Clinical trial results:
A Multicenter, Randomized, Open-label Parallel Group Pilot Study to Evaluate Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) plus Standard Medical Treatment (SMT) versus SMT alone in Hospitalized Subjects with COVID-19

Summary

EudraCT number	2020-001696-32
Trial protocol	ES
Global end of trial date	03 March 2021

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	GC2004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04432324
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A.
Sponsor organisation address	Can Guasch, 2 08150 Parets del Vallès, Barcelona, Spain,
Public contact	Department of Clinical Trials, Instituto Grifols, S.A, 34 935712000, IGregulatory.affairs@grifols.com
Scientific contact	Department of Clinical Trials, Instituto Grifols, S.A, 34 935712000, IGregulatory.affairs@grifols.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2021
Global end of trial reached?	Yes
Global end of trial date	03 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if high dose IVIG plus SMT can reduce the proportion of subjects dying or requiring intensive care unit (ICU) admission on or before Day 29 or who are dependent on high flow oxygen devices or invasive mechanical ventilation on Day 29 versus SMT alone in hospitalized subjects with COVID-19.

Protection of trial subjects:

Documented approval from appropriate ECs was to be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. The protocol dated 14 Apr 2020, all 3 subsequent amendments, and the Informed Consent Form were reviewed an approved by the EC of each participating research study center prior to implementation.

Modifications to the study protocol could not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator could implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior EC/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment was to be submitted to the EC/sponsor. Any deviations from the protocol had to be fully explained and documented by the investigator.

Background therapy:

Concomitant prophylaxis for potential venous thrombosis or thromboembolism in hospitalized subjects with COVID-19 was supported within this study according to institutional standard practices. Subjects could receive drugs such as azithromycin, tocilizumab and other potential COVID-19 disease modifying drugs as indicated based on clinical status and the investigator's discretion.

Evidence for comparator:

At the time of designing the clinical study protocol, there were no approved treatments for COVID-19 and no approved prophylactic, post-exposure, or therapeutic treatment modalities existed for SARS-CoV-2. Standard medical treatment for COVID-19 was guided by disease severity and reflected a dynamic approach for an optimal disease management, considering the clinical experience and the evidence emerging from clinical trials.

Actual start date of recruitment	01 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	0
Adults (18-64 years)	81
From 65 to 84 years	17
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 10 centers in Spain; 2 of the 10 centers did not enroll any subjects. The first subject was enrolled in the study on 01 Jun 2020, and the last subject completed their last visit 03 Mar 2021.

Pre-assignment

Screening details:

Subjects were assessed for trial eligibility during the screening period. Subjects had to meet all inclusion criteria and none of the exclusion criteria to be eligible for enrollment. A total of 100 subjects were screened and randomized into the study; no subjects screen failed.

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	Intravenous Immune Globulin + Standard Medical Treatment

Arm description:

Subjects in the Intravenous Immune Globulin + Standard Medical Treatment (IVIG + SMT) arm received high dose intravenous immune globulin (IVIG), Flebogamma DIF plus standard medical treatment (SMT) based on their research study center's standard practices for the management of COVID-19 patients.

Arm type	Experimental
Investigational medicinal product name	Flebogamma 5 and 10% DIF
Investigational medicinal product code	J06BA02
Other name	human normal immunoglobulin, IGIV3I, IVIG
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

A total net dose of 2g/kg (capped to maximum 160g for subjects >80kg) was to be administered in divided doses over consecutive days, either into (a) infusions of 500mg/kg body weight over 4 days, or (b) 400mg/kg body weight over 5 days. To calculate dose for each infusion, the weight of the subject (kg) was to be multiplied by the dose in mg/kg. IVIG was to be infused using a separate line by itself, without mixing with other IV fluids or medications the subject could be receiving. IVIG infusion line could be flushed with 5% dextrose in water or 0.9% sodium chloride for injection. IVIG was to be initially administered at a rate of 0.01mL/kg/min for 30 minutes. If Flebogamma DIF was well tolerated, the rate could be gradually increased to a maximum infusion rate of 0.1 mL/kg/min and 0.08 mL/kg/min, for Flebogamma DIF 5% and 10%, respectively. For subjects aged >65 years, the maximum rate was 0.06mL/kg/min with Flebogamma DIF 5% and 0.04mL/kg/min with Flebogamma DIF 10%.

Arm title	Standard Medical Treatment

Arm description:

Subjects in the Standard Medical Treatment (SMT) received medical care based on their research study center's standard practices for the management of COVID-19 patients.

Arm type	Standard Medical Treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Intravenous Immune Globulin + Standard Medical Treatment	Standard Medical Treatment
Started	50	50
Completed	44	47
Not completed	6	3
Adverse event, non-fatal	2	-
Lost to follow-up	1	3
Consent withdrawn by subject	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Intravenous Immune Globulin + Standard Medical Treatment
Reporting group description:	
Subjects in the Intravenous Immune Globulin + Standard Medical Treatment (IVIG + SMT) arm received high dose intravenous immune globulin (IVIG), Flebogamma DIF plus standard medical treatment (SMT) based on their research study center's standard practices for the management of COVID-19 patients.	
Reporting group title	Standard Medical Treatment
Reporting group description:	
Subjects in the Standard Medical Treatment (SMT) received medical care based on their research study center's standard practices for the management of COVID-19 patients.	

Reporting group values	Intravenous Immune Globulin + Standard Medical Treatment	Standard Medical Treatment	Total
Number of subjects	50	50	100
Age categorical			
Collected for Intention to Treat population			
Units: Subjects			
>=18 and <65 years	41	40	81
>=65 years	9	10	19
Age continuous			
Units: years			
median	53.0	54.5	
full range (min-max)	23 to 90	27 to 86	-
Gender categorical			
Units: Subjects			
Female	10	11	21
Male	40	39	79
Race			
Units: Subjects			
White	47	46	93
Black or African American	1	2	3
Asian	1	0	1
American Indian or Alaskan Native	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	1	1
Body Mass Index (BMI)			
Units: kg/m2			
median	29.45	27.6	
full range (min-max)	17.7 to 42.5	19.3 to 39.1	-
Weight			
Units: kg			
median	84.5	80.10	
full range (min-max)	43.7 to 120.0	58.0 to 121.0	-
Duration of COVID-19 exposure			
Date of randomization - Date of first potential COVID-19 exposure + 1			
Units: Days			

arithmetic mean	13.2	12.7	
standard deviation	± 4.10	± 4.66	-
Duration of first COVID-19 symptoms			
Date of randomization - Date of first COVID-19 symptoms + 1.			
Units: Days			
arithmetic mean	10.5	9.8	
standard deviation	± 5.47	± 3.57	-
Duration of first positive RT-PCR/NAT or other commercial or other public health assay result			
Date of randomization - Date of first PCR (RT-PCR)/NAT or other commercial or public health assay positive + 1			
Units: Days			
arithmetic mean	3.0	2.6	
standard deviation	± 2.93	± 1.96	-
7-Point Ordinal Scale			
Ordinal scale measure of clinical status: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities			
Units: Point			
arithmetic mean	4.3	4.2	
standard deviation	± 0.45	± 0.40	-
National Early Warning Score (NEWS)			
Used to assess clinical status. Only collected in 49 subjects in the IVIG+SMT arm and 49 subjects in the SMT only arm.			
Units: Point			
arithmetic mean	3.2	2.9	
standard deviation	± 1.59	± 1.56	-

End points

End points reporting groups

Reporting group title	Intravenous Immune Globulin + Standard Medical Treatment
Reporting group description:	
Subjects in the Intravenous Immune Globulin + Standard Medical Treatment (IVIG + SMT) arm received high dose intravenous immune globulin (IVIG), Flebogamma DIF plus standard medical treatment (SMT) based on their research study center's standard practices for the management of COVID-19 patients.	
Reporting group title	Standard Medical Treatment
Reporting group description:	
Subjects in the Standard Medical Treatment (SMT) received medical care based on their research study center's standard practices for the management of COVID-19 patients.	
Subject analysis set title	Intention to Treat: IVIG + SMT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects	
Subject analysis set title	Per Protocol: IVIG + SMT
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of subjects included in the ITT population who did not present major protocol violations which might had an impact on the primary efficacy endpoint and completed at least 80% of the investigational product	
Subject analysis set title	Safety: IVIG + SMT
Subject analysis set type	Safety analysis
Subject analysis set description:	
Defined for the combination arm as the subset of subjects who received at least any amount of Flebogamma® DIF in addition to SMT. The Safety Population for the SMT alone arm included all subjects randomized to this arm, because by definition SMT was universally provided and hence all randomized subjects would have received SMT	
Subject analysis set title	Intention to Treat: SMT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects	
Subject analysis set title	Per Protocol: SMT
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of subjects included in the ITT population who did not present major protocol violations which might had an impact on the primary efficacy endpoint and completed at least 80% of the investigational product	
Subject analysis set title	Safety: SMT
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomized	

Primary: Number of subjects dying, requiring ICU admission, or dependent on high flow oxygen devices on or before Day 29

End point title	Number of subjects dying, requiring ICU admission, or dependent on high flow oxygen devices on or before Day 29
End point description:	
This efficacy endpoint is the proportion of subjects dying or requiring ICU admission on or before Day 29 or who are dependent on high flow oxygen devices or invasive mechanical ventilation on Day 29. ICU=intensive care unit, IMV=invasive mechanical ventilation, CI=Confidence Interval	
End point type	Primary

End point timeframe:

Up to Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Subjects				
Dying on or Before Day 29	0	0		
Requiring ICU Admission on or before Day 29	1	2		
Dependent on High Flow Oxygen Devices on Day 29	0	0		
Depend on IMV on Day 29	0	0		
Meeting Primary Endpoint	1	2		

Statistical analyses

Statistical analysis title	(IVIG+SMT)-SMT

Statistical analysis description:

The difference in the proportions of subjects meeting the primary efficacy endpoint between the treatment groups.

Comparison groups	Intention to Treat: IVIG + SMT v Intention to Treat: SMT
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	7.1

Secondary: Assessment of Clinical Severity: Change in NEWS from baseline

End point title	Assessment of Clinical Severity: Change in NEWS from baseline

End point description:

The NEWS was calculated based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: Score				
least squares mean (confidence interval 95%)				
Day 15	-2.2 (-2.7 to -1.6)	-1.8 (-2.3 to -1.2)		
Day 29	-2.0 (-2.6 to -1.5)	-1.7 (-2.2 to -1.2)		
Average across all post-baseline visits	-1.5 (-2.0 to -1.0)	-1.2 (-1.7 to -0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to clinical response: NEWS <= 2 maintained for 24 hours

End point title	Time to clinical response: NEWS <= 2 maintained for 24 hours

End point description:

Clinical response is defined as the NEWS score <=2 maintained for 24 hours from Day 1 through Day 29. The time to the first occurrence of clinical response was estimated using the Kaplan-Meier (KM) method.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (confidence interval 95%)				
25th Percentile	3 (2 to 4)	2 (2 to 4)		
50th Percentile (Median)	5 (4 to 8)	5 (4 to 7)		
75th Percentile	9 (7 to 16)	10 (7 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to hospital discharge: defined as duration of hospitalization

End point title	Time to hospital discharge: defined as duration of hospitalization

End point description:

Time to hospital discharge is defined as duration of hospitalization from Day 1 through Day 29. The proportion of subjects who were discharged from the hospital was estimated using the Cumulative Incidence Function. Deaths that occurred prior to discharge from the hospital was treated as a competing risk.

End point type	Secondary

End point timeframe:

Post-randomization through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	8.1 (± 4.73)	8.8 (± 4.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: If admitted to ICU: Duration of ICU stay

End point title	If admitted to ICU: Duration of ICU stay

End point description:

The duration of ICU stay from post-randomization through Day 29 was calculated based on ICU admission and discharge dates. Number of days in the ICU was compared between treatment groups using an ANOVA model, including number of days in the ICU as a dependent variable and treatment group as a fixed effect.

End point type	Secondary

End point timeframe:

Post-randomization through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	0.0 (± 0.28)	0.3 (± 1.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of any oxygen use

End point title	Duration of any oxygen use

End point description:

The duration of any oxygen use from Day 1 through Day 29 was calculated based on the start/stop date of using oxygen supplementation. Number of days on oxygen was compared between treatment groups using an analysis of variance (ANOVA) model, including number of days on oxygen as a dependent variable and treatment group as a fixed effect.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	5.6 (± 6.37)	6.0 (± 5.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: If requiring mechanical ventilation: Duration mechanical ventilation

End point title	If requiring mechanical ventilation: Duration mechanical ventilation

End point description:

The duration on mechanical ventilation from post randomization through Day 29 was calculated based on the start/stop dates of mechanical ventilation. Number of days on mechanical ventilation was compared between treatment groups using an ANOVA model, including number of days on mechanical ventilation as a dependent variable and treatment group as a fixed effect.

End point type	Secondary

End point timeframe:

Post-randomization through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	0.0 (± 0.00)	0.0 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute value and mean change from baseline in the Ordinal scale

End point title	Absolute value and mean change from baseline in the Ordinal scale

End point description:

The absolute value and change from baseline in the Ordinal scale from Day 1 through Day 29 was summarized by treatment group and visit using descriptive statistics.
The 7-point Ordinal scale is as follows:
1) Death;
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen;
6) Not hospitalized, limitation on activities;
7) Not hospitalized, no limitations on activities.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Scale				
least squares mean (confidence interval 95%)				
Day 15	2.44 (2.255 to 2.63)	2.36 (2.18 to 2.55)		
Day 29	2.55 (2.36 to 2.75)	2.58 (2.39 to 2.77)		
Average across all post-baseline visits	0.62 (0.44 to 0.81)	0.91 (0.73 to 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale

End point title	Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale

End point description:

The proportion of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29 was tabulated. The difference in severity category distribution between treatment groups at Day 15 and Day 29 was examined using proportional-odds cumulative logit model.
The 7- point Ordinal scale is as follows:
1) Death;
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen;
6) Not hospitalized, limitation on activities;
7) Not hospitalized, no limitations on activities.

End point type	Secondary

End point timeframe:

At Day 15 and Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Percentage of subjects				
number (not applicable)				
Day 15: Scale 1	0.0	0.0		
Day 15: Scale 2	0.0	0.0		
Day 15: Scale 3	2.3	0.0		
Day 15: Scale 4	2.3	6.3		
Day 15: Scale 5	4.5	8.3		
Day 15: Scale 6	6.8	8.3		
Day 15: Scale 7	84.1	77.1		
Day 29: Scale 1	0.0	0.0		
Day 29: Scale 2	0.0	0.0		
Day 29: Scale 3	0.0	0.0		
Day 29: Scale 4	4.3	2.1		
Day 29: Scale 5	2.2	0.0		
Day 29: Scale 6	6.5	17.0		
Day 29: Scale 7	87.0	80.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to sustained normalization of temperature and proportion of patients with normalization of fever at all time points, defined as temperature < 36.6 °C armpit, < 37.2 °C oral, or < 37.8 °C rectal sustained for at least 24 hours

End point title	Time to sustained normalization of temperature and proportion

	of patients with normalization of fever at all time points, defined as temperature < 36.6 °C armpit, < 37.2 °C oral, or < 37.8 °C rectal sustained for at least 24 hours

End point description:

Sustained normalization of temperature is defined as the temperature <36.6 ºC armpit (axillary), <37.2 ºC oral, or <37.8 ºC rectal sustained for at least 24 hours through Day 29.
The value '2' for 25th Percentile CI% is not correct and represents "not estimable value". Validation error occurs if I use any other value than "2".

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (confidence interval 95%)				
25th Percentile	2 (2 to 3)	2 (2 to 2)		
50th Percentile (Median)	3 (3 to 4)	2 (2 to 3)		
75th Percentile	6 (4 to 9)	4 (3 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS)

End point title	Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS)

End point description:

Berlin criteria for ARDS was assessed on Day 1, 5, 15, and 29. The presence of ARDS and the degree of ARDS by Berlin criteria (Mild, Moderate, Severe) was tabulated by treatment group at each visit.

End point type	Secondary

End point timeframe:

On Day 1, 5, 15, and 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Number of subjects				
Baseline	0	0		
Day 5	0	5		

Day 15	1	0		
Day 29	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of time to clinical progression (defined as the time to death, mechanical ventilation, or ICU admission)

End point title	Length of time to clinical progression (defined as the time to death, mechanical ventilation, or ICU admission)

End point description:

Clinical progression is defined as death, start of mechanical ventilation, or ICU admission through Day 29, whichever occurred first. The time to clinical progression was estimated using the KM method. '999999' represents Not Estimable.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Intention to Treat: IVIG + SMT	Intention to Treat: SMT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (confidence interval 95%)				
25th Percentile	999999 (999999 to 999999)	999999 (999999 to 999999)		
50th Percentile (Median)	999999 (999999 to 999999)	999999 (999999 to 999999)		
75th Percentile	999999 (999999 to 999999)	999999 (999999 to 999999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 29

Adverse event reporting additional description:

Safety population included subjects who received any amount of Flebogamma DIF in addition to SMT. For the SMT alone arm, the Safety population included all subjects randomized to this arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Intravenous Immune Globulin + Standard Medical Treatment

Reporting group description:

Subjects in the Intravenous Immune Globulin + Standard Medical Treatment (IVIG + SMT) arm received high dose intravenous immune globulin (IVIG), Flebogamma DIF plus standard medical treatment (SMT) based on their research study center's standard practices for the management of COVID-19 patients.

Reporting group title	Standard Medical Treatment

Reporting group description:

Subjects in the standard medical treatment (SMT) arm received medical care based on their research study center's standard practices for the management of COVID-19 patients.

Serious adverse events	Intravenous Immune Globulin + Standard Medical Treatment	Standard Medical Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Intravenous Immune Globulin + Standard Medical Treatment	Standard Medical Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 47 (61.70%)	25 / 50 (50.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 47 (4.26%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Phlebitis			
subjects affected / exposed	2 / 47 (4.26%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Secondary hypertension			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 47 (4.26%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 47 (4.26%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Face oedema			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Infusion site extravasation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Acute respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Lung infiltration			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Organising pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Sputum discoloured			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	3 / 47 (6.38%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Confusional state			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Investigations			
Transaminases increased			
subjects affected / exposed	3 / 47 (6.38%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Interleukin level increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Sinus tachycardia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 47 (10.64%)	2 / 50 (4.00%)	
occurrences (all)	5	2	
Dizziness			
subjects affected / exposed	1 / 47 (2.13%)	2 / 50 (4.00%)	
occurrences (all)	1	2	

Paraesthesia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 47 (8.51%)	1 / 50 (2.00%)	
occurrences (all)	4	1	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Hepatitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hepatitis acute			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 47 (4.26%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	1 / 47 (2.13%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 47 (2.13%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Bronchitis haemophilus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Fungal disease carrier			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Gingivitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Infected skin ulcer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Nosocomial infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Hyponatraemia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Dyslipidaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypophosphataemia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2020	The purpose of this amendment was to: - Reduce the frequency of safety due diligence interim analyses to one instance at approximately 50 patients (25/group) for simplicity without adjustments given exploratory, pilot nature of study. - Add analysis of concomitant and potentially COVID-19 disease modifying treatments between arms. - Emphasize importance of recording concomitant, potentially COVID-19 disease modifying treatments during the study. - Provide additional detail to describe nature of specimen to be obtained for quantitative viral load.
27 May 2020	The purpose of this amendment was to: - Clarify broader window for documented positive COVID-19 test results and emphasizing allowance for other commercial/public health assays for documentation of COVID-19 diagnosis. - Expand the window or documented positive test results in order to avoid limitations due to the timing of test procedures.
25 June 2020	The purpose of this amendment was to: - Modify eligibility criteria reflective of COVID-19 patient population recently admitted to hospital. Provision of table to derive PaO2/FiO2 ratio using SpO2 (if patient not on mechanical ventilation in absence of blood gas). - Indicate that Daily Assessments for Day 6 through Day 10 are required for as long as subjects are hospitalized, to clarify in-hospital daily evaluations. The Day 5±1 day assessments including laboratory parameters and Berlin criteria are mandatory to be performed for all subjects, and this is important because it also corresponds potentially to the last day of Flebogamma DIF infusion in the combination arm.

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.

None reported

Notes: