Clinical trial results:
Use of Defibrotide to reduce progression of acute respiratory failure rate in
patients with COVID-19 pneumonia

Summary

EudraCT number	2020-001513-20
Trial protocol	IT
Global end of trial date	25 January 2022

Results information

Result version number	v1 (current)
This version publication date	28 October 2022
First version publication date	28 October 2022
Summary attachment (see zip file)	AR-ASH Abstract (AR-ASH Abstract-fin.pdf)

Trial information

Trial identification

Sponsor protocol code	DEFI-VID19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04335201
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IRCCS OSPEDALE SAN RAFFAELE
Sponsor organisation address	VIA OLGETTINA 60, MILAN, Italy,
Public contact	URC-SCP, IRCCS Ospedale San Raffaele, +39 0226434289, urc.scp@hsr.it
Scientific contact	URC-SCP, IRCCS Ospedale San Raffaele, +39 0226434289, urc.scp@hsr.it
Sponsor organisation name	IRCCS OSPEDALE SAN RAFFAELE
Sponsor organisation address	VIA OLGETTINA 60, MILAN, Italy,
Public contact	UFFICIO SPERIMENTAZIONI CLINICHE, IRCCS OSPEDALE SAN RAFFAELE , +39 0226434289, urc.ul@hsr.it
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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	25 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2021
Global end of trial reached?	Yes
Global end of trial date	25 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the treatment with Defibrotide administered intravenously in addition to the best available therapy according to institutional guidelines is able to reduce the progression of acute respiratory failure, the need of mechanical ventilation, the transfer to the intensive care unit or death, in patients with severe COVID-19 pneumonia

Protection of trial subjects:

The patient’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (Low n. 675/1996 and amendments) and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
An identification number will be automatically attributed to each patient enrolled in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, date of birth will also be reported on forms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2020
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	Italy: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From May 2020 to May 2021 , we enrolled 52 patients consecutive hospitalized with COVID-19 acute pneumonia with and without ARDS/CPAP dependency.

Pre-assignment

Screening details:

Both male and female were included (>18 years), each with documented COVID-19 pneumonia defined as upper respiratory tract specimen (nasopharyngeal swab (NPS) or viral throat swab) positive for COVID-19 and/or imaging at computed tomography scan suggestive of COVID-19 pneumonia. Written informed consent.

Period 1

Period 1 title	Overll Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Defibrotide

Arm description:

Patients will be treated according to the standard institutional procedures and will receive the best available treatment as per institutional guidelines in association with the experimental drug: Defibrotide 25 mg/kg body weight total dose in 2 hours duration infusion each, every 6 hours (Defibrotide 6.25 mg/kg body
weight each dose).Treatment duration = 14 days
Any medication that the participant is receiving at the time of enrollment or receives during the study must be recorded indicating the reason for use, the dates of administration including start and end dates and dosage information including dose and frequency.

Arm type	Experimental
Investigational medicinal product name	Defibrotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Defibrotide 25 mg/kg body weight total dose in 2 hours duration infusion each, every 6 hours (Defibrotide 6.25 mg/kg body weight each dose)
Treatment duration = 14 days

Number of subjects in period 1	Defibrotide
Started	52
Completed	34
Not completed	18
Adverse event, serious fatal	8
Consent withdrawn by subject	2
Adverse event, non-fatal	6

screening failure	2

Baseline characteristics

Reporting groups

Reporting group title	Overll Trial

Reporting group description: -

Reporting group values	Overll Trial	Total	
Number of subjects	52	52	
Age categorical Units: Subjects			
Adults (18-64 years)	42	42	
From 65-84 years	10	10	
Age continuous Units: years			
median	60.5		
full range (min-max)	53 to 71	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	35	35	

Subject analysis sets

Subject analysis set title	Primary endpoint
Subject analysis set type	Full analysis

Subject analysis set description:

The percentage of subjects with respiratory rate failure at day+14 will be estimated and will be reported along with the corresponding 95% Confidence Intervals (CI).

Subject analysis set title	Secondary endpoints
Subject analysis set type	Full analysis

Subject analysis set description:

The time to event endpoints will be described using the Kaplan-Meier approach and estimates at pre-defined time points will be obtained along with 95%Cis.
Continuous variables will be summarized with indices of location (i.e. mean or median) and dispersion (i.e. standard deviation or interquartile range), as appropriate. All relevant estimates will be reported with the corresponding 95% Confidence Intervals (CI). As for safety analysis, the number of ADR (expected/unexpected) and SAEs (expected/unexpected and/or related/not related) and the percentage of subjects experiencing ADR and SAEs in the 3 months of observation of the study will be summarized by severity and within body system involved. Narratives will also be presented. The rate of occurrence of these events will also be estimated. The same approach will be used for the analysis of infections.Subgroup analyses and regression models (i.e. logistic model on proportions and Cox model on time to event outcomes) will be perform.

Reporting group values	Primary endpoint	Secondary endpoints	
Number of subjects	48	48	
Age categorical Units: Subjects			
Adults (18-64 years)	34	34	
From 65-84 years	0	0	

Age continuous Units: years			
median	60.5	60.5	
full range (min-max)	53 to 71	53 to 71	
Gender categorical Units: Subjects			
Female	8	8	
Male	26	26	

End points

End points reporting groups

Reporting group title	Defibrotide

Reporting group description:

Patients will be treated according to the standard institutional procedures and will receive the best available treatment as per institutional guidelines in association with the experimental drug: Defibrotide 25 mg/kg body weight total dose in 2 hours duration infusion each, every 6 hours (Defibrotide 6.25 mg/kg body
weight each dose).Treatment duration = 14 days
Any medication that the participant is receiving at the time of enrollment or receives during the study must be recorded indicating the reason for use, the dates of administration including start and end dates and dosage information including dose and frequency.

Subject analysis set title	Primary endpoint
Subject analysis set type	Full analysis

Subject analysis set description:

The percentage of subjects with respiratory rate failure at day+14 will be estimated and will be reported along with the corresponding 95% Confidence Intervals (CI).

Subject analysis set title	Secondary endpoints
Subject analysis set type	Full analysis

Subject analysis set description:

The time to event endpoints will be described using the Kaplan-Meier approach and estimates at pre-defined time points will be obtained along with 95%Cis.
Continuous variables will be summarized with indices of location (i.e. mean or median) and dispersion (i.e. standard deviation or interquartile range), as appropriate. All relevant estimates will be reported with the corresponding 95% Confidence Intervals (CI). As for safety analysis, the number of ADR (expected/unexpected) and SAEs (expected/unexpected and/or related/not related) and the percentage of subjects experiencing ADR and SAEs in the 3 months of observation of the study will be summarized by severity and within body system involved. Narratives will also be presented. The rate of occurrence of these events will also be estimated. The same approach will be used for the analysis of infections.Subgroup analyses and regression models (i.e. logistic model on proportions and Cox model on time to event outcomes) will be perform.

Primary: The Respiratory-failure rate

End point title	The Respiratory-failure rate[1]

End point description:

End point type	Primary

End point timeframe:

The rate will be calculated as the proportion of patients who experienced at least one of the events above by day+14 from treatment start

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses complete we have.
The incidence of RFR at day 14 was 25 (+/- 6)%, and at day 28, 27 (+/- 6)%.

End point values	Defibrotide	Primary endpoint		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	48	48		
Units: percent				
number (confidence interval 95%)	25 (19 to 31)	25 (19 to 31)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: from day 0 to day 60	
Adverse event reporting additional description: -patients' chart -laboratory reports -doctor's letter -nurses documentation	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were not recorded.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2020	With reference to the AIFA press release "Management of clinical trials in Italy in progress COVID-19 emergency (coronavirus disease 19) (Version 2 of 7 April 2020) ", per adding centers to clinical trials already approved exclusively for COVID-19 studies, we proceed by submitting a substantial amendment "Previous". The date indicated as the date of the opinion of the Satellite Ethics Committee interested is the one in which it was decided to include the new center.
29 June 2020	Change of Principal Investigator Satellite Clinical Center IRCCS Foundation Polyclinic San Matteo of Pavia.
21 April 2021	The substantive amendment request concerns the new DEFI-VID19 Protocol, Version 4.0 dated March 25, 2021.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported