Clinical trial results:
Study of efficacy of low-dose recombinant human interleukin-2 in immunological changes associated with depression (IL2REG)

Summary

EudraCT number	2019-001696-36
Trial protocol	IT
Global end of trial date	06 April 2023

Results information

Result version number	v1 (current)
This version publication date	29 March 2024
First version publication date	29 March 2024

Trial information

Trial identification

Sponsor protocol code	IL2REG

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ospedale San Raffaele
Sponsor organisation address	60 Olgettina, Milano, Italy, 20132
Public contact	Psichaitria e Psicobiologia Clinica, Francesco Benedetti, hsrsanraffaele@hsr.postecert.it
Scientific contact	Psichaitria e Psicobiologia Clinica, Francesco Benedetti, hsrsanraffaele@hsr.postecert.it

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	26 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

prove the improvement of T regulatory cells response following add-on treatment with IL-2 (Aldesleukin) in patients affected by mood disorder win an ongoing depressive episode

Protection of trial subjects:

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.

These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 623 and 622 of the Italian Penal Code (R.D. 19 ottobre 1930, n. 1398)). During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.

Under no circumstances will the names and addresses of the subjects be shown.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	30 June 2019
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	Italy: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	32
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment has taken place from November 2019 to April 2023. The first patient was recruited on January 2020

Pre-assignment

Screening details:

Inclusion criteria: age 18-65 years, a depressive episode according to DSM-V criteria in the course of bipolar or major depressive disorder, a score at the MADRS> 17, and be already on an anti-depressant and/or mood stabilizer. 108 patients have been screened, 66 refused, 6 didn't met inclusion criteria

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, Carer, Assessor

Blinding implementation details:

Treatments was manufactured according to a list provided by an independent person and assigning a treatment arm to each treatment number.
• randomization lists were kept strictly confidential until the time of un-blinding, and were not accessible by anyone involved in the study;
• the treatment was administered by a physician who did not participate in any other phase of the study preventing the identification of treatment by patients, investigators and study personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	IL-2

Arm description:

Subjects treated with aldesleukin

Arm type	Experimental
Investigational medicinal product name	Aldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Injection

Dosage and administration details:

1±10% MIU/day in a volume of 0,07 ml for subcutaneous injection

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Water per injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

0.07 ml of sterile water for injection was subcutaneously injected

Number of subjects in period 1	IL-2	Placebo
Started	24	12
induction phase	24	12
maintenance phase	18	11
Completed	18	10
Not completed	6	2
Physician decision	1	-
Adverse event, non-fatal	1	-
covid lockwdown	-	2
Lost to follow-up	2	-
covid lockdown	2	-

Baseline characteristics

Reporting groups	
Reporting group title	IL-2
Reporting group description:	
Subjects treated with aldesleukin	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	IL-2	Placebo	Total
Number of subjects	24	12	36
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			
Baseline age of all subjects divided per arm			
Units: years			
arithmetic mean	52.12	48.23	
standard deviation	± 10.46	± 15.76	-
Gender categorical			
Units: Subjects			
Female	14	8	22
Male	10	4	14
MADRS			
depression severity as measured by the Montgomery–Åsberg Depression Rating Scale			
Units: points			
arithmetic mean	32.87	31.61	
standard deviation	± 7.52	± 7.47	-

Subject analysis sets	
Subject analysis set title	BD-IL2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Changes in regulatory t cells in patients with bipolar disorder treated with IL2	
Subject analysis set title	MDD-IL2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Changes in T regulatory cells in patients with Major depression treated with IL-2

Subject analysis set title	BD-Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Bipolar depressed patients treated with Placebo

Subject analysis set title	MDD-Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Changes in regulatory t cells in patients with Major depression treated with placebo

Reporting group values	BD-IL2	MDD-IL2	BD-Placebo
Number of subjects	12	12	6
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Baseline age of all subjects divided per arm			
Units: years arithmetic mean standard deviation	 53.09 ± 5.48	 16.17 ± 18.82	 50.00 ± 13.91
Gender categorical Units: Subjects			
Female	6	6	3
Male	6	6	3
MADRS			
depression severity as measured by the Montgomery–Åsberg Depression Rating Scale			
Units: points arithmetic mean standard deviation	 ±	 ±	 ±

Reporting group values	MDD-Placebo		
Number of subjects	6		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Baseline age of all subjects divided per arm			
Units: years arithmetic mean standard deviation	 46.17 ± 13.78		
Gender categorical Units: Subjects			
Female Male	3 3		
MADRS			
depression severity as measured by the Montgomery–Åsberg Depression Rating Scale			
Units: points arithmetic mean standard deviation	 ±		

End points

End points reporting groups

Reporting group title	IL-2
Reporting group description: Subjects treated with aldesleukin	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	BD-IL2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Changes in regulatory t cells in patients with bipolar disorder treated with IL2	
Subject analysis set title	MDD-IL2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Changes in T regulatory cells in patients with Major depression treated with IL-2	
Subject analysis set title	BD-Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Bipolar depressed patients treated with Placebo	
Subject analysis set title	MDD-Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Changes in regulatory t cells in patients with Major depression treated with placebo	

Primary: Change in T regulatory cells

End point title	Change in T regulatory cells
End point description: change in T regulatory cells after the induction period. delta score Day 0-Day5	
End point type	Primary
End point timeframe: baseline-day5	

End point values	IL-2	Placebo	BD-IL2	MDD-IL2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	12	12	12
Units: frequences				
arithmetic mean (standard deviation)	1.20 (± 2.36)	0.22 (± 1.24)	1.82 (± 2.38)	0.65 (± 2.30)

End point values	BD-Placebo	MDD-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: frequences				

arithmetic mean (standard deviation)	0.06 (± 1.10)	0.40 (± 1.48)		

Statistical analyses

Statistical analysis title	primary endpoint
Comparison groups	IL-2 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	LR chi-square type I test
Parameter estimate	Likelihood ratio
Point estimate	4.603
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.602
upper limit	4.604
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[1] - Homogeneity of slopes analysis within the generalized linear model, likelihood ratio method to estimate significance, per protocol sample (28 completers)
Confidence limits not available (only available for Wald estimates within the GLZM)

[2] - Confidence limits not available for LR chi square type I testing (only available for Wald estimates within the GLZM),
relevant fields have been completed with dummy numbers just to allow to go on in saving the page

Secondary: Effect of treatment on depressive symptoms

End point title	Effect of treatment on depressive symptoms
End point description:	
Changes in depressive symptoms at the end of the study	
End point type	Secondary
End point timeframe:	
Baseline-end of follow-up	

End point values	IL-2	Placebo	BD-IL2	MDD-IL2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	12	12	12
Units: points				
arithmetic mean (standard deviation)	22.83 (± 11.63)	18.75 (± 11.22)	21.36 (± 10.57)	24.07 (± 12.76)

End point values	BD-Placebo	MDD-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: points				
arithmetic mean (standard deviation)	21.00 (± 12.57)	15.60 (± 9.39)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall trial	
Adverse event reporting additional description: NA	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	patients treated with IL2
Reporting group description: All subjects treated with IL-2	

Serious adverse events	patients treated with IL2		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	patients treated with IL2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 24 (12.50%)		
General disorders and administration site conditions			
allergic reaction	Additional description: 2 mild allergic reaction which resolved spontaneously 1 mild allergic reaction which resolved with antihistamine treatment		
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial started at the beginning of 2020 in coincidence with the covid-19 pandemia. Lock-downs have affected the compliance of the patients to come to the hospital for treatment administration and controls

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38367846