Clinical trial results:
The SYNBioSe Study
A proof-of-concept study involving synergetic B-cell imunnomodulation in patients with refractory systemic lupus erythematosus

Summary

EudraCT number	2014-000488-42
Trial protocol	NL
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021
Summary attachment (see zip file)	Synbiose-1 publication (20191217 Synbiose-1 study Revision.pdf)

Trial information

Trial identification

Sponsor protocol code	P14.065

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02284984
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Leiden University Medical Center
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands, 2333 ZA
Public contact	Teng, Leiden University Medical Center, 31 715268157, y.k.o.teng@lumc.nl
Scientific contact	Teng, Leiden University Medical Center, 31 715268157, y.k.o.teng@lumc.nl

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	06 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2018
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this proof-of-concept study the primary objective is to assess whether a combination treatment ofrituximab (anti-CD20) and belimumab (anti-BAFF) will lead to a sustained reduction of pathogenic autoantibodies and thereby inhibition of NET formation, which portentially forms the basis of a new therapeutic approach in severe SLE.

Protection of trial subjects:

Within the study safety and toxicity monitoring includes:
- the recording of adverse events according to WHO Toxicity criteria
- evaluation of the time to immune reconstitution of B-cells
- the recording of infectious events, with special interest for serious infections, including herpes zoster and opportunistic infections
- Serious hypersensitivity or infusion reactions
- Malignancy
- Suicidal thought, intent or behaviour

In accordance to Good Clinical Practice (GCP) guidelines, serious adverse events and SUSARs will be reported to the METC.

In order to guarantee the feasibility of the study, the principal investigators will meet every 3 months to evaluate all adverse events (AEs). For every AE the severity and relation to the study treatment will be recorded. An advice will be formulated when an AE or a series of AEs necessitates a protocol change or a consideration to terminate the study. The METC will advise to continue the study, to implement protocol changes or to terminate this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2014
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	Netherlands: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

31 subjects were screened of which 16 patients were eligible for the study. 1 patient dropped out during screening while treated with intravenous methylprednisolone as remission induction treatment

Pre-assignment

Screening details:

the majority of SLE patients was female and had severe disease with major organ involvement. The median [range] SLEDAI was 18
[6-29] and 13 patients (81%) had active lupus nephritis (LN) with a median [range] proteinuria of 2.3 g/day [1e8.2]. One patient had
transverse myelitis at inclusion and presented with paralysis of the lower extremities.

Period 1

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

Blinding implementation details:

n.a.

Arms

Arm title	overall trial

Arm description: -

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

Dosage and administration details:

Patients will be intravenously treated with Rituximab 1000mg on day 0 and day 14. Before every infusion of Rituximab patients will receive intravenous methylprednisolon 100mg together with oral acetaminophen 1000 mg and intravenous Tavegil 2 mg

Investigational medicinal product name	belimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients will be intravenously treated with Belimumab 10mg/kg on day 28, day 42 and day 56. Thereafter, patients will receive Belimumab 10mg/kg every 4 weeks. No pre-medication is administered.

Number of subjects in period 1	overall trial
Started	15
Completed	15

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

sixteen patients(88% female) were included, with median age of 31 years[19;51]. All patients had refractory disease, of which 12(80%) had active LN at baseline. One patient experienced severe hypogammaglobulinemia at week 8 after completion of methylprednisolone and RTX, therefore BLM treatment was not initiated. This patient was excluded from the long-term follow-up study.

Reporting group values	overall trial	Total	
Number of subjects	15	15	
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	31		
full range (min-max)	19 to 51	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	1	1	

Subject analysis sets

Subject analysis set title	All subjects
Subject analysis set type	Full analysis

Subject analysis set description:

15 subjects who completed the study were included in the analysis

Reporting group values	All subjects		
Number of subjects	15		
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 Units: years median full range (min-max)	 31 19 to 51		
Gender categorical Units: Subjects			
Female Male	14 1		

End points

End points reporting groups

Reporting group title	overall trial
Reporting group description: -	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
15 subjects who completed the study were included in the analysis	

Primary: Reduction of pathogenic autoantibodies

End point title	Reduction of pathogenic autoantibodies[1]
End point description:	
Anti-dsDNA levels of 268AU/mL[50;827] at baseline decreased at week 24 to 29.6[0;104.5](p=0.02) equal to a median decrease of 87%[-100;+3].	
End point type	Primary
End point timeframe:	
- Reduction of pathogenic autoantibodies, i.e.. a sustained reduction of pathogenic autoantibodies, in particular anti-dsDNA autoantibodies, at 24 weeks after 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: This is a single-arm study with immunological endpoint compared to each subject's baseline value.
In accordance to mail correspondence: "Please note that inserting the statistical analysis related to an endpoint is not mandatory. You can delete the statistical analysis, however you need to provide a justification in the correct field"

End point values	All subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: IU/mL				
median (full range (min-max))	29.6 (0 to 104.5)			

Attachments (see zip file)	Primary endpoint adsDNA/20200316 Figure 4 Synbiose_Teng.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the complete study from 0-104 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	WHO
Dictionary version	1

Reporting groups	
Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Hospitalisation			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 15 (73.33%)		
Injury, poisoning and procedural complications			
Infusion-related reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Immune system disorders			
Hypogammglobulinemia	Additional description: IgG < 4.0 g/L		
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Infections and infestations			

Minor infection	Additional description: Upper respiratory tract 9 (60.0) Lower respiratory tract 3 (20.0) Urinary tract 4 (26.7) Urogenital infection 2 (13.3) Sinusitis 1 (6.7) Influenza 1 (6.7) Herpes simplex 1 (6.7)		
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	22		

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.

As defined by the study protocol, sujects that faile study treatment were withdrawn from the study and no further follow-up was available. In total 8/15 subjects completed 104 weeks. Hence, 7 subjects no complete follow-up of 104 weeks was recorded

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29636274