Clinical trial results:
Efficacy of infusions of mesenchymal stem cells from Wharton jelly in the moderate to severe SARS-Cov-2 related acute respiratory distress syndrome (COVID-19) : A Phase IIa double-blind randomized controlled trial
Brief name : MSC-COVID19

Summary

EudraCT number	2020-002772-12
Trial protocol	FR
Global end of trial date	01 September 2021

Results information

Result version number	v1 (current)
This version publication date	19 October 2023
First version publication date	19 October 2023

Trial information

Trial identification

Sponsor protocol code	2020PI088

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04625738
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHRU de NANCY
Sponsor organisation address	29 avenue du Maréchal de Lattre de Tassigny - CO 60034, NANCY Cedex, France, 54035
Public contact	Project Manager, Délégation à la Recherche Clinique et à l'Innovation, 0033 383155286, dripromoteur@chru-nancy.fr
Scientific contact	Project Manager, Délégation à la Recherche Clinique et à l'Innovation, 0033 383155286, dripromoteur@chru-nancy.fr

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	02 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2021
Global end of trial reached?	Yes
Global end of trial date	01 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate efficacy of WJ-MSCs, compared to a placebo, on respiratory function in patients with SARS-CoV-2 related moderate to severe ARDS.

Protection of trial subjects:

Patients were included in emergency situation.
The involved risks are minor compared to the expected benefit.
The standard of care for COVID-19 was at the discretion of the physicians. The use of corticosteroids, vasopressors, tocilizumab, and antibiotics was allowed.

Background therapy: -

Evidence for comparator:

In the control group, patients were assigned to receive three infusions of placebo (albumin 4%, NaCl 0.9%, and ACD formula A, 75 to 100 mL) with an interval of two days between two infusions.

Actual start date of recruitment	10 November 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	17
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted between 10 Nov 2020 (first inclusion) and 01 Sep 2021 (last patient last visit) in 2 French intensive care units (ICUs), in the Nancy University Hospital. The patients admitted in ICUs were included in emergency situation with inclusion/exclusion criteria verification.

Pre-assignment

Screening details:

Not applicable

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Patients were randomly assigned in a 1:1 ratio to receive either WJ-MSCs plus standard of care (experimental group) or placebo plus standard of care (control group).
Randomization was performed using a computer-generated allocation sequence, with permuted blocks of four and stratified according to the PaO2 / FiO2 ratio at inclusion (≤ 100 or > 100).

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental group

Arm description:

Patients were assigned to receive three infusions of WJ-MSCs at a total dose of 2. 106/ kg, in a solution of albumin 4% (40% of final volume), NaCl 0,9% (50% of final volume), and ACD formula A (10% of final volume).
This treatment was planned to be administered intravenously for ten minutes according to the following scheme:
- 1x106 MSC/kg of body weight (with a maximum of 80x106 MSC) at day 0 (or day 1) of inclusion,
- then two infusions 0.5x106 MSC/kg (with a maximum of 40x106 MSC) with an interval of 48 hours (+/- 5 hours) minimum and 72 hours (+/- 5 hours) maximum between each injection. The maximum duration of treatment is 7 days.

Arm type	Experimental
Investigational medicinal product name	Mesenchymal Stem Cells (MSCs) from wharton jelly
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 injections over a period of 7 days

Investigational medicinal product name	VIALEBEX 40 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Included in the 3 injections of MSCWJ suspension
Total dose : 225 ml
Concentration : 40 g/l

Investigational medicinal product name	Chlorure de Sodium 0.9 %, solution pour perfusion
Investigational medicinal product code	
Other name	SODIUM CHLORIDE SOLUTION 0.9%
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Included in CSMWJ suspension
Total dose = 0.9 %

Investigational medicinal product name	ACD formule A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Included in MSCWJ suspension
Total dose = 10 %
Medical device ANTICOAGULANT CITRATE DEXTROSE A : monohydrate citric acid, trisodium citrate dihydrate and glucose solution

Arm title	Control group

Arm description:

Patients were assigned to receive three infusions of placebo (albumin 4%, NaCl 0.9%, and ACD formula A, 75 to 100 mL) according to the same scheme as the experimental group.

Arm type	Placebo
Investigational medicinal product name	Chlorure de Sodium 0.9 %, solution pour perfusion
Investigational medicinal product code	
Other name	SODIUM CHLORIDE SOLUTION 0.9%
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Total dose = 0.9 %
50% of final volume

Investigational medicinal product name	ACD formule A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Total dose = 10 %
10% of final volume
Medical device ANTICOAGULANT CITRATE DEXTROSE A : monohydrate citric acid, trisodium citrate dihydrate and glucose solution

Investigational medicinal product name	VIALEBEX 40 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Total dose : 225 ml
Concentration : 40 g/l

Number of subjects in period 1	Experimental group	Control group
Started	15	15
Completed	11	10
Not completed	4	5
Adverse event, serious fatal	3	3
Consent withdrawn by subject	1	2

Baseline characteristics

Reporting groups

Reporting group title	Experimental group

Reporting group description:

Patients were assigned to receive three infusions of WJ-MSCs at a total dose of 2. 106/ kg, in a solution of albumin 4% (40% of final volume), NaCl 0,9% (50% of final volume), and ACD formula A (10% of final volume).
This treatment was planned to be administered intravenously for ten minutes according to the following scheme:
- 1x106 MSC/kg of body weight (with a maximum of 80x106 MSC) at day 0 (or day 1) of inclusion,
- then two infusions 0.5x106 MSC/kg (with a maximum of 40x106 MSC) with an interval of 48 hours (+/- 5 hours) minimum and 72 hours (+/- 5 hours) maximum between each injection. The maximum duration of treatment is 7 days.

Reporting group title	Control group

Reporting group description:

Patients were assigned to receive three infusions of placebo (albumin 4%, NaCl 0.9%, and ACD formula A, 75 to 100 mL) according to the same scheme as the experimental group.

Reporting group values	Experimental group	Control group	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	61	66	
inter-quartile range (Q1-Q3)	49 to 66	61 to 70	-
Gender categorical Units: Subjects			
Female	2	8	10
Male	13	7	20
Comorbidities : Chronic heart failure Units: Subjects			
Yes	0	1	1
No	15	14	29
Comorbisities : HTA Units: Subjects			
Yes	5	10	15
No	10	5	15
Comorbidities : Diabetes Units: Subjects			

Yes	3	4	7
No	12	11	23
Invasive mechanical ventilation Units: Subjects			
Yes	15	15	30
No	0	0	0
Prone positioning Units: Subjects			
Yes	7	7	14
No	8	8	16
Corticosteroids Units: Subjects			
Yes	6	9	15
No	9	6	15
Vasopressors Units: Subjects			
Yes	6	7	13
No	9	8	17
Renal replacement therapy Units: Subjects			
Yes	0	0	0
No	15	15	30
BMI Units: kg/m²			
median	30	34	
inter-quartile range (Q1-Q3)	27 to 35	32 to 36	-
Symptoms duration Units: Days			
median	9	7	
inter-quartile range (Q1-Q3)	5 to 11	4 to 13	-
SAPS II Units: other			
median	31	41	
inter-quartile range (Q1-Q3)	25 to 42	34 to 47	-
SOFA Units: other			
median	4	5	
inter-quartile range (Q1-Q3)	3 to 6	3 to 8	-
Pa02/Fi02 Units: other			
arithmetic mean	138	137	
standard deviation	± 49	± 36	-
PEEP Units: cmH20			
median	13	12.5	
inter-quartile range (Q1-Q3)	12 to 15	10 to 14	-
Compliance Units: mL/cmH2O			
median	38	33	
inter-quartile range (Q1-Q3)	32 to 50	27 to 39	-

End points

End points reporting groups

Reporting group title	Experimental group
Reporting group description:	
Patients were assigned to receive three infusions of WJ-MSCs at a total dose of 2. 106/ kg, in a solution of albumin 4% (40% of final volume), NaCl 0,9% (50% of final volume), and ACD formula A (10% of final volume). This treatment was planned to be administered intravenously for ten minutes according to the following scheme: - 1x106 MSC/kg of body weight (with a maximum of 80x106 MSC) at day 0 (or day 1) of inclusion, - then two infusions 0.5x106 MSC/kg (with a maximum of 40x106 MSC) with an interval of 48 hours (+/- 5 hours) minimum and 72 hours (+/- 5 hours) maximum between each injection. The maximum duration of treatment is 7 days.	
Reporting group title	Control group
Reporting group description:	
Patients were assigned to receive three infusions of placebo (albumin 4%, NaCl 0.9%, and ACD formula A, 75 to 100 mL) according to the same scheme as the experimental group.	

Primary: Percentage of patients with a PaO2/FiO2 ratio > 200 at D10 of treatment with MSC-GW or placebo

End point title	Percentage of patients with a PaO2/FiO2 ratio > 200 at D10 of treatment with MSC-GW or placebo
End point description:	

End point type	Primary
End point timeframe:	
at D10 of treatment with MSC-GW or placebo	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	13		
Units: number				
PaO2/FiO2 ratio > 200	2	2		
PaO2/FiO2 ratio <= 200	9	11		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [1]
Method	Fisher exact

Notes:

[1] - No significant difference between the two groups has been detected in our sample.

Primary: Percentage of patients with a PaO2/FiO2 ratio > 200 at D10 of treatment with MSC-GW or placebo (imputed)

End point title	Percentage of patients with a PaO2/FiO2 ratio > 200 at D10 of treatment with MSC-GW or placebo (imputed)

End point description:

If patient did not have the value at D10 (hospital discharge before D10 for example), the last collected value was taken.

End point type	Primary

End point timeframe:

at D10 of treatment

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
PaO2/FiO2 <=200	10	11		
PaO2/FiO2 > 200	5	4		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [2]
Method	Fisher exact

Notes:

[2] - No significant difference between the two groups was detected in our sample.

Secondary: respiratory function evolution

End point title	respiratory function evolution

End point description:

As it is not possible to indicate evolution of a parameter, baseline PaO2/FiO2 was described in each group.
Analysis indicated concerned the evolution of PaO2/FiO2.

End point type	Secondary

End point timeframe:

During the 14 days following the first injection (between D0 or D1 and D13 or D14)

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: other				
arithmetic mean (standard error)	138.5 (± 49.3)	137.1 (± 36)		

Attachments (see zip file)	Evolution of PaO2/FiO2 between the two groups/Graphique

Statistical analyses

Statistical analysis title	Repeated mesure ANOVA
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [3]
Method	Repeated mesure ANOVA

Notes:

[3] - The p-value indicates that no difference about evolution of PaO2/FiO2 between the first 14 days after the first injection was detected in our sample between experimental or control group.

Secondary: Respiratory assistance

End point title	Respiratory assistance

End point description:

the proportion of days without invasive respiratory assistance during the hospital stay and maximum on Day 28 (number of days without invasive respiratory assistance / number of hospital days fixed at day 28)

End point type	Secondary

End point timeframe:

between day 0 (or 1) and day 28

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: percent				
arithmetic mean (standard deviation)	41.93 (± 36.59)	24.2 (± 30.97)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - No significant difference between the two groups was detected in our sample.

Secondary: Organ failure 1 : SOFA change D14 - D0

End point title	Organ failure 1 : SOFA change D14 - D0

End point description:

Difference in sequential organ failure assessment score (SOFA score), grading 0 (best) to 4 (worst), between D14-Day 0

End point type	Secondary

End point timeframe:

Day 0 to day 14

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: other				
median (inter-quartile range (Q1-Q3))	-1 (-2 to 0)	-2.5 (-4 to -0.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - No significant difference between the two groups was detected in our sample.

Secondary: organ failures 2 : proportion of days without extra-renal treatment at day 28

End point title	organ failures 2 : proportion of days without extra-renal treatment at day 28

End point description:

proportion of days without extra-renal treatment during 28 first days

End point type	Secondary
End point timeframe: day 0 to day 28	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: other				
median (inter-quartile range (Q1-Q3))	100 (100 to 100)	100 (100 to 100)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - No significant difference between the two groups was detected in our sample.

Secondary: organ failures 3 : vasopressor support	
End point title	organ failures 3 : vasopressor support
End point description: Percent of days without vasopressor support during the first 28 days	
End point type	Secondary
End point timeframe: day 0 to day 28	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: other				
median (inter-quartile range (Q1-Q3))	90 (69 to 97)	86 (72 to 97)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - No significant difference between groups was detected in our sample.

Secondary: Duration of intensive care

End point title	Duration of intensive care

End point description:

The duration of stay in intensive care unit

End point type	Secondary

End point timeframe:

day 0 to 90

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: days				
median (inter-quartile range (Q1-Q3))	19 (12 to 30)	23 (13 to 42)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - No significant difference between groups was detected in our sample.

Secondary: Death at D90

End point title	Death at D90

End point description:

number of death on Day 90 was described for the two groups.
Log rank test with a Kaplan Meier curve was performed to detect a difference between the two groups.

End point type	Secondary

End point timeframe:

day 0 to 90

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number	3	3		

Attachments (see zip file)	Death at D90 - Kaplan-Meier curve/Figure 3 KM_publi_V2.pdf

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92 [9]
Method	Logrank

Notes:
[9] - No significant difference between groups was detected in our sample.

Secondary: respiratory morbidity at Day 90

End point title	respiratory morbidity at Day 90
End point description: respiratory morbidity on Day 90	
End point type	Secondary
End point timeframe: day 90	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: number				
Yes	13	12		
No	2	2		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [10]
Method	Fisher exact

Notes:

[10] - No significant difference between groups was detected in our sample.

Secondary: viral load

End point title	viral load

End point description:

he evolution of the viral load is evaluated by RT PCR SARS-Cov-2 monitoring on a nasopharyngeal swab (or any other sample) at diagnosis, at Day 7, Day 14, Day 21, Day 28 or on the last day of hospitalisation

End point type	Secondary

End point timeframe:

day 0 to day 28 (or last day of hospitalization if before day 28)

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: number				
Positive	10	8		
Negative	3	7		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [11]
Method	Fisher exact

Notes:

[11] - No significant difference between groups was detected in our sample.

Secondary: Anti-HLA antibody rate

End point title	Anti-HLA antibody rate

End point description:

The anti-HLA antibody rate measured on Day 0 (before initiating treatment), on Day 28 and on Day 90 The rate on Day 90 was described.

End point type	Secondary

End point timeframe:
day 0 to day 90

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: number				
Yes	2	0		
No	8	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Immediate hypersensitivity reactions

End point title	Immediate hypersensitivity reactions

End point description:

The number of patients with at least one reaction of immediate hypersensitivity occuring after one of the three injections was described.

End point type	Secondary

End point timeframe:

After each injection day 0, day 3, day 5 (+/- 1day)

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
Yes	10	15		
No	5	0		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [12]
Method	Fisher exact

Notes:

[12] - The CSM group does not present more immediate hypersensitivity reactions than the placebo group.
The Fisher exact test is significativ but in defavor of the placebo group.

Secondary: Severity of respiratory morbidity

End point title	Severity of respiratory morbidity

End point description:

End point type	Secondary

End point timeframe:

At D90

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: number				
Non severe	3	1		
Moderate	1	1		
Severe	4	2		
Very severe	5	8		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61 [13]
Method	Fisher exact

Notes:

[13] - No significant difference between the two groups has been detected in our sample.

Secondary: Thromboembolic adverse events

End point title	Thromboembolic adverse events

End point description:

See adverse events section for this endpoint

End point type	Secondary

End point timeframe:

During follow-up

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
Yes	4	3		
No	11	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Infectious adverse events

End point title	Infectious adverse events

End point description:

See adverse events section for this endpoint.

End point type	Secondary

End point timeframe:

During follow-up

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number				
Yes	9	9		
No	6	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Angiopoietin 2 change

End point title	Angiopoietin 2 change

End point description:

End point type	Other pre-specified

End point timeframe:

The change is evaluated between the day after the third injection and the day before the first injection

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	914 (183 to 3037)	105 (-715 to 1471)		

Statistical analyses

Statistical analysis title	Mann-Whitney
Comparison groups	Experimental group v Control group
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - No significant difference between the two groups was detected in our sample.

Other pre-specified: RAGE change

End point title	RAGE change

End point description:

End point type	Other pre-specified

End point timeframe:

RAGE change between the day after the last injection and the day before the first infection

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	-2656 (-3761 to -1599)	-5469 (-9859 to -1801)		

Statistical analyses

Statistical analysis title	Fisher Exact test
Comparison groups	Experimental group v Control group

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - No significant difference between the two groups was detected in our sample.

Other pre-specified: CRP evolution

End point title	CRP evolution

End point description:

CRP at Day 1 was described between groups.
Evolution of CRP for the two groups is shown in a chart.

End point type	Other pre-specified

End point timeframe:

Evolution of CRP is evaluated between Day 0 (or Day 1 depending on the date of first injection) and Day 13 (or Day 14)

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	109 (41 to 127)	98 (57 to 218)		

Attachments (see zip file)	Evolution of CRP/Graphique evolution CRP.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasmatic cytokines

End point title	Plasmatic cytokines

End point description:

Description of galectine 9 before the first infection is described.
Violon plot for each cytokines before the first infection an at Day10 is shown : galectine-9, LAP, galectine-3, il10, IL1 alpha, IP10, IFN gamma, IL6, IL8, TNF alpha, VEGF A

End point type	Other pre-specified

End point timeframe:

The day before first injection and Day 10

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: unit				
median (inter-quartile range (Q1-Q3))	29.5 (18.3 to 45.1)	28.9 (13.5 to 45.3)		

Attachments (see zip file)	Plasmatic cytokins/graphiques_cytokines_bygroupe - EUDRA

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Evolution of lymphocyte sub-population

End point title	Evolution of lymphocyte sub-population

End point description:

Description of CD3 before the first infection is described.
Charts of evolution of lymphocyte sub-population by groups is joined

End point type	Other pre-specified

End point timeframe:

The day before the first injection, Day 3, Day 5, Day 7, Day10, Day 14 and Day 28

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: /mm3				
median (inter-quartile range (Q1-Q3))	0.37 (0.30 to 0.71)	0.5 (0.37 to 0.67)		

Attachments (see zip file)	Evolution of lymphocyte sub-

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE and SAE were collected and transmitted without delay to the sponsor from the enrollment until the end of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	experimental group

Reporting group description:

administration of allogeneic mesenchymal stem cells from Wharton's Jell

Reporting group title	control group

Reporting group description:

administration of a placebo

Serious adverse events	experimental group	control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	7 / 15 (46.67%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events	4	2	
Vascular disorders			
Shock			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			

subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bradycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer perforation			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Brain abscess			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Peritonitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fungal peritonitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyopneumothorax			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
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	experimental group	control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	14 / 15 (93.33%)	
Vascular disorders			
Cyanosis			
subjects affected / exposed	5 / 15 (33.33%)	1 / 15 (6.67%)	
occurrences (all)	5	1	
Haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Hypertension			
subjects affected / exposed	5 / 15 (33.33%)	3 / 15 (20.00%)	
occurrences (all)	7	5	
Hypotension			
subjects affected / exposed	5 / 15 (33.33%)	2 / 15 (13.33%)	
occurrences (all)	9	3	
Thrombosis			
subjects affected / exposed	4 / 15 (26.67%)	3 / 15 (20.00%)	
occurrences (all)	4	3	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Respiratory distress			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Emphysema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Pulmonary fibrosis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Hypoventilation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Lung opacity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pneumomediastinum			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	2	
Snoring			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Delirium tremens			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device occlusion			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	3 / 15 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Blood sodium increased			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Eschar			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Acute coronary syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Neurological decompensation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Neuromyopathy			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy			
subjects affected / exposed	2 / 15 (13.33%)	4 / 15 (26.67%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 15 (26.67%)	3 / 15 (20.00%)	
occurrences (all)	6	4	
Iron deficiency anaemia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Eosinophilia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 15 (40.00%)	5 / 15 (33.33%)	
occurrences (all)	7	5	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dysphagia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Melaena			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Peptic ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Livedo reticularis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Rash			

subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 15 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Bladder dilatation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Acute kidney injury			
subjects affected / exposed	0 / 15 (0.00%)	5 / 15 (33.33%)	
occurrences (all)	0	5	
Endocrine disorders			
Glucocorticoid deficiency			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Fungal infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nosocomial infection			
subjects affected / exposed	9 / 15 (60.00%)	9 / 15 (60.00%)	
occurrences (all)	12	14	
Paronychia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Hyperkalaemia			
subjects affected / exposed	3 / 15 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Hyperlactacidaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypernatraemia			
subjects affected / exposed	4 / 15 (26.67%)	4 / 15 (26.67%)	
occurrences (all)	4	4	
Hypocalcaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	4 / 15 (26.67%)	5 / 15 (33.33%)	
occurrences (all)	12	13	
Hypophosphataemia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypovolaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Granuloma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Medical device site haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	6 / 15 (40.00%)	3 / 15 (20.00%)	
occurrences (all)	8	4	
Oedema			
subjects affected / exposed	4 / 15 (26.67%)	4 / 15 (26.67%)	
occurrences (all)	4	4	
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2020	Change on principal investigator in one of the 2 investigator sites
18 January 2021	Reasons: Increase inclusion opportunities by simplifying the study process. Allow close monitoring by adding biological analyses to the protocol Improve the feasibility of surveillance Description of the changes Biological assays, procedures, and measurements, which were planned on a routine basis, become systematic to allow close monitoring, at the request of the Independent Monitoring Board. The evaluation criterion on thromboembolic risks, relating to secondary objective No. 5, is thus adapted. The injection dates have been reworded, thus expanding the possible days for inclusion. This increases the exposure time to the investigational drug from 6 to 7 days. The inclusion criteria have been clarified: a negative ßHCG test must be obtained for any woman under 60 years of age; only long-term immunosuppressive treatment (not ongoing) is a non-inclusion criterion. Concerning the release of the final product, and in particular the count: the number of cells obtained after defrosting and before injection to the patient In case the dose of 1.106 MSC/kg or 0.5.106 MSC/kg of patient weight cannot be reached, it was decided ito give preference to the administration of 3 injections whatever the number of cells, without exceeding the maximum defined dosage. These changes have no impact on the safety of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported