropth	19	0	-	-	0	-	-
Tropth	20	0	-	-	0	-	-
Tropth	21	0	-	-	0	-	-
Tropth	22	0	-	-	0	-	-
Tropth	23	0	-	-	0	-	-
Tropth	24	1	35 [35, 35]	1 (100%)	0	-	-
Tropth	25	0	-	-	0	-	-
Tropth	26	1	65 [65, 65]	1 (100%)	0	-	-
Tropth	27	1	65 [65, 65]	1 (100%)	0	-	-
Tropth	28	0	-	-	0	-	-
Trop1h	0	24	23 [7.225, 31.25]	7 (29.2%)	33	15 [6, 49]	9 (27.3%)
Trop1h	1	9	7.6 [6, 21]	2 (22.2%)	6	116.05 [32.875, 552.775]	4 (66.7%)
Trop1h	2	5	4.7 [3, 12]	0 (0%)	6	60.5 [7, 114.75]	3 (50%)
Trop1h	3	5	4.7 [3.8, 5]	0 (0%)	7	45 [7, 74]	4 (57.1%)
Trop1h	4	2	4.55 [3.575, 5.525]	0 (0%)	2	31.25 [17.875, 44.625]	1 (50%)
Trop1h	5	2	16 [13.5, 18.5]	0 (0%)	3	16 [9.75, 59.5]	1 (33.3%)
Trop1h	6	3	9.4 [6.75, 18.7]	0 (0%)	2	65.6 [34.9, 96.3]	1 (50%)

Lab	Day	N	Active	Abnormal	N	Placebo	Abnormal
Trop1h	7	0	-	-	1	139 [139, 139]	1 (100%)
Trop1h	8	1	22 [22, 22]	0 (0%)	1	38 [38, 38]	1 (100%)
Trop1h	9	0	-	-	0	-	-
Trop1h	10	0	-	-	0	-	-
Trop1h	11	0	-	-	1	45 [45, 45]	1 (100%)
Trop1h	12	0	-	-	0	-	-
Trop1h	13	0	-	-	1	281 [281, 281]	1 (100%)
Trop1h	14	0	-	-	1	323 [323, 323]	1 (100%)
Trop1h	15	0	-	-	0	-	-
Trop1h	16	1	194 [194, 194]	1 (100%)	0	-	-
Trop1h	17	0	-	-	0	-	-
Trop1h	18	0	-	-	0	-	-
Trop1h	19	0	-	-	0	-	-
Trop1h	20	0	-	-	0	-	-
Trop1h	21	0	-	-	0	-	-
Trop1h	22	0	-	-	0	-	-
Trop1h	23	0	-	-	0	-	-
Trop1h	24	1	37 [37, 37]	1 (100%)	0	-	-
Trop1h	25	0	-	-	0	-	-
Trop1h	26	0	-	-	0	-	-
Trop1h	27	0	-	-	0	-	-
Trop1h	28	0	-	-	0	-	-
Troptc	0	3	16 [8.05, 42]	3 (100%)	1	1 [1, 1]	1 (100%)
Troptc	1	1	51 [51, 51]	1 (100%)	0	-	-
Troptc	2	0	-	-	1	35 [35, 35]	1 (100%)
Troptc	3	0	-	-	0	-	-
Troptc	4	0	-	-	0	-	-
Troptc	5	0	-	-	1	7 [7, 7]	1 (100%)
Troptc	6	0	-	-	0	-	-
Troptc	7	0	-	-	0	-	-
Troptc	8	0	-	-	0	-	-
Troptc	9	0	-	-	0	-	-
Troptc	10	0	-	-	0	-	-
Troptc	11	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Troptc	12	0	-	-	0	-	-
Troptc	13	0	-	-	0	-	-
Troptc	14	0	-	-	0	-	-
Troptc	15	0	-	-	0	-	-
Troptc	16	0	-	-	0	-	-
Troptc	17	0	-	-	0	-	-
Troptc	18	0	-	-	0	-	-
Troptc	19	1	0.01 [0.01, 0.01]	0 (0%)	0	-	-
Troptc	20	0	-	-	0	-	-
Troptc	21	0	-	-	0	-	-
Troptc	22	0	-	-	0	-	-
Troptc	23	0	-	-	0	-	-
Troptc	24	0	-	-	0	-	-
Troptc	25	0	-	-	0	-	-
Troptc	26	0	-	-	0	-	-
Troptc	27	0	-	-	0	-	-
Troptc	28	0	-	-	0	-	-

12.4.1.1 Individual Patient Changes

12.4.1.2 Individual Clinically Significant Abnormalities

12.5 Vital Signs

Vital signs are summarized in the tables below by study day including the median [IQR] value.

TXA-127

Table 31 TXA-127 Vital Signs

Vital	Day	N	Active	N	Placebo
Temp	0	176	36.7 [36.4, 37]	172	36.6 [36.4, 36.9]
Temp	1	167	36.6 [36.4, 36.9]	167	36.7 [36.4, 36.9]
Temp	2	161	36.6 [36.4, 36.9]	159	36.7 [36.4, 36.9]
Temp	3	151	36.6 [36.4, 36.9]	142	36.6 [36.4, 36.9]
Temp	4	135	36.6 [36.5, 36.95]	127	36.7 [36.5, 36.8]
Temp	5	123	36.7 [36.4, 36.9]	110	36.7 [36.4, 36.9]
Temp	6	104	36.6 [36.38, 36.9]	91	36.7 [36.45, 37]
Temp	7	95	36.6 [36.4, 36.9]	82	36.7 [36.4, 37.08]
Temp	8	87	36.6 [36.4, 36.95]	67	36.7 [36.4, 37.1]
Temp	9	73	36.7 [36.5, 37.1]	59	36.7 [36.5, 37.05]
Temp	10	66	36.75 [36.5, 37.08]	52	36.7 [36.4, 37.2]
Temp	11	61	36.8 [36.5, 37.2]	50	36.8 [36.6, 37.1]
Temp	12	54	36.7 [36.5, 37.1]	45	36.8 [36.6, 37.2]
Temp	13	49	36.8 [36.5, 37.2]	40	36.9 [36.48, 37.12]
Temp	14	44	36.65 [36.4, 37.12]	38	36.7 [36.52, 37.18]
Temp	15	43	36.8 [36.4, 37.35]	35	36.7 [36.45, 37.2]
Temp	16	41	36.7 [36.4, 36.9]	34	36.85 [36.6, 37.27]
Temp	17	37	36.6 [36.4, 37]	32	36.75 [36.48, 37.02]
Temp	18	34	36.8 [36.6, 37.1]	27	36.7 [36.5, 37]
Temp	19	33	36.8 [36.6, 37.4]	25	36.7 [36.1, 36.9]
Temp	20	32	36.65 [36.4, 37.15]	25	36.8 [36.5, 37.1]
Temp	21	29	36.7 [36.5, 37.2]	22	36.9 [36.4, 37.42]
Temp	22	29	36.8 [36.6, 37.2]	22	36.65 [36.32, 36.88]
Temp	23	29	36.7 [36.5, 37.2]	22	36.75 [36.52, 37.15]
Temp	24	27	36.8 [36.6, 37.25]	20	36.8 [36.68, 36.9]
Temp	25	25	36.7 [36.7, 37.1]	20	36.8 [36.38, 37.25]
Temp	26	24	36.7 [36.6, 37.2]	18	36.6 [36.4, 36.9]
Temp	27	22	36.75 [36.6, 37.05]	17	36.8 [36.4, 37.3]
Temp	28	21	36.8 [36.6, 37.2]	15	36.8 [36.55, 37.35]
HR	0	177	79 [68, 90]	174	81 [72.25, 89]
HR	1	171	75 [64, 87.5]	165	73 [66, 83]
HR	2	162	71 [63, 84]	159	72 [64, 83]
HR	3	153	72 [64, 84]	143	74 [65, 84.5]
HR	4	137	72 [65, 87]	128	75.5 [66, 89.25]

Vital	Day	N	Active	N	Placebo
HR	5	124	73 [64, 89.5]	111	75 [64, 92.5]
HR	6	105	76 [66, 92]	91	77 [67, 90.5]
HR	7	96	75.5 [66.75, 88]	82	76 [70, 90]
HR	8	87	78 [68, 91]	65	82 [70, 94]
HR	9	75	78 [66.5, 95.5]	57	77 [63, 85]
HR	10	67	80 [70.5, 91]	52	79.5 [68.5, 96]
HR	11	61	80 [73, 95]	51	87 [80, 99.5]
HR	12	54	82 [75.25, 102.5]	45	88 [79, 100]
HR	13	49	85 [79, 97]	41	88 [79, 100]
HR	14	46	81 [69.25, 94.75]	38	88 [79.5, 97]
HR	15	43	84 [70, 98.5]	35	86 [77.5, 94]
HR	16	41	81 [70, 95]	34	83 [75.5, 89]
HR	17	38	85.5 [74.25, 95.75]	32	82 [74, 96.5]
HR	18	34	83 [75, 100.25]	27	80 [67.5, 94]
HR	19	32	86 [76.5, 102.75]	25	80 [69, 94]
HR	20	31	80 [74.5, 93.5]	25	90 [72, 96]
HR	21	29	84 [75, 94]	23	91 [73, 107]
HR	22	29	89 [82, 108]	22	88 [73.5, 97]
HR	23	29	95 [80, 108]	22	93.5 [79.75, 103.25]
HR	24	27	87 [72.5, 103]	20	95 [85.5, 104]
HR	25	25	96 [77, 106]	20	94.5 [84, 105]
HR	26	24	93.5 [81.75, 111.5]	18	96.5 [91.5, 107.25]
HR	27	22	99 [82.25, 113.25]	17	89 [83, 104]
HR	28	21	102 [85, 107]	15	100 [80.5, 105.5]
SystolicBP	0	177	126 [115, 139]	174	124.5 [113.25, 138]
SystolicBP	1	170	126.5 [116.25, 138]	169	124 [110, 137]
SystolicBP	2	163	125 [113, 138]	161	122 [111, 140]
SystolicBP	3	154	122 [114, 139]	146	125 [113, 140.75]
SystolicBP	4	136	125 [111.75, 138.25]	127	125 [112, 137.5]
SystolicBP	5	123	120 [110, 135]	111	126 [110.5, 140]
SystolicBP	6	103	125 [111.5, 135]	91	119 [109.5, 134.5]
SystolicBP	7	96	117.5 [106.75, 131.25]	82	124 [108.25, 134.75]
SystolicBP	8	87	124 [112.5, 137]	66	123 [116, 131]
SystolicBP	9	75	117 [105.5, 136.5]	58	118.5 [107.25, 128]
SystolicBP	10	66	124.5 [109.5, 136]	51	116 [105, 129]
SystolicBP	11	60	119.5 [108.5, 134.25]	51	117 [111, 132]
SystolicBP	12	53	123 [112, 140]	45	118 [111, 130]
SystolicBP	13	48	125 [107, 135.5]	40	121.5 [110, 140.25]
SystolicBP	14	46	120.5 [104, 144.75]	37	124 [103, 138]
SystolicBP	15	43	129 [110, 138.5]	35	115 [108, 130.5]
SystolicBP	16	41	126 [112, 143]	34	115 [109.25, 136.25]
SystolicBP	17	38	123.5 [111, 141]	31	121 [108.5, 130.5]
SystolicBP	18	35	121 [114, 135]	27	116 [108, 129]
SystolicBP	19	33	128 [103, 136]	25	113 [103, 127]
SystolicBP	20	31	123 [114, 138.5]	25	116 [110, 128]

Vital	Day	N	Active	N	Placebo
SystolicBP	21	29	117 [107, 129]	23	118 [109.5, 135.5]
SystolicBP	22	29	115 [106, 130]	21	118 [106, 139]
SystolicBP	23	29	122 [116, 137]	21	115 [110, 129]
SystolicBP	24	27	121 [111.5, 138]	20	116 [107.5, 126.25]
SystolicBP	25	25	117 [105, 127]	19	112 [103, 127.5]
SystolicBP	26	24	118 [108.75, 127.25]	17	117 [110, 127]
SystolicBP	27	22	119 [111.5, 123.75]	16	117 [106.5, 131.5]
SystolicBP	28	21	114 [105, 129]	15	125 [111.5, 140]
DiastolicBP	0	177	75 [68, 82]	174	74 [67, 82]
DiastolicBP	1	170	74.5 [66, 81]	169	72 [64, 81]
DiastolicBP	2	163	72 [64, 82]	161	73 [65, 82]
DiastolicBP	3	154	72.5 [65, 81]	146	74 [67.25, 81.75]
DiastolicBP	4	136	72 [64, 81.25]	127	73 [66, 81.5]
DiastolicBP	5	123	71 [64.5, 78]	111	73 [64, 81]
DiastolicBP	6	103	72 [65, 79]	91	73 [63.5, 79.5]
DiastolicBP	7	96	69 [62, 76]	82	70 [63, 81]
DiastolicBP	8	87	73 [62, 78]	66	71 [62.25, 81.5]
DiastolicBP	9	75	67 [58, 77]	58	66 [60, 74.75]
DiastolicBP	10	66	67.5 [61, 80]	51	68 [61.5, 79]
DiastolicBP	11	60	70 [61.75, 77.25]	51	71 [62, 79]
DiastolicBP	12	53	71 [60, 77]	45	67 [58, 77]
DiastolicBP	13	48	71 [61, 77.25]	40	71 [58, 82]
DiastolicBP	14	46	69 [59.25, 78]	37	70 [59, 81]
DiastolicBP	15	43	72 [63, 81.5]	35	68 [55, 80]
DiastolicBP	16	41	69 [61, 78]	34	67 [55, 77]
DiastolicBP	17	38	67 [57.25, 75.75]	31	66 [58, 78.5]
DiastolicBP	18	35	67 [62, 79]	27	64 [56, 73.5]
DiastolicBP	19	33	67 [54, 79]	25	61 [56, 77]
DiastolicBP	20	31	68 [56.5, 73.5]	25	63 [56, 77]
DiastolicBP	21	29	63 [58, 73]	23	63 [55.5, 79.5]
DiastolicBP	22	29	62 [53, 81]	21	67 [58, 78]
DiastolicBP	23	29	68 [55, 78]	21	59 [55, 74]
DiastolicBP	24	27	71 [58.5, 78]	20	60 [50.5, 77.25]
DiastolicBP	25	25	69 [60, 76]	19	63 [50.5, 75]
DiastolicBP	26	24	65.5 [60.75, 79.25]	17	66 [57, 78]
DiastolicBP	27	22	65.5 [60.25, 73.75]	16	69.5 [56.5, 79]
DiastolicBP	28	21	65 [59, 75]	15	75 [59, 83.5]
MAP	0	177	92.67 [84.33, 99]	174	91.83 [83.33, 99]
MAP	1	170	90.67 [83, 99.92]	169	90.33 [80.33, 98.33]
MAP	2	163	91 [81.67, 101.33]	161	90.67 [83.33, 100]
MAP	3	154	90.17 [82.33, 100]	146	91.83 [83.75, 101]
MAP	4	136	88.67 [81.92, 99.5]	127	91 [81.83, 100.67]
MAP	5	123	88 [81.5, 96.5]	111	90.67 [80.83, 100.67]
MAP	6	103	90 [81.17, 97]	91	89.33 [79.17, 98.5]
MAP	7	96	84.83 [77.25, 95]	82	87.17 [79.08, 98.92]
MAP	8	87	90.33 [82, 96.67]	66	89.33 [79.33, 96.92]

Vital	Day	N	Active	N	Placebo
MAP	9	75	86 [75.83, 93]	58	83.83 [77.58, 91.92]
MAP	10	66	86.83 [77.42, 98.83]	51	85.67 [76.83, 94.67]
MAP	11	60	87 [79.08, 94.67]	51	87 [77.67, 94.33]
MAP	12	53	89.33 [77.33, 96.67]	45	84.33 [77.33, 93]
MAP	13	48	88 [78.17, 96.25]	40	85.83 [77.67, 99.83]
MAP	14	46	85.5 [75.33, 100.42]	37	87.67 [76.33, 98.67]
MAP	15	43	90 [80.17, 101]	35	82.67 [74.33, 95.67]
MAP	16	41	88 [78, 99.33]	34	80 [75.08, 97]
MAP	17	38	85.67 [74.67, 95.92]	31	84.67 [76.83, 95.33]
MAP	18	35	88 [79.67, 96.33]	27	81.67 [76, 92.83]
MAP	19	33	85 [74.33, 96]	25	81 [71.67, 91.67]
MAP	20	31	86.67 [79.5, 90]	25	81 [77, 89.67]
MAP	21	29	84 [74.67, 90]	23	86.33 [74.5, 91.17]
MAP	22	29	82 [74, 91.67]	21	85 [75.67, 95.33]
MAP	23	29	86 [77.33, 93.67]	21	80.33 [74.67, 86.33]
MAP	24	27	90.33 [77, 95]	20	82.33 [67.5, 92.17]
MAP	25	25	85 [75.67, 90.67]	19	77.33 [70, 91.5]
MAP	26	24	84.67 [76, 95.42]	17	86.33 [72.33, 90.67]
MAP	27	22	82.67 [78.75, 92.67]	16	87.83 [73.75, 94]
MAP	28	21	82 [76.33, 93]	15	89.33 [79.67, 101.33]
RespRate	0	176	20 [18, 25]	174	21 [18, 24]
RespRate	1	167	20 [18, 25]	166	20 [18, 24]
RespRate	2	158	20 [18, 24]	158	20 [18, 23.75]
RespRate	3	153	20 [18, 25]	143	20 [18, 24]
RespRate	4	136	20 [18, 24]	127	20 [18, 23]
RespRate	5	122	20 [18, 24]	109	20 [18, 23]
RespRate	6	103	20 [18, 24]	90	20 [18, 24]
RespRate	7	94	20 [18, 25]	80	20 [18, 24.25]
RespRate	8	86	20 [18, 24]	65	22 [18, 24]
RespRate	9	70	21.5 [18, 26]	54	21 [18, 25.75]
RespRate	10	65	20 [18, 24]	50	22 [20, 26]
RespRate	11	59	20 [18, 24]	51	22 [19, 28]
RespRate	12	52	20 [18, 24]	44	20 [18, 26]
RespRate	13	48	20 [18, 24]	39	20 [17.5, 25.5]
RespRate	14	45	20 [18, 25]	37	22 [18, 28]
RespRate	15	42	21.5 [18, 27.75]	33	20 [18, 30]
RespRate	16	40	20 [18, 24.25]	32	20 [18, 26.25]
RespRate	17	37	18 [17, 23]	31	23 [20, 31]
RespRate	18	34	19.5 [18, 27]	27	23 [18, 30.5]
RespRate	19	32	19 [18, 26.5]	25	24 [18, 32]
RespRate	20	30	20 [18, 30.75]	22	21.5 [18.25, 25.5]
RespRate	21	29	20 [18, 26]	21	23 [19, 32]
RespRate	22	28	22.5 [18.75, 30]	21	22 [18, 26]
RespRate	23	28	20 [18, 30.25]	20	21.5 [18, 26.5]
RespRate	24	27	20 [18, 27.5]	19	22 [18, 30]
RespRate	25	24	20 [18, 25.25]	18	21.5 [16.5, 28.75]

Vital	Day	N	Active	N	Placebo
RespRate	26	23	20 [18, 27.5]	17	21 [18, 27]
RespRate	27	22	21.5 [18, 29.5]	16	21.5 [17.75, 30]
RespRate	28	20	18 [16, 26]	14	26 [20, 28.5]

TRV-027

Table 32 TRV-027 Vital Signs

Vital	Day	N	Active	N	Placebo
Temp	0	147	36.6 [36.4, 36.9]	145	36.7 [36.4, 36.9]
Temp	1	143	36.6 [36.4, 36.8]	141	36.7 [36.4, 36.9]
Temp	2	136	36.6 [36.4, 36.8]	135	36.7 [36.4, 36.9]
Temp	3	121	36.6 [36.4, 36.9]	119	36.6 [36.4, 36.9]
Temp	4	111	36.7 [36.5, 37]	107	36.7 [36.5, 36.9]
Temp	5	103	36.7 [36.4, 37]	92	36.7 [36.4, 36.92]
Temp	6	89	36.7 [36.4, 37]	74	36.7 [36.5, 37]
Temp	7	83	36.7 [36.4, 36.9]	66	36.7 [36.4, 37]
Temp	8	72	36.7 [36.4, 37]	57	36.7 [36.4, 37.1]
Temp	9	66	36.75 [36.4, 37.08]	48	36.7 [36.58, 37.1]
Temp	10	55	36.8 [36.4, 37.15]	43	36.7 [36.4, 37.3]
Temp	11	51	36.7 [36.4, 37.15]	41	36.8 [36.6, 37.1]
Temp	12	43	36.8 [36.5, 37.2]	38	36.75 [36.52, 37.2]
Temp	13	41	36.9 [36.6, 37.3]	34	36.9 [36.5, 37.18]
Temp	14	37	36.8 [36.5, 37.2]	32	36.7 [36.5, 37.2]
Temp	15	33	36.9 [36.6, 37.3]	29	36.7 [36.5, 37.2]
Temp	16	31	36.9 [36.6, 37.45]	28	36.9 [36.58, 37.3]
Temp	17	26	36.9 [36.52, 37.38]	25	36.8 [36.4, 37.2]
Temp	18	25	36.9 [36.7, 37.4]	23	36.7 [36.5, 37.05]
Temp	19	24	36.75 [36.3, 37.35]	22	36.7 [36.15, 36.88]
Temp	20	20	37 [36.77, 37.4]	22	36.8 [36.5, 37.08]
Temp	21	20	37.2 [36.77, 37.82]	19	36.9 [36.4, 37.35]
Temp	22	20	36.9 [36.68, 37.25]	19	36.6 [36.3, 36.85]
Temp	23	17	36.9 [36.7, 37.11]	19	36.7 [36.55, 36.95]
Temp	24	16	36.9 [36.58, 37.1]	18	36.8 [36.62, 36.9]
Temp	25	16	36.8 [36.38, 37]	18	36.75 [36.32, 37.18]
Temp	26	15	36.5 [36.3, 36.55]	16	36.6 [36.38, 36.9]
Temp	27	14	36.45 [36.3, 36.68]	15	36.8 [36.4, 37.25]
Temp	28	14	36.55 [36.35, 36.7]	14	36.8 [36.52, 37.18]
HR	0	149	79 [67, 90]	147	80 [71, 88]
HR	1	146	73 [64, 84.75]	140	73 [66, 82.25]
HR	2	136	73.5 [62.75, 83]	135	72 [64.5, 82. 5]
HR	3	122	70.5 [61, 82.75]	120	74 [65, 85]
HR	4	111	72 [64, 84.5]	107	75 [66, 89.5]
HR	5	103	74 [62, 84.5]	93	74 [64, 89]
HR	6	91	73 [62.5, 84.5]	74	78 [67, 91]
HR	7	83	74 [61.5, 85.5]	66	76.5 [70, 92]
HR	8	71	75 [64.5, 91.5]	55	83 [72, 96]
HR	9	65	78 [67, 93]	46	77.5 [60.25, 89.5]
HR	10	55	76 [65.5, 97]	43	79 [66.5, 93]
HR	11	50	84 [71.25, 99]	43	86 [78.5, 98]
HR	12	44	92 [77.25, 106.5]	38	88 [79, 101.5]
HR	13	40	86 [77, 100.5]	35	88 [76, 98.5]
HR	14	37	89 [77, 106]	32	86.5 [77.25, 97]
HR	15	33	86 [68, 103]	29	84 [74, 94]
HR	16	31	95 [69.5, 109.5]	28	82 [75, 90.5]

Vital	Day	N	Active	N	Placebo
HR	17	28	90.5 [79.75, 101.5]	25	81 [74, 98]
HR	18	25	87 [72, 103]	23	81 [66, 94]
HR	19	24	86.5 [79.75, 104.5]	22	81.5 [70.75, 94.75]
HR	20	20	93 [77.75, 104.5]	22	90 [73.5, 97.5]
HR	21	20	94.5 [67.25, 114]	20	91 [73.5, 109]
HR	22	20	99 [74.75, 119.25]	19	92 [74, 99.5]
HR	23	18	100.5 [93.25, 115.75]	19	91 [81.5, 102.5]
HR	24	15	93 [81.5, 108.5]	18	96 [85.75, 106]
HR	25	16	102 [77.25, 114.5]	18	95 [84.5, 107]
HR	26	15	92 [76.5, 109]	16	98.5 [93.75, 108]
HR	27	13	96 [81, 108]	15	91 [84, 105.5]
HR	28	14	92.5 [75.5, 107.25]	14	100 [79.25, 106.75]
SystolicBP	0	149	123 [110, 134]	147	124 [113, 138]
SystolicBP	1	145	122 [109, 137]	143	124 [111, 136.5]
SystolicBP	2	135	126 [113.5, 140]	137	123 [111, 138]
SystolicBP	3	122	129 [117, 144]	123	124 [111.5, 139]
SystolicBP	4	111	127 [114.5, 139]	106	123.5 [112, 137.5]
SystolicBP	5	103	130 [116, 145.5]	93	126 [110, 138]
SystolicBP	6	90	125 [114.25, 135]	74	117.5 [111, 133.75]
SystolicBP	7	83	124 [109, 137.5]	66	124.5 [106.75, 137]
SystolicBP	8	73	124 [110, 134]	57	122 [112, 131]
SystolicBP	9	65	115 [105, 130]	48	118 [105.75, 128.75]
SystolicBP	10	56	118 [106, 130.25]	43	119 [105, 129]
SystolicBP	11	51	118 [108, 129]	43	119 [112, 131.5]
SystolicBP	12	44	120 [107.75, 132]	38	118 [110.25, 130.75]
SystolicBP	13	40	115 [107, 125.25]	34	121.5 [110, 142.5]
SystolicBP	14	36	122 [107, 136.75]	31	113 [102, 137]
SystolicBP	15	33	123 [110, 132]	29	113 [108, 128]
SystolicBP	16	31	114 [107.5, 130]	28	112.5 [104, 133.25]
SystolicBP	17	27	126 [108, 134.5]	24	117.5 [105.75, 127]
SystolicBP	18	25	130 [111, 142]	23	116 [107, 124.5]
SystolicBP	19	24	118 [109.75, 129.75]	22	112 [103, 126]
SystolicBP	20	21	124 [113, 137]	22	115.5 [108.5, 132.5]
SystolicBP	21	20	119.5 [109.75, 131.25]	20	119 [107.25, 135.25]
SystolicBP	22	20	121.5 [103.75, 143.5]	18	115.5 [105.25, 138.75]
SystolicBP	23	18	114.5 [99.25, 133.25]	18	115 [110, 126.5]
SystolicBP	24	16	119.5 [109.5, 133]	18	117.5 [109, 128.75]
SystolicBP	25	16	117.5 [106.25, 130.5]	17	112 [102, 137]
SystolicBP	26	15	122 [110, 143.5]	15	115 [108.5, 126.5]
SystolicBP	27	14	123 [113.25, 134.5]	14	119 [104.25, 132.5]
SystolicBP	28	13	125 [114, 139]	14	121.5 [111.25, 142]
DiastolicBP	0	149	73 [67, 82]	147	74 [66, 82]
DiastolicBP	1	145	74 [65, 82]	143	72 [65, 81]
DiastolicBP	2	135	73 [66, 84]	137	73 [64, 81]
DiastolicBP	3	122	76 [66.25, 86]	123	75 [67, 81]
DiastolicBP	4	111	74 [66.5, 84]	106	73 [66, 80.75]
DiastolicBP	5	103	74 [65, 83]	93	71 [64, 79]
DiastolicBP	6	90	73 [68.25, 82.5]	74	73 [60, 79]
DiastolicBP	7	83	72 [63, 78]	66	71 [62.25, 80.75]
DiastolicBP	8	73	71 [63, 78]	57	69 [62, 79]
DiastolicBP	9	65	68 [62, 76]	48	66 [60, 74]
DiastolicBP	10	56	67 [57.75, 75]	43	68 [61.5, 78.5]
DiastolicBP	11	51	65 [57, 73]	43	72 [62.5, 79]
DiastolicBP	12	44	66.5 [58, 76]	38	66 [58.25, 76.75]

Vital	Day	N	Active	N	Placebo
DiastolicBP	13	40	64 [58.75, 74.25]	34	67 [58, 77.25]
DiastolicBP	14	36	66 [56.75, 74.25]	31	65 [58, 77.5]
DiastolicBP	15	33	68 [59, 78]	29	68 [52, 77]
DiastolicBP	16	31	63 [57.5, 69]	28	60 [54, 74.5]
DiastolicBP	17	27	66 [59, 75]	24	65 [56, 71.25]
DiastolicBP	18	25	67 [60, 86]	23	63 [56, 71.5]
DiastolicBP	19	24	70.5 [59.75, 74.25]	22	61 [56, 76]
DiastolicBP	20	21	68 [56, 75]	22	64.5 [55.25, 77]
DiastolicBP	21	20	65.5 [59.75, 74.5]	20	63 [54.25, 81]
DiastolicBP	22	20	68.5 [58.5, 77]	18	69 [52, 78]
DiastolicBP	23	18	68 [56, 76.5]	18	59 [55, 73.5]
DiastolicBP	24	16	70.5 [58, 73.75]	18	60 [51.75, 78.5]
DiastolicBP	25	16	69 [60.5, 74.25]	17	63 [50, 77]
DiastolicBP	26	15	69 [59.5, 80.5]	15	66 [57.5, 79.5]
DiastolicBP	27	14	69.5 [60.5, 79.25]	14	69.5 [57.5, 77.75]
DiastolicBP	28	13	68 [58, 81]	14	70 [58, 82]
MAP	0	149	90 [82.33, 99.33]	147	91.67 [83, 97.67]
MAP	1	145	91 [80.33, 98.67]	143	91.33 [80.5, 98.67]
MAP	2	135	92 [82.83, 102]	137	90.67 [81.33, 99.33]
MAP	3	122	94.5 [84.67, 105.42]	123	91.67 [83.17, 99.67]
MAP	4	111	90.67 [84, 103.17]	106	90.17 [81.67, 96.33]
MAP	5	103	92.33 [83.33, 102.33]	93	90 [80.67, 99]
MAP	6	90	90.67 [84.67, 100]	74	88.67 [78.5, 95.67]
MAP	7	83	86.67 [79.83, 99.67]	66	89.17 [79.08, 99.67]
MAP	8	73	88.67 [80.67, 96.67]	57	86.67 [78.67, 96]
MAP	9	65	84.67 [77.67, 91.67]	48	83.5 [77.25, 91.75]
MAP	10	56	83.17 [74.5, 92.67]	43	85.67 [76.83, 93.67]
MAP	11	51	83 [76.5, 91.67]	43	87.33 [79.17, 94.33]
MAP	12	44	82.83 [76, 94.67]	38	83.33 [77.42, 91.42]
MAP	13	40	82.5 [72.25, 91.42]	34	85.67 [77.17, 99.5]
MAP	14	36	83.17 [76, 94.58]	31	83 [75.17, 93.5]
MAP	15	33	85.33 [76.33, 99.67]	29	82 [74, 90]
MAP	16	31	79.33 [72.5, 88.83]	28	78.83 [73.75, 94.42]
MAP	17	27	84 [80.67, 95.83]	24	81.33 [74.58, 91.25]
MAP	18	25	88.33 [76.67, 101.67]	23	80.67 [75.5, 85.17]
MAP	19	24	86.17 [71.83, 91]	22	80.83 [71.67, 90.83]
MAP	20	21	89.33 [75, 98.33]	22	81 [75.75, 90.92]
MAP	21	20	85.17 [76.25, 90.75]	20	86.5 [73.42, 93.5]
MAP	22	20	88.5 [79.92, 93]	18	85 [73.92, 99.75]
MAP	23	18	82.67 [75.08, 92.58]	18	79.5 [75.17, 86.33]
MAP	24	16	85.33 [77.83, 91.67]	18	82.33 [69.08, 93.17]
MAP	25	16	88.17 [74.92, 92.17]	17	77.33 [69.67, 94.33]
MAP	26	15	87.33 [76.67, 95.17]	15	86.33 [73.67, 90.33]
MAP	27	14	88.33 [83.75, 92.58]	14	87.83 [74.58, 96.67]
MAP	28	13	83.33 [74.67, 101]	14	88.67 [77, 102.33]
RespRate	0	143	20 [18, 24]	147	21 [18, 24]
RespRate	1	143	20 [18, 24]	140	20 [18, 24]
RespRate	2	134	20 [18, 24]	134	20 [18, 24]
RespRate	3	121	20 [18, 25]	120	20 [18, 24.25]
RespRate	4	110	20 [18, 25]	106	20 [18, 24]
RespRate	5	102	20 [18, 24]	91	20 [18, 23]
RespRate	6	91	20 [18, 24]	74	20 [18, 24]
RespRate	7	81	20 [18, 25]	64	20 [18, 25]
RespRate	8	72	20 [18, 24.25]	55	22 [20, 25.5]
RespRate	9	64	20 [18, 25]	43	21 [18, 26.5]
RespRate	10	55	20 [18, 25]	41	23 [21, 26]

Vital	Day	N	Active	N	Placebo
RespRate	11	49	22 [18, 24]	42	24.5 [19.25, 28]
RespRate	12	42	21 [18.25, 27]	37	22 [18, 27]
RespRate	13	40	21 [18, 25.25]	33	21 [17, 27]
RespRate	14	35	20 [17.5, 29.5]	31	24 [18, 29]
RespRate	15	31	21 [18, 25.5]	27	22 [19, 30]
RespRate	16	31	22 [18, 26.5]	26	21 [18.25, 28.5]
RespRate	17	27	21 [20, 29]	24	23.5 [20, 35]
RespRate	18	24	23 [20, 28.5]	23	24 [19, 30.5]
RespRate	19	23	21 [19, 28]	22	24 [18.25, 32]
RespRate	20	20	25 [17, 33]	19	22 [18.5, 25]
RespRate	21	19	27 [19, 29]	18	24.5 [19.25, 32.75]
RespRate	22	20	27.5 [20, 31]	18	23 [18.5, 26]
RespRate	23	17	27 [18, 29]	17	22 [18, 28]
RespRate	24	14	22.5 [18, 25.75]	17	26 [18, 30]
RespRate	25	14	24 [20.5, 30.5]	16	21.5 [17.5, 30]
RespRate	26	14	25 [20.25, 28.75]	15	21 [18, 28]
RespRate	27	12	23.5 [18.75, 30]	14	21.5 [17.75, 30]
RespRate	28	13	21 [17, 28]	13	26 [20, 27]

Fostamatinib

Table 33 Fostamatinib Vital Signs

Vital	Day	N	Active	N	Placebo
Temp	0	204	36.6 [36.4, 36.9]	201	36.6 [36.3, 36.9]
Temp	1	197	36.6 [36.3, 36.8]	194	36.5 [36.3, 36.8]
Temp	2	165	36.5 [36.3, 36.8]	165	36.5 [36.3, 36.8]
Temp	3	142	36.6 [36.3, 36.8]	140	36.6 [36.3, 36.8]
Temp	4	118	36.5 [36.3, 36.8]	116	36.6 [36.38, 36.8]
Temp	5	102	36.5 [36.3, 36.7]	96	36.6 [36.3, 36.73]
Temp	6	94	36.5 [36.3, 36.8]	79	36.5 [36.4, 36.8]
Temp	7	85	36.6 [36.3, 36.8]	71	36.6 [36.4, 36.8]
Temp	8	72	36.5 [36.3, 36.82]	58	36.6 [36.4, 36.9]
Temp	9	61	36.6 [36.3, 36.9]	49	36.7 [36.4, 36.9]
Temp	10	54	36.6 [36.4, 37.18]	45	36.6 [36.4, 36.9]
Temp	11	51	36.6 [36.3, 36.95]	41	36.7 [36.5, 36.9]
Temp	12	48	36.6 [36.4, 37]	33	36.7 [36.4, 36.8]
Temp	13	48	36.6 [36.48, 36.9]	27	36.7 [36.45, 36.95]
Temp	14	37	36.7 [36.5, 36.8]	26	36.7 [36.23, 37.18]
Temp	15	28	36.8 [36.48, 37.25]	22	36.7 [36.5, 37.12]
Temp	16	26	36.7 [36.6, 37.2]	21	36.8 [36.7, 37]
Temp	17	24	36.75 [36.55, 37.1]	19	36.7 [36.6, 37.05]
Temp	18	21	37 [36.8, 37.3]	18	36.7 [36.6, 36.88]
Temp	19	21	37 [36.6, 37.3]	16	36.7 [36.4, 36.95]
Temp	20	19	36.7 [36.45, 36.9]	16	36.6 [36.45, 37]
Temp	21	18	36.75 [36.45, 37.12]	12	36.6 [36.3, 36.82]
Temp	22	16	36.6 [36.4, 37.1]	12	36.65 [36.6, 36.9]
Temp	23	16	36.7 [36.5, 36.92]	12	36.7 [36.48, 36.9]
Temp	24	14	36.7 [36.4, 37.38]	10	36.65 [36.32, 36.8]
Temp	25	12	36.75 [36.68, 37.1]	11	36.7 [36.35, 37.1]

Vital	Day	N	Active	N	Placebo
Temp	26	11	36.9 [36.65, 37.75]	11	36.6 [36.35, 36.75]
Temp	27	10	37.1 [36.5, 37.4]	10	36.65 [36.4, 36.88]
Temp	28	10	36.8 [36.23, 37.12]	10	36.6 [36.42, 36.75]
HR	0	206	78 [69, 90]	205	77 [67, 88]
HR	1	196	72 [62.75, 85.25]	195	73 [65, 84]
HR	2	167	70 [62, 80]	165	73 [66, 83]
HR	3	142	69 [61.25, 81.75]	138	71.5 [62, 84.75]
HR	4	120	73 [63.75, 84]	117	70 [62, 82]
HR	5	103	74 [64.5, 86.5]	96	75.5 [62.75, 87.25]
HR	6	94	76 [66, 89.5]	78	75 [60.5, 88]
HR	7	85	76 [69, 92]	72	79 [64, 93]
HR	8	72	79 [67.75, 90.5]	57	76 [68, 92]
HR	9	62	81.5 [70.5, 96.5]	48	77 [69, 95]
HR	10	53	83 [71, 96]	45	78 [65, 86]
HR	11	50	86.5 [74.25, 99.5]	42	80.5 [68.5, 101.5]
HR	12	48	87.5 [78.75, 99.75]	33	84 [77, 98]
HR	13	48	83 [74, 99.25]	27	89 [73, 109]
HR	14	37	85 [75, 99]	26	88 [73.25, 103.5]
HR	15	29	91 [85, 102]	22	86.5 [74.5, 102]
HR	16	26	91.5 [84.25, 104]	21	90 [75, 99]
HR	17	24	97 [87, 107.5]	20	90.5 [82, 110]
HR	18	21	99 [88, 109]	18	97 [78, 102]
HR	19	21	101 [89, 108]	16	95.5 [79.5, 102]
HR	20	19	91 [87.5, 105]	16	92 [79.5, 96.75]
HR	21	18	98 [88.5, 104.75]	13	100 [89, 109]
HR	22	16	97.5 [87.75, 105]	13	97 [90, 103]
HR	23	16	103.5 [90, 117.25]	12	94 [87.75, 106.5]
HR	24	14	96 [90, 118.25]	11	90 [89, 96]
HR	25	12	105 [90.75, 114]	11	95 [87, 106]
HR	26	11	106 [101, 112.5]	11	100 [90.5, 108]
HR	27	10	114 [93, 125.75]	10	89.5 [72.75, 113.25]
HR	28	10	107 [92, 124.75]	10	95.5 [83.25, 112.25]
SystolicBP	0	207	124 [111, 136]	204	123 [112, 133]
SystolicBP	1	198	128 [114, 142.75]	196	128 [115, 141]
SystolicBP	2	167	130 [115, 146]	167	129 [116, 142]
SystolicBP	3	142	133 [119.25, 149.75]	140	129 [113, 140]
SystolicBP	4	120	128.5 [115.75, 145.5]	116	127 [117, 140.5]
SystolicBP	5	103	127 [117, 140]	96	124 [109.5, 136.5]
SystolicBP	6	94	133.5 [120, 143.5]	79	125 [111, 138.5]
SystolicBP	7	85	126 [114, 145]	72	124.5 [105.75, 135.25]
SystolicBP	8	72	127.5 [114.5, 143]	58	124 [106, 132]
SystolicBP	9	62	133 [115, 141]	49	122 [102, 138]
SystolicBP	10	54	118 [108, 131.5]	45	126 [111, 140]
SystolicBP	11	51	117 [103, 136.5]	42	128 [112.25, 139.5]
SystolicBP	12	48	122 [107.75, 134.75]	33	118 [113, 129]

Vital	Day	N	Active	N	Placebo
SystolicBP	13	48	119.5 [106, 134.75]	27	122 [113, 131.5]
SystolicBP	14	37	119 [108, 132]	26	124.5 [108.75, 137.5]
SystolicBP	15	29	120 [102, 127]	22	127.5 [110, 138.5]
SystolicBP	16	26	116 [107, 129.75]	21	128 [110, 136]
SystolicBP	17	24	118 [101, 125]	19	128 [115.5, 135]
SystolicBP	18	21	111 [101, 127]	18	120.5 [108, 134.25]
SystolicBP	19	21	113 [98, 125]	16	126.5 [114.75, 147.25]
SystolicBP	20	19	117 [106, 128.5]	16	124.5 [115, 132.5]
SystolicBP	21	18	116.5 [103, 131.5]	13	124 [113, 136]
SystolicBP	22	16	115.5 [98, 128.75]	13	119 [110, 138]
SystolicBP	23	16	111.5 [106.75, 125.25]	12	118 [115.25, 120]
SystolicBP	24	14	111 [96, 122]	11	121 [118, 130.5]
SystolicBP	25	12	110.5 [100.5, 122.5]	11	133 [111, 141.5]
SystolicBP	26	11	117 [99.5, 132.5]	11	126 [114, 130]
SystolicBP	27	10	116 [108.25, 122.25]	10	115.5 [109, 132.75]
SystolicBP	28	10	114.5 [102, 125.75]	10	123 [112.5, 140]
DiastolicBP	0	207	73 [64, 80.5]	204	71.5 [63, 79]
DiastolicBP	1	198	74 [66, 83]	196	74 [64, 80]
DiastolicBP	2	167	76 [67.5, 85]	167	74 [65, 83]
DiastolicBP	3	142	78.5 [69.25, 86]	140	72 [63, 81.25]
DiastolicBP	4	120	77 [65.75, 86]	116	72.5 [64.75, 81]
DiastolicBP	5	103	74 [67, 85]	96	71.5 [63, 80]
DiastolicBP	6	94	75.5 [65.25, 83]	79	70 [62.5, 77.5]
DiastolicBP	7	85	74 [66, 82]	72	68.5 [60, 79.25]
DiastolicBP	8	72	72 [63.75, 81.25]	58	70 [62, 79.75]
DiastolicBP	9	62	76 [65, 82]	49	69 [60, 75]
DiastolicBP	10	54	69 [61.75, 77]	45	69 [60, 79]
DiastolicBP	11	51	70 [62.5, 79.5]	42	69 [62, 78.75]
DiastolicBP	12	48	69 [58, 76.25]	33	67 [61, 77]
DiastolicBP	13	48	69 [63, 79.75]	27	65 [57, 73.5]
DiastolicBP	14	37	64 [58, 74]	26	65 [57.5, 71.5]
DiastolicBP	15	29	70 [58, 74]	22	70.5 [61, 76.75]
DiastolicBP	16	26	65 [58.75, 71]	21	67 [58, 74]
DiastolicBP	17	24	67 [59.75, 71.5]	19	70 [57.5, 77.5]
DiastolicBP	18	21	59 [56, 69]	18	70 [60.25, 76]
DiastolicBP	19	21	65 [60, 71]	16	71.5 [60.75, 77.75]
DiastolicBP	20	19	64 [61, 73.5]	16	69.5 [55.75, 77.25]
DiastolicBP	21	18	66 [58.5, 72.5]	13	73 [56, 84]
DiastolicBP	22	16	65 [58, 69.75]	13	73 [59, 79]
DiastolicBP	23	16	66 [57.75, 72]	12	71.5 [61.25, 75.5]
DiastolicBP	24	14	60.5 [55.5, 69]	11	74 [64.5, 83]
DiastolicBP	25	12	61 [58, 69.5]	11	71 [53.5, 77.5]
DiastolicBP	26	11	62 [52, 72.5]	11	68 [65.5, 81.5]
DiastolicBP	27	10	63 [56.5, 76.75]	10	66.5 [65.25, 72.5]
DiastolicBP	28	10	62.5 [57.75, 72.5]	10	67.5 [60, 72]

Vital	Day	N	Active	N	Placebo
MAP	0	207	90 [81.83, 97.83]	204	88.83 [81.67, 95.75]
MAP	1	198	92.67 [84.08, 100.33]	196	92 [83.92, 99.08]
MAP	2	167	95.33 [84.83, 102.33]	167	92.33 [84.33, 100.67]
MAP	3	142	96.83 [87.08, 107.17]	140	90.17 [81.67, 100.08]
MAP	4	120	94.33 [85.17, 103.42]	116	92.33 [82.58, 101.67]
MAP	5	103	92.33 [85, 101.83]	96	90.5 [78.25, 99]
MAP	6	94	95.33 [86, 101.58]	79	89.33 [79.33, 94.17]
MAP	7	85	91.67 [84, 101.67]	72	85.83 [77.92, 97.67]
MAP	8	72	91.33 [81.5, 101]	58	88.17 [76.5, 97.33]
MAP	9	62	93.83 [83.42, 102.25]	49	85.67 [77.67, 97.67]
MAP	10	54	86 [78.67, 92.83]	45	90.33 [81.67, 96.67]
MAP	11	51	86.33 [78.17, 98.67]	42	87.83 [80.33, 95.25]
MAP	12	48	85.67 [75.25, 93.75]	33	87.33 [80.67, 90.67]
MAP	13	48	86.67 [77.83, 97.33]	27	83.33 [77.5, 93.5]
MAP	14	37	83.33 [76.33, 90.67]	26	84.67 [77, 94.17]
MAP	15	29	85.33 [79.67, 90.33]	22	89.17 [78.25, 93.83]
MAP	16	26	81.5 [71.08, 91.33]	21	88 [77.33, 95]
MAP	17	24	80.67 [77.42, 91.33]	19	87.33 [76.17, 95.83]
MAP	18	21	75 [71, 92.33]	18	86.67 [76.17, 94.25]
MAP	19	21	80.67 [73.33, 88.33]	16	90.67 [86.67, 93.33]
MAP	20	19	81 [77.17, 89]	16	89.17 [80.42, 92.08]
MAP	21	18	82.5 [75.5, 89.33]	13	89 [77.33, 98]
MAP	22	16	81 [71.58, 88.33]	13	90 [79.33, 95]
MAP	23	16	82.17 [73, 86.75]	12	87 [79.75, 95.42]
MAP	24	14	75.83 [71.58, 88.33]	11	91.33 [82.67, 99]
MAP	25	12	78.5 [73.25, 86.42]	11	88.67 [78.5, 97.83]
MAP	26	11	73 [69.17, 91.17]	11	89.67 [84.67, 92.5]
MAP	27	10	79.17 [76, 90.42]	10	85.33 [81.75, 88.42]
MAP	28	10	77.33 [74.17, 86.83]	10	86.83 [81.92, 91.67]
RespRate	0	204	18 [17.75, 22]	202	19 [18, 22]
RespRate	1	195	18 [17, 20]	196	18 [17, 20]
RespRate	2	163	18 [17, 21]	165	18 [18, 21]
RespRate	3	138	18 [17, 20]	136	18 [17, 20]
RespRate	4	117	18 [17, 22]	117	18 [17, 20]
RespRate	5	99	18 [17, 22]	95	18 [17.5, 21]
RespRate	6	92	19 [18, 21.25]	79	18 [17, 22]
RespRate	7	84	18 [16.75, 21]	72	18 [16, 22]
RespRate	8	72	18 [16, 21.5]	56	20 [17, 23.25]
RespRate	9	60	18 [17, 20.25]	47	18 [16, 21.5]
RespRate	10	52	19 [17.75, 21]	44	18.5 [16, 21.25]
RespRate	11	50	18 [17, 23.75]	42	20 [18, 23.75]
RespRate	12	46	18 [17, 21.75]	33	20 [18, 25]
RespRate	13	45	18 [16, 20]	27	20 [18, 22.5]
RespRate	14	35	19 [18, 22.5]	26	21 [20, 26.75]
RespRate	15	28	20 [18, 24.75]	21	20 [18, 25]
RespRate	16	25	19 [17, 23]	21	20 [18, 28]

Vital	Day	N	Active	N	Placebo
RespRate	17	23	20 [18, 25]	20	21 [18, 30]
RespRate	18	21	20 [18, 26]	18	21 [18, 25.5]
RespRate	19	21	20 [18, 24]	16	21 [18, 25.25]
RespRate	20	19	18 [18, 21.5]	15	20 [18, 24.5]
RespRate	21	18	18 [17, 21.5]	13	20 [18, 28]
RespRate	22	16	18 [16.75, 20.25]	13	20 [19, 24]
RespRate	23	16	18 [16.75, 23]	12	19 [18, 25.75]
RespRate	24	14	22 [17.25, 27.75]	11	20 [19.5, 20.5]
RespRate	25	12	18.5 [17.75, 24.75]	11	22 [18, 24]
RespRate	26	11	22 [19.5, 27]	11	20 [18, 26]
RespRate	27	10	19 [18, 23.75]	10	20 [18.25, 26.25]
RespRate	28	10	19.5 [18, 23.75]	10	20 [20, 26]

12.6 Safety Conclusions

TXA-127 and TRV-027

The frequency of the safety events and outcomes were between the active and placebo groups for both the TXA-127 and TRV-027 trials.

Fostamatinib

Transaminase elevation occurred more commonly in the fostamatinib group than in the placebo group. Other safety outcomes were similar between groups.

13 DISCUSSION AND OVERALL STUDY CONCLUSIONS

TXA-127 and TRV-027

Among adults hospitalized with severe COVID-19, RAS modulation with either TXA-127 or TRV-027 did not improve oxygen-free days compared with placebo. These results do not support the hypotheses that pharmacological interventions that selectively block the angiotensin II type 1 receptor or increase angiotensin (1-7) improve outcomes for patients with severe COVID-19.In these multicenter, blinded, placebo-controlled randomized clinical trials including 510 adults hospitalized with COVID-19–associated hypoxemia, pharmacological interventions aimed at blocking angiotensin II and increasing angiotensin (1-7) activity did not improve clinical outcomes, including days alive and free from supplemental oxygen therapy (oxygen-free days) or mortality. In these trials, RAS modulation with either synthetic angiotensin (1-7) (TXA-127) or an angiotensin II type 1 receptor–biased ligand (TRV-027) did not improve the number of oxygen-free days and trended toward inferiority (worse outcomes compared with placebo). These results suggest attempting to reverse RAS imbalances anticipated from SARS-CoV-2 infection through exogenous angiotensin (1-7) administration or blockade of the primary receptor for angiotensin II does not provide clinical benefit.

SARS-CoV-2 binds to ACE2, which leads to cellular entry of the virus and also a reduction in the conversion of host angiotensin II to angiotensin (1-7).[2–5] An elevated

ratio of angiotensin II to angiotensin (1-7) has been hypothesized as a key mechanism driving lung injury in COVID-19, and potentially in acute respiratory distress syndrome (ARDS) from other etiologies as well.[5–7] Thus, there has been significant interest in RAS modulation as a potential therapeutic approach for severe COVID-19 and for ARDS generally.[5,8–10] The COVID-19 pandemic presented an opportunity to evaluate RAS modulation in a population of severely ill patients with lung injury caused by a single etiology known to directly result in RAS dysfunction (SARS-CoV-2 infection).[11]

The current trial results add to the growing literature suggesting RAS modulation with on-market agents, such as ARBs, and investigational agents intended to reverse the effects of an elevated ratio of angiotensin II to angiotensin (1-7) do not provide benefit for patients with COVID-19.[12–15] Why this therapeutic approach has failed to demonstrate benefit is not definitively known. One possibility is that SARS-CoV-2 infection may not result in unopposed angiotensin II activity in the lung as hypothesized. The physiology of the RAS is complex, with multiple feedback mechanisms that could prevent SARS-CoV-2 infection from resulting in end-organ exposure to elevated angiotensin II. For example, in a recent postmortem study, Gerard et al[16] found that patients who died of COVID-19 ARDS had increased expression of ACE2 in the lung and serum and increased concentration of serum angiotensin (1-7) compared with control patients without COVID-19. This suggests that endogenous host feedback mechanisms may respond to SARS-CoV-2–induced destruction of ACE2 with increased expression of additional ACE2, thereby rendering pharmacological RAS interventions (e.g., ARBs, TXA-127, and TRV-027) as not beneficial and potentially harmful. Mechanistic changes in components of the RAS, including angiotensin II, ACE2, and angiotensin (1-7), in response to SARS-CoV-2 infection and RAS modulation therapies will be important to evaluate to gain further understanding of COVID-19 pathophysiology and the host response to these therapies.

The two trials had several strengths, including their multicenter, blinded, placebo-controlled design, high adherence to treatment assignment, robust collection of outcome and safety data, use of oxygen-free days as an outcome to capture death and lung-related morbidity, use of a shared placebo group, Bayesian stopping rules to efficiently conduct the trials, and the evaluation of 2 agents active in the RAS pathway with distinct mechanisms.

Fostamatinib

Among adults hospitalized with COVID-19 and hypoxemia, fostamatinib did not increase the number of oxygen-free days compared with placebo. These results do not support the hypothesis that targeting immunothrombosis with fostamatinib improves outcomes among a population of predominantly vaccinated patients with COVID-19 during the omicron era.

In this multicenter, blinded, placebo-controlled randomized clinical trial involving 400 adults hospitalized with COVID-19 infection and hypoxemia, fostamatinib did not increase the number of days alive and free from supplemental oxygen therapy or decrease mortality. These results suggest targeting immunothrombosis and NET release in the

pulmonary vasculature with fostamatinib does not improve recovery from COVID-19 infection in a population of largely vaccinated patients during the omicron era.

Two previous randomized trials examined fostamatinib in adults hospitalized with COVID-19. A 59-patient phase 2 safety study, performed early in the pandemic in a primarily unvaccinated population, reported numerically better secondary clinical outcomes with fostamatinib, including mortality, oxygen-free days, and clinical recovery at day 15 on an ordinal scale.[17] Further, a preliminary report from an unpublished 280-patient phase 3 trial suggested that fostamatinib might increase the number of oxygen-free days and increase the incidence of clinical recovery at day 15.[18,19] That previous trial enrolled over 80% of participants outside of the United States early in the pandemic, a population in which comorbidities were infrequent, vaccination was uncommon, and use of antivirals was rare. The suggestion from these previous trials that fostamatinib my benefit patients hospitalized with COVID-19 infection, particularly those patients with increased severity of lung injury, was the rationale for the design of our current trial.[17–19] Our trial, however, did not find that fostamatinib was effective for hospitalized adults with COVID-19 infection, despite enrolling a trial population in which more than 25% of participants were receiving high-flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation at the time of randomization. Our heterogeneity of treatment effect analysis evaluating differences in efficacy stratified by World Health Organization severity at randomization also did not suggest efficacy.

At least five potential explanations exist for the difference in findings between our trial and the previous trials. First, our phase 3 trial's large sample size may have provided more precise estimates of treatment effect and a lower risk of type I error than prior, earlier-phase studies lacking familywise type-I error control. Second, the two previous trials were conducted earlier in the pandemic when most participants were unvaccinated. In our trial, 72% of participants were vaccinated, which may have diminished participants' inflammatory response and decreased the opportunity for benefit from a drug targeting immunothrombosis.[20,21] Third, differences in the predominant SARS-CoV-2 virus variant between the previous trials and our trial may have led to differences in virus transmissibility, vaccine response, pathogenesis of disease, and clinical manifestations. Fourth, compared to the trials conducted earlier in the pandemic, the participants in our trial were older and had a greater number of underlying chronic medical conditions, including chronic lung disease and chronic receipt of supplemental oxygen.[22,23] This may have resulted in a lower proportion of participants' hypoxemia being attributable to lung injury from COVID-19, and therefore potentially less amenable to a drug targeting immunothrombosis. Fifth, administration of antivirals was infrequent in prior trials. In contrast, these treatments were commonly administered in the time and settings in which our trial occurred, which may have diminished any additive effect of fostamatinib.

Recent research has highlighted heterogeneity in the development and repair of lung injury. Whether the effect of fostamatinib on outcomes differed for participants with versus without biomarkers of proinflammatory cellular response, including NET formation, may help inform whether fostamatinib should be evaluated in other thromboinflammatory processes. [9,13]

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Version	Protocol Date
1.3	6/2/2021
1.6	9/20/2021
1.7	10/6/2021
1.8	12/17/2021
1.9	3/22/2022
2.0	6/7/2022
3.0	9/16/2022
4.0	10/18/2022

16.1.2 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

Case Report Forms for deaths, serious adverse events, and other significant adverse events are archived at the VUMC Coordinating Center and will be provided as required.

16.4 Individual patient data listings for safety data

16.4.1 Listing of Adverse Events by Subject

The table below lists all adverse events for all ex-US participants enrolled as part of the ACTIV 4 Host Tissue platform, the study day on which the adverse event occurred, its seriousness, relatedness, expectedness, and whether the adverse event represented an adverse event of special interest (AESI, liver transaminase elevations of more than 5x the

local laboratory upper limit of normal or baseline measurement at day 0). For participants that received a placebo, the "Eligibility" field lists the trials for which the participant was eligible. For example, a placebo participant with eligibility "TXA-TRV-Fos" was eligible for all three trials and thus would be part of the placebo group for all three trials.

Table 34 Listing of Adverse Events by Subject

Subject ID	Trial	Treatment	Eligibility	Day	Serious	Relatedness	Unexpected	AESI
201-0001	Fos	Active		23	Yes	Probably Not Related	No	Not an AESI
201-0001	Fos	Active		55	Yes	Definitely Not Related	No	Not an AESI
201-0001	Fos	Active		73	Yes	Probably Not Related	No	Not an AESI
203-0001	Fos	Placebo	Fos	34	Yes	Probably Not Related	No	Not an AESI
203-0004	Fos	Active		1	No	Probably Not Related	Yes	Not an AESI
203-0004	Fos	Active		1	No	Probably Not Related	Yes	Not an AESI
203-0004	Fos	Active		13	Yes	Probably or Possibly Related	No	Not an AESI
203-0004	Fos	Active		13	Yes	Probably or Possibly Related	No	Not an AESI
203-0004	Fos	Active		13	No	Probably Not Related	Yes	Not an AESI
204-0001	Fos	Placebo	Fos	4	No	Probably Not Related	No	Not an AESI
204-0001	Fos	Placebo	Fos	9	Yes	Probably Not Related	Yes	Not an AESI
205-0001	Fos	Placebo	Fos	5	Yes	Probably Not Related	Yes	Not an AESI
205-0005	Fos	Active		22	Yes	Probably Not Related	Yes	Not an AESI
205-0008	Fos	Placebo	Fos	4	Yes	Probably or Possibly Related	No	>5x ULN or baseline
206-0003	Fos	Placebo	Fos	67	Yes	Definitely Not Related	No	Not an AESI
211-0001	Fos	Active		2	No	Probably Not Related	Yes	Not an AESI
211-0001	Fos	Active		2	No	Probably Not Related	No	Not an AESI
211-0001	Fos	Active		7	No	Probably or Possibly Related	Yes	Not an AESI
211-0001	Fos	Active		9	No	Probably Not Related	No	Not an AESI
211-0001	Fos	Active		12	Yes	Probably Not Related	Yes	Not an AESI
212-0001	Fos	Placebo	Fos	3	No	Probably Not Related	Yes	Not an AESI
212-0001	Fos	Placebo	Fos	3	No	Probably Not Related	Yes	Not an AESI
212-0001	Fos	Placebo	Fos	6	No	Probably Not Related	Yes	Not an AESI
216-0001	Fos	Active		9	Yes	Probably Not Related	Yes	Not an AESI
222-0003	Fos	Active		3	No	Probably or Possibly Related	No	>5x ULN or baseline
222-0003	Fos	Active		14	Yes	Definitely Not Related	Yes	Not an AESI

16.4.2 Listing of Deaths and PSESEs

The table below lists all deaths for all ex-US participants enrolled as part of the ACTIV 4 Host Tissue platform and the primary and secondary causes of death. For participants that received a placebo, the "Eligibility" field lists the trials for which the participant was eligible. For example, a placebo participant with eligibility "TXA-TRV-Fos" was eligible for all three trials and thus would be part of the placebo group for all three trials. The individual listing of PSESEs is attached as a separate document due to its size.

Table 35 Deaths

Subject ID	Trial	Treatment	Eligibility	Primary cause of death	Secondary cause of death
203-0001	Fosta	Placebo	Fos	COVID-19-virus identified	Unknown

Subject ID	Trial	Treatment	Eligibility	Primary cause of death	Secondary cause of death
205-0001	Fosta	Placebo	Fos	Other (specify)	Other (specify)
211-0001	Fosta	Active		Pulmonary embolism	COVID-19- virus identified
222-0002	Fosta	Placebo	Fos	Unknown	Diseases of heart

16.4.3 Narratives of Serious Adverse Events

Narratives of serious adverse events and AESIs are contained in a separate attachment named "A4HT Abbreviated CSR - SAE and AESI Narrative Listing".

17 ABBREVIATED EFFICACY EVALUATION SUMMARY

In adults with severe COVID-19, RAS modulation (TXA-127 or TRV-027) or treatment with Fostamatinib did not improve oxygen-free days vs placebo.

Analysis of primary efficacy outcome in the mITT cohort

Oxygen-free days to day 28, mean (SD)	Active	Placebo	Unadjusted absolute difference (95% CI)[a]	aOR (95% CI)[b]
TXA-127 trial	N = 170	N = 173	-2.3 (-4.8, 0.2)	0.88 (0.59 - 1.30)
	9.0 (10.9)	11.3 (11.5)		
TRV-027 trial	N = 145	N = 145	-2.4 (-5.1, 0.3)	0.74 (0.48 - 1.13)
	8.1 (10.8)	10.5 (11.5)		
Fostamatinib trial	N = 199	N = 201	-0.8 (-3.3 - 1.7)	0.82 (0.58 - 1.17)
	13.4 (12.4)	14.2 (12.1)		

Footnotes:

a. Binomial distribution with improper beta prior was used for each binary outcome.

b. aOR = adjusted Odds Ratio. Odds ratios were calculated using multivariable proportional odds logistic regression adjusting for age group, sex, and baseline WHO COVID-19 clinical progression scale. (aOR <1.0 is direction of inferiority of active agent)

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