Clinical trial results:
A Phase 3 randomized, multi-center, open label study to assess the efficacy, safety, and tolerability of monoclonal antibody VIR-7831 (sotrovimab) given intramuscularly versus intravenously for the treatment of mild/moderate coronavirus disease 2019 (COVID-19) in high-risk non-hospitalized patients

Summary

EudraCT number	2021-000623-13
Trial protocol	FR AT IT
Global end of trial date	10 May 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	VIR-7831-5008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04913675
WHO universal trial number (UTN)	-
Other trial identifiers	GSK: 217114

Notes:

Sponsors

Sponsor organisation name	Vir Biotechnology, Inc.
Sponsor organisation address	499 Illinois St , San Francisco , United States, 94158
Public contact	n/a, Vir Biotechnology, Inc. , 1415 654-5281, clinicaltrials@vir.bio
Scientific contact	n/a, Vir Biotechnology, Inc. , 1415 654-5281, clinicaltrials@vir.bio
Sponsor organisation name	Vir Biotechnology, Inc.
Sponsor organisation address	499 Illinois St , San Francisco , United States, 94158
Public contact	n/a, GlaxoSmithKline (Ireland) Limited, 1415 6545281, na.na@na.com, 1415 654-5281, clinicaltrials@vir.bio
Scientific contact	n/a, GlaxoSmithKline (Ireland) Limited, 1415 6545281, na.na@na.com, 1415 654-5281, clinicaltrials@vir.bio

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002899-PIP01-20

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy of two dose levels of intramuscular (IM) VIR-7831 versus (vs) intravenous (IV) VIR-7831 in preventing the progression of mild/moderate COVID-19

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ukraine: 2
Country: Number of subjects enrolled	United States: 981
Worldwide total number of subjects	983
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	3
Adults (18-64 years)	750
From 65 to 84 years	217
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

This was a randomized, open label, non-inferiority study of intramuscular (IM) versus intravenous (IV) administration of sotrovimab (VIR-7831), a monoclonal antibody against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) for the treatment of mild/moderate coronavirus disease 2019 (COVID-19) in participants aged 12 years and older.

Pre-assignment

Screening details:

A total of 983 participants were enrolled in this study, of which 10 participants did not receive study intervention. Safety Population (973 participants) consisted of all randomized participants who were exposed to study intervention.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sotrovimab 500 mg IV

Arm description:

Participants received a single dose of sotrovimab 500 milligram (mg), IV infusion over 15 minutes on Day 1.

Arm type	Active comparator
Investigational medicinal product name	Sotrovimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sotrovimab was administered IV infusion in a single dose

Arm title	Sotrovimab 500 mg IM

Arm description:

Participants received a single dose of sotrovimab 500 mg, IM dose as 2*4 milliliter (mL) injections in each dorsogluteal muscle on Day 1.

Arm type	Experimental
Investigational medicinal product name	Sotrovimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Sotrovimab was administered IM injection in a single dose

Arm title	Sotrovimab 250 mg IM

Arm description:

Participants received a single dose of sotrovimab 250 mg, IM dose either as a single 250 mg (4 mL) injection in the dorsogluteal muscle or as 2*2 mL injections in each deltoid muscle on Day 1.

Arm type	Experimental

Investigational medicinal product name	Sotrovimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Sotrovimab was administered IM injection in a single dose

Number of subjects in period 1[1]	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM
Started	393	385	195
Completed	356	341	176
Not completed	37	44	19
Consent withdrawn by subject	25	33	12
Physician decision	-	1	1
Death	-	2	2
Lost to follow-up	12	8	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 983 participants were enrolled in the study, of which 10 participants did not receive study treatment. Hence, 973 participants were considered in the Safety Population.

Baseline characteristics

Reporting groups	
Reporting group title	Sotrovimab 500 mg IV
Reporting group description:	
Participants received a single dose of sotrovimab 500 milligram (mg), IV infusion over 15 minutes on Day 1.	
Reporting group title	Sotrovimab 500 mg IM
Reporting group description:	
Participants received a single dose of sotrovimab 500 mg, IM dose as 2*4 milliliter (mL) injections in each dorsogluteal muscle on Day 1.	
Reporting group title	Sotrovimab 250 mg IM
Reporting group description:	
Participants received a single dose of sotrovimab 250 mg, IM dose either as a single 250 mg (4 mL) injection in the dorsogluteal muscle or as 2*2 mL injections in each deltoid muscle on Day 1.	

Reporting group values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM
Number of subjects	393	385	195
Age categorical Units: Subjects			
All Participants	393	385	195
Age continuous			
Baseline characteristics were reported for Safety Population which consisted of all randomized participants who were exposed to study intervention.			
Units: years			
arithmetic mean	50.8	51.2	48.3
standard deviation	± 16.69	± 16.77	± 16.00
Gender categorical			
Baseline characteristics were used for Safety Population which consisted of all randomized participants who were exposed to study intervention.			
Units: Subjects			
Female	224	197	113
Male	169	188	82
Race/ Ethnicity, Customized			
Baseline characteristics were used for Safety Population which consisted of all randomized participants who were exposed to study intervention.			
Units: Subjects			
Asian - Central/South Asian Heritage	1	2	0
Asian - South East Asian Heritage	0	1	0
Black or African American	17	19	8
Native Hawaiian or Other Pacific Islander	1	0	0
White - Arabic/North African Heritage	10	21	8
White - White/Caucasian/European	362	336	176
Mixed Race	1	2	1
Unknown	0	3	1
Missing	1	1	1

Reporting group values	Total		

Number of subjects	973		
Age categorical Units: Subjects			
All Participants	973		

Age continuous			
Baseline characteristics were reported for Safety Population which consisted of all randomized participants who were exposed to study intervention.			
Units: years arithmetic mean standard deviation	- -		
Gender categorical			
Baseline characteristics were used for Safety Population which consisted of all randomized participants who were exposed to study intervention.			
Units: Subjects			
Female	534		
Male	439		
Race/ Ethnicity, Customized			
Baseline characteristics were used for Safety Population which consisted of all randomized participants who were exposed to study intervention.			
Units: Subjects			
Asian - Central/South Asian Heritage	3		
Asian - South East Asian Heritage	1		
Black or African American	44		
Native Hawaiian or Other Pacific Islander	1		
White - Arabic/North African Heritage	39		
White - White/Caucasian/European	874		
Mixed Race	4		
Unknown	4		
Missing	3		

End points

End points reporting groups

Reporting group title	Sotrovimab 500 mg IV
Reporting group description:	
Participants received a single dose of sotrovimab 500 milligram (mg), IV infusion over 15 minutes on Day 1.	
Reporting group title	Sotrovimab 500 mg IM
Reporting group description:	
Participants received a single dose of sotrovimab 500 mg, IM dose as 2*4 milliliter (mL) injections in each dorsogluteal muscle on Day 1.	
Reporting group title	Sotrovimab 250 mg IM
Reporting group description:	
Participants received a single dose of sotrovimab 250 mg, IM dose either as a single 250 mg (4 mL) injection in the dorsogluteal muscle or as 2*2 mL injections in each deltoid muscle on Day 1.	

Primary: Percentage of Participants who had Progression of COVID-19 through Day 29 by Hospitalization >24 hours or Death due to any cause (Weekly and Daily Imputation)

End point title	Percentage of Participants who had Progression of COVID-19 through Day 29 by Hospitalization >24 hours or Death due to any cause (Weekly and Daily Imputation)
End point description:	
Progression of COVID-19 through Day 29 as defined by hospitalization >24 hours for acute management of illness due to any cause or death. Percentage values are rounded off. Primary Analysis Population consisted of all randomized participants excluding participants who were randomized under Protocol Amendment Version 1 and were immunocompetent and fully vaccinated at randomization and participants who did not meet key eligibility criteria. The statistical analysis was performed only for 500 mg IV versus 500 mg IM dose. It was not planned for 250 mg IM dose per statistical analysis plan.	
End point type	Primary
End point timeframe:	
Up to Day 29	

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	378	376	183	
Units: Percentage of participants				
number (not applicable)	1.3	2.7	5.5	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Analysis was performed using a binomial regression model with identity link function and with treatment (Sotrovimab 500mg IM, 500mg IV), age (<65, =>65 years old) and gender (male, female) as covariates.	

Comparison groups	Sotrovimab 500 mg IV v Sotrovimab 500 mg IM
Number of subjects included in analysis	754
Analysis specification	Post-hoc
Analysis type	non-inferiority[1]
Parameter estimate	Risk difference (RD)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	3.26

Notes:

[1] - This outcome measure was analyzed using a hypothetical estimand and assessing non-inferiority of 500 mg IM dose versus 500 mg IV using a non-inferiority margin of 3.5 percent (%) on the risk difference scale. Weekly imputation algorithm imputes the missing outcome iteratively for each week, where missing outcomes at Day 8, 15, 22, 29 are imputed.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis was performed using a binomial regression model with identity link function and with treatment (Sotrovimab 500mg IM, 500mg IV), age (<65, =>65 years old) and gender (male, female) as covariates.

Comparison groups	Sotrovimab 500 mg IV v Sotrovimab 500 mg IM
Number of subjects included in analysis	754
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Risk difference (RD)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	3.56

Notes:

[2] - This outcome measure was analyzed using a hypothetical estimand and assessing non-inferiority of 500 mg IM dose versus 500 mg IV using a non-inferiority margin of 3.5% on the risk difference scale. Daily imputation algorithm imputes the missing outcome iteratively for each study day starting with Day 2 and ending at Day 29.

Secondary: Number of Participants With Common Non-Serious Adverse Events (non-SAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Common Non-Serious Adverse Events (non-SAEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. An SAE is defined as any serious adverse event that, at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, significant medical events that may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed before. Adverse events which were not serious were considered as non-serious adverse events. Common (>=1%) non-SAEs and SAEs are presented. Safety Population consisted of all randomized participants who were exposed to study intervention.

End point type	Secondary

End point timeframe:

Up to Week 36

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	385	195	
Units: Participants				
Common Non-SAEs	8	5	12	
SAEs	3	7	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With any Infusion- or Injection-related Reaction Including Hypersensitivity

End point title	Number of Participants With any Infusion- or Injection-related Reaction Including Hypersensitivity

End point description:

Data for number of participants with any infusion- or injection-related reaction including hypersensitivity has been presented. Safety Population.

End point type	Secondary

End point timeframe:

Up to Week 36

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	385	195	
Units: Participants	2	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With any Local Site Reaction by Maximum Severity After IM Administration

End point title	Number of Participants With any Local Site Reaction by Maximum Severity After IM Administration[3]

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. AESIs included any local site reactions. AESI were graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007, Food and Drug Administration, where Grade 1=Mild toxicity; Grade 2=Moderate toxicity; Grade 3=Severe toxicity; and Grade 4=

Potentially life-threatening toxicity. Higher Grade indicates higher severity. Data for any worst case post-Baseline has been presented. Safety Population.

End point type	Secondary

End point timeframe:

Up to Week 36

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	195		
Units: Participants				
Grade 1	39	22		
Grade 2	7	2		
Grade 3	1	0		
Grade 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With any Disease Related Events

End point title	Number of Participants With any Disease Related Events

End point description:

AEs related to expected progression, signs, or symptoms of COVID-19, unless more severe than expected for the participant’s current clinical status and medical history, were reported as a disease related events. Safety Population.

End point type	Secondary

End point timeframe:

Up to Week 36

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	385	195	
Units: Participants	18	16	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Positive Anti-drug

Antibody

End point title	Number of Participants With Treatment-emergent Positive Anti-drug Antibody

End point description:

Serum samples were collected for the determination of treatment-emergent anti-drug antibodies (ADA) using a validated electrochemiluminescent (ECL) immunoassay. The assay involved screening, confirmation and titration steps. If serum samples tested positive in the screening assay, they were considered 'potentially positive' and were further analyzed for the specificity using the confirmation assay. Samples that confirmed positive in the confirmation assay were reported as 'positive'. Confirmed treatment-emergent positive ADA samples were further characterized in the titration assay to quasi-quantitate the amount of ADA in the sample. Safety Population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	385	195	
Units: Participants	25	51	26	

Statistical analyses

No statistical analyses for this end point

Secondary: Titers of Anti-drug Antibodies Against Sotrovimab

End point title	Titers of Anti-drug Antibodies Against Sotrovimab

End point description:

Serum samples were collected for the determination of treatment-emergent ADA using a validated ECL immunoassay. The assay involved screening, confirmation and titration steps. If serum samples contained treatment-emergent ADA, they were further analyzed for the specificity of antibodies by a confirmation assay. Confirmed treatment-emergent positive samples were titrated to obtain the titers of antibodies. Titers were categorized as treatment-induced, treatment-boosted, and treatment-unaffected. Treatment-induced=those who are ADA negative or missing data and who have at least one post-dose ADA positive sample; Treatment boosted=those who are ADA positive and have a >4*Baseline titer; Treatment unaffected=those who are positive and (post-Baseline titer <=4*Baseline titer or all post-Baseline positive). Safety Population. Only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).99999 indicates, data not available

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	385	195	
Units: Titers				
median (full range (min-max))				
Treatment-induced, n=41,104,57	80.0 (40 to 5120)	80.0 (40 to 5120)	80.0 (40 to 20480)	
Treatment-boosted, n=1,4,0	1280.0 (1280 to 1280)	400.0 (40 to 640)	99999 (99999 to 99999)	
Treatment-unaffected, n=20,4,15	40.0 (40 to 320)	40.0 (40 to 80)	40.0 (40 to 160)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who had Progression of COVID-19 through Day 29 by Emergency Room visit or Hospitalization or Death (Weekly Imputation)

End point title	Percentage of Participants who had Progression of COVID-19 through Day 29 by Emergency Room visit or Hospitalization or Death (Weekly Imputation)

End point description:

Progression of COVID-19 through Day 29 as defined by visit to a hospital emergency room for management of illness or hospitalization for acute management of illness for any duration and for any cause or death. Percentage values are rounded off. Primary Analysis Population. The statistical analysis was performed only for 500 mg IV versus 500 mg IM dose. It was not planned for 250 mg IM dose per statistical analysis plan.

End point type	Secondary

End point timeframe:

Up to Day 29

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	378	376	183	
Units: Percentage of participants				
number (not applicable)	2.4	3.2	6.0	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis was performed using a binomial regression model with identity link function and with treatment (Sotrovimab 500mg IM, 500mg IV), age (<65, =>65 years old) and gender (male, female) as covariates.

Comparison groups	Sotrovimab 500 mg IV v Sotrovimab 500 mg IM

Number of subjects included in analysis	754
Analysis specification	Post-hoc
Analysis type	non-inferiority[4]
Parameter estimate	Risk difference (RD)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	3.28

Notes:

[4] - This outcome measure was analyzed using a hypothetical estimand and assessing non-inferiority of IM dose versus IV using a non-inferiority margin of 3.5% on the risk difference scale. Weekly imputation algorithm imputes the missing outcome iteratively for each week, where missing outcomes at Day 8, 15, 22, 29 are imputed.

Secondary: Percentage of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 by Visit

End point title	Percentage of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 by Visit

End point description:

Participants were defined as progressing to develop severe respiratory COVID-19 if they required supplemental oxygen either by nasal cannula, face mask, high-flow oxygen devices, or non-invasive ventilation. Participants were defined as progressing to develop critical respiratory COVID-19 if they required invasive mechanical ventilation or extracorporeal membrane oxygenation. Percentage values are rounded off. Intent-to-Treat (ITT) Population consisted of all randomized participants excluding participants who were randomized under Protocol Amendment Version 1 and were immunocompetent and fully vaccinated at randomization.

End point type	Secondary

End point timeframe:

Day 8, Day 15, Day 22, and Day 29

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	385	383	185	
Units: Percentage of participants				
number (not applicable)				
Day 8	0.3	1.0	3.8	
Day 15	0.3	1.3	4.3	
Day 22	0.3	1.6	4.3	
Day 29	0.3	1.6	4.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Area Under the Curve (AUC) of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Viral Load From Day 1 to Day 8

End point title	Mean Area Under the Curve (AUC) of Severe Acute Respiratory

	Syndrome Coronavirus-2 (SARS-CoV-2) Viral Load From Day 1 to Day 8

End point description:

AUC of SARS-CoV-2 viral load was measured by Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 in nasopharyngeal swab samples. Virology Population consisted of all participants in the ITT Population with a central laboratory confirmed quantifiable Baseline nasopharyngeal swab at Day 1. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Day 1 to Day 8

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	287	278	136	
Units: Day*log10 copies/mL				
geometric mean (geometric coefficient of variation)	25.42 (± 34.144)	25.56 (± 36.936)	25.46 (± 37.899)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean AUC of SARS-CoV-2 Viral Load From Day 1 to Day 8 After Administration of Sotrovimab 500 mg IV and IM

End point title	Mean AUC of SARS-CoV-2 Viral Load From Day 1 to Day 8 After Administration of Sotrovimab 500 mg IV and IM[5]

End point description:

AUC of SARS-CoV-2 viral load was measured by qRT-PCR from Day 1 to Day 8 in nasopharyngeal swab samples. Least squares geometric mean and 90 percent (%) confidence interval has been presented. Virology Population. Only those participants with data available at the specified time points were analyzed. The statistical analysis was performed only for 500 mg IV versus 500 mg IM dose. It was not planned for 250 mg IM dose per statistical analysis plan.

End point type	Secondary

End point timeframe:

Day 1 to Day 8

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	278		
Units: Day*log10 copies/mL				
least squares mean (confidence interval 90%)	25.03 (24.45 to 25.63)	25.96 (25.35 to 26.59)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

LS geometric mean was calculated for 500mg IV versus IM by using an Analysis of Covariance (ANCOVA) Model with treatment group (sotrovimab 500mg IM, 500mg IV), age (<65, =>65 years old), gender (male, female) and Baseline viral load as covariates.

Comparison groups	Sotrovimab 500 mg IV v Sotrovimab 500 mg IM
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	Ratio of least square(LS) geometric mean
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.07

Notes:

[6] - IM dose was assessed for equivalence to IV based on the two-sided 90% confidence interval for the treatment ratio falling within equivalence bounds of 0.5 to 2.0.

Secondary: Change from Baseline in Viral Load as Measured by qRT-PCR at Day 8

End point title	Change from Baseline in Viral Load as Measured by qRT-PCR at Day 8

End point description:

Viral load was based on nasopharyngeal swab samples and was measured by qRT-PCR. Baseline was defined as the latest non-missing value prior to dosing (or latest value on or prior to nominal Day 1 for participants that were not dosed). Change from Baseline was calculated by subtracting the Baseline value from the post-dose visit value.
Virology Population. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Day 8

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	279	271	132	
Units: Log10 copies/mL				
arithmetic mean (standard deviation)	-2.979 (± 1.6965)	-2.752 (± 1.7594)	-2.488 (± 1.6628)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Persistently High SARS-CoV-2 Viral Load at Day 8

End point title	Percentage of Participants with Persistently High SARS-CoV-2 Viral Load at Day 8

End point description:

Percentage of participants with a persistently high viral load were categorized as >=4.1 log10 copies/mL and <4.1 log10 copies/mL. Percentage of participants with a persistently high SARS-CoV-2 viral load at Day 8 was assessed via qRT-PCR in nasopharyngeal swab samples. Percentage values are rounded off. Virology Population. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

At Day 8

End point values	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	279	271	132	
Units: Percentage of participants				
number (not applicable)				
>=4.1 log 10 copies/mL	13	12	17	
<4.1 log 10 copies/mL	87	88	83	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Sotrovimab After Intravenous Administration

End point title	Serum Concentration of Sotrovimab After Intravenous Administration[7]

End point description:

Blood samples were collected at indicated time points for pharmacokinetic (PK) analysis of Sotrovimab. Pharmacokinetic Population consisted of all participants in the Safety Population who had at least 1 non-missing PK assessment (non-quantifiable values were considered as non-missing values). Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates that, data was not available as all concentration values were below the lower limit of quantification.

End point type	Secondary

End point timeframe:

Day 1: Pre-dose, Day 8, Day 15, Day 29, Week 12, Week 20 and Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	Sotrovimab 500 mg IV			
Subject group type	Reporting group			
Number of subjects analysed	393			
Units: Microgram per mL				
geometric mean (geometric coefficient of variation)				
Day 1: Pre-dose, n=363	99999 (± 99999)			
Day 8: n=337	53.67 (± 54.21)			
Day 15: n=338	44.62 (± 51.54)			
Day 29: n=356	33.89 (± 72.61)			
Week 12: n=353	19.10 (± 55.20)			
Week 20: n=325	9.96 (± 53.24)			
Week 24: n=344	7.66 (± 56.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Sotrovimab After Intramuscular Administration

End point title	Serum Concentration of Sotrovimab After Intramuscular Administration[8]

End point description:

Blood samples were collected at indicated time points for PK analysis of Sotrovimab. Pharmacokinetic Population. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates that, data was not available as all concentration values were below the lower limit of quantification.

End point type	Secondary

End point timeframe:

Day 1: Pre-dose, Day 8, Day 15, Day 29, Week 12, Week 20 and Week 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	195		
Units: Microgram per mL				
geometric mean (geometric coefficient of variation)				
Day 1: Pre-dose, n=365,187	99999 (± 99999)	99999 (± 99999)		
Day 8: n=339,166	20.50 (± 88.70)	10.93 (± 92.47)		
Day 15: n=344,166	20.60 (± 84.01)	10.90 (± 77.68)		
Day 29: n=355,174	18.92 (± 77.00)	10.20 (± 61.80)		
Week 12: n=333,171	11.15 (± 64.01)	6.15 (± 54.22)		
Week 20: n=315,167	5.83 (± 65.44)	3.19 (± 57.05)		
Week 24: n=315,168	4.48 (± 71.57)	2.34 (± 62.49)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All-cause mortality, SAEs were collected up to Week 36; non-serious AEs were collected through Week 12	
Adverse event reporting additional description:	
Safety Population consisted of all randomized participants who were exposed to study intervention.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Sotrovimab 500 mg IV
Reporting group description:	
Participants received a single dose of sotrovimab 500 milligram (mg), IV infusion over 15 minutes on Day 1.	
Reporting group title	Sotrovimab 500 mg IM
Reporting group description:	
Participants received a single dose of sotrovimab 500 mg, IM dose as 2*4 milliliter (mL) injections in each dorsogluteal muscle on Day 1.	
Reporting group title	Sotrovimab 250 mg IM
Reporting group description:	
Participants received a single dose of sotrovimab 250 mg, IM dose either as a single 250 mg (4 mL) injection in the dorsogluteal muscle or as 2*2 mL injections in each deltoid muscle on Day 1.	

Serious adverse events	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 393 (0.76%)	7 / 385 (1.82%)	3 / 195 (1.54%)
number of deaths (all causes)	0	2	2
number of deaths resulting from adverse events			
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 385 (0.00%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial mass			
subjects affected / exposed	0 / 393 (0.00%)	0 / 385 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 393 (0.00%)	0 / 385 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 385 (0.00%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 393 (0.00%)	0 / 385 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 393 (0.00%)	0 / 385 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 393 (0.25%)	0 / 385 (0.00%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 385 (0.26%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Sotrovimab 500 mg IV	Sotrovimab 500 mg IM	Sotrovimab 250 mg IM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 393 (2.04%)	5 / 385 (1.30%)	12 / 195 (6.15%)
Investigations			
Activated partial thromboplastin time prolonged			

subjects affected / exposed	5 / 393 (1.27%)	2 / 385 (0.52%)	3 / 195 (1.54%)
occurrences (all)	5	2	3
Alanine aminotransferase increased			
subjects affected / exposed	2 / 393 (0.51%)	3 / 385 (0.78%)	2 / 195 (1.03%)
occurrences (all)	2	3	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 393 (0.00%)	0 / 385 (0.00%)	2 / 195 (1.03%)
occurrences (all)	0	0	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 385 (0.00%)	4 / 195 (2.05%)
occurrences (all)	1	0	4
Gastroenteritis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 385 (0.00%)	2 / 195 (1.03%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2021	Amendment 1: The major changes and rationale for the changes from the original protocol to protocol amendment 1 are as follows: Study Design: Change from placebo to active comparator of VIR-7831 IV, removal of Lead-in, addition of 250 milligram (mg) IM arm; Change from placebo to active comparator of VIR-7831 IV, removal of Lead-in, addition of 250 mg IM arm; Study population: Study population was expanded to include ages 12-17 years of age with risk factors for severe disease; Allow participants who previously received COVID-19 vaccines; Changed high-risk adult definition to include those with body mass index less than or equal to (<=)30, immunocompromised participants, those receiving immunosuppressive medicines, and chronic liver disease; Post treatment observation of vital signs and local tolerability assessments timepoints on Day 1 may be reduced if recommended by the Joint Safety Review Team after the first 300 participants; Biostatistics: Number of statistical hypotheses changed from 1 to 2 for primary endpoint analysis, sample size, analysis sets, primary endpoint analysis method, interim analysis and Independent Data Monitoring Committee removed, estimand method as new approach for primary endpoint analysis, multiplicity strategy for primary endpoint analysis changed.
29 June 2021	Amendment 2: The major changes and rationale for the changes from the protocol amendment 1 to protocol amendment 2 are as follows: Added an Independent Data Monitoring Committee and provisions for one interim analysis to assess for safety, futility, and efficacy; Removed the option to decrease post-treatment monitoring time to 15 minutes. All participants will be monitored for 30 minutes after treatment; Added exclusion criteria to exclude fully vaccinated immunocompetent participants; Added a new exploratory objective to assess the incidence and severity of Long COVID symptoms at Week 12 and Week 24.
04 October 2021	Amendment 3: The major changes and rationale for the changes from protocol amendment 2 to protocol amendment 3 are as follows: Updated clinical pharmacology background information with new data about sotrovimab half-life and extended the study duration from 24 weeks to 36 weeks of follow up; Enrollment into the 250 mg IM arm was discontinued which resulted in changes to the overall study design, the planned interim analysis and primary endpoint analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The pre-specified daily imputation resulted in overly high inflation in the estimated progression rates for missing data. To reduce this bias and to account for progression history, weekly imputation was used for final conclusions.

Notes: