



## Clinical trial results:

### Comparison of the efficacy of two rituximab treatment regimens in patients with lupus nephropathy resistant to conventional treatment

#### Summary

EudraCT number	2011-005856-32
Trial protocol	ES
Global end of trial date	27 September 2017

#### Results information

Result version number	v1 (current)
This version publication date	28 March 2021
First version publication date	28 March 2021
Summary attachment (see zip file)	Final report of results (Informe Final-EECC-RITULUP- _27-Sep-2017_.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	RITULUP
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Fundación Pública Andaluza Progreso y Salud
Sponsor organisation address	Parque Científico y Tecnológico Cartuja, Avda. Américo Vespucio, 15. Edificio S-2. 41092 , Seville, Spain, 41092
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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	27 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2017
Global end of trial reached?	Yes
Global end of trial date	27 September 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Rate of complete or partial response to the 12, 18 and 24 months, defined as:

-Complete response: proteinuria < 0.75 mg per minute (or equivalent in 24h urine, proteinuria or urine protein/creatinine index) while maintaining estimated glomerular filtration rate or serum creatinine within the normal range.

- Partial response: improvement ? 50% and stabilization of kidney function (glomerular filtration of  $\pm$  25% compared to the basal value or serum creatinine within the normal range ).

Protection of trial subjects:

The trial will be carried out in accordance with the principles of the Declaration of Helsinki (Annex VIII), and in accordance with the current legal regulations in force (Royal Decree 223/2004), and shall not be will not commence until the approval of the IRB/IEC of reference, the agreement of the the conformity of the Directors of the Institutions, and the authorisation of the Spanish Agency for Medicines and Health Products.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2012
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: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	9
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All subjects must meet the American College of Rheumatology (ACR) criteria for LES and be diagnosed with active NL. The activity criteria will be established by biopsy (class III or IV, with or without associated class V, of NL according to the 2003 LN International Society of Nephrology/Renal Pathology Society [ISN/RPS] criteria).

### Pre-assignment

Screening details:

All subjects must meet the American College of Rheumatology (ACR) criteria for LES and be diagnosed with active NL. The activity criteria will be established by biopsy (class III or IV, with or without associated class V, of NL according to the 2003 LN International Society of Nephrology/Renal Pathology Society [ISN/RPS] criteria).

### Period 1

Period 1 title	Recruitment and follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

2 cycles 4 weekly infusions of RTX at a dose of 375 mg/m<sup>2</sup> each, intravenously (on days 0, 7, 14 and 21). The second cycle 6 months after the first cycle.

<b>Arm title</b>	Control
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Arm description: -

Arm type	Control
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 cycle of 4 weekly infusions of RTX at a dose of 375 mg/m<sup>2</sup> each, intravenously, (on days 0, 7, 14 and 21).

<b>Number of subjects in period 1</b>	Experimental	Control
Started	5	4
Completed	1	0
Not completed	4	4
Infusional reaction	-	1
Pregnancy	2	1
Lost to follow-up	2	1
Not randomised	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Recruitment and follow-up
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Reporting group description: -

Reporting group values	Recruitment and follow-up	Total	
Number of subjects	9	9	
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	9	
Age continuous			
Units: years			
arithmetic mean	40		
full range (min-max)	18 to 65	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	4	4	

## End points

### End points reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

### Primary: Response, full or partial

End point title	Response, full or partial <sup>[1]</sup> <sup>[2]</sup>
End point description:	

End point type	Primary
End point timeframe:	
12, 18 and 24 months	

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: Only one patient in the trial completed follow-up. There is therefore insufficient data available to complete this section.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only one patient in the trial completed follow-up. There is therefore insufficient data available to complete this section.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participant	1			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

During the study

Assessment type	Systematic
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### Dictionary used

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Dictionary name	Not known
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Dictionary version	1
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Frequency threshold for reporting non-serious adverse events: 4 %

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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 adverse events were reported.



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2012	<p>A secondary objective was added to assess the need to add immunosuppressive treatment to the patient's treatment. As a consequence, it was also to assess the administration of mycophenolate, azathioprine and cyclophosphamide, azathioprine and cyclophosphamide.</p> <p>The inclusion criteria were modified from a single, overly broad and confusing criterion, to four clearly defined criteria. In this In this sense, one of the criteria for withdrawal from the study was also clarified and some more criteria related to the appearance of neoplasms in the patients or the loss of follow-up due to failure to attend scheduled visits. A change was made to the glucocorticoid regimen to be administered in conjunction with rituximab. The need to use antimalarials during treatment was also introduced.</p> <p>In relation to the safety assessment, was include the different evaluations to be carried out in order to assess the safety profile of rituximab in these patients. These assessments included ECG, vital signs and laboratory tests. With regard to the safety section, this was completed with the information provided by the "Information guide on the safety of rituximab" received from the AEMPS.</p>
11 June 2012	<p>A modification was made to the wording of the main objective of the study, making it clearer. Likewise, secondary objectives that were already implicitly included in the development of the study were eliminated. As a consequence of the modifications made to the objectives, some changes were made to certain variables of the study.</p> <p>In addition to the changes in objectives and variables, minor modifications were made to the study design, with patients who had not received rituximab in the previous year being recruited instead of in the 2 years prior to inclusion in the study. Another change in the study design was the elimination of the initial cycles of cyclophosphamide administered together with rituximab. Some inclusion criteria were also modified. On the one hand, the above-mentioned change in prior rituximab treatment was modified, and on the other hand, the length of time that potentially fertile patients should use contraception was modified.</p> <p>In relation to the study design and the concomitant medication to be administered during rituximab infusions, the schedule of glucocorticoids to be administered with each rituximab infusion was modified. Likewise, the immunosuppressive regimen to be administered in case of non-response to treatment was also changed.</p> <p>Finally, various laboratory tests were added.</p>

29 October 2012	<p>In relation to the definition of complete response included among the study variables, some of the elements that make up the definition of complete response were modified, the most relevant change being the replacement of the assessment of serum creatinine level by the glomerular filtration rate. Related to this change in the assessment parameter, a change was made in one of the items that make up the definition of partial response, taking into account glomerular filtration rate instead of serum creatinine level.</p> <p>The assessment of Selena-sledai response was introduced as a secondary endpoint. In addition, partial and complete response rate at 12, 18 and 24 months was added as a secondary variable.</p> <p>In relation to the selection criteria, there was a modification in them, taking into account the diagnosis by renal biopsy in the 24 weeks prior to inclusion in the study and discarding those patients whose renal biopsy showed interstitial fibrosis/tubular atrophy and/or glomerular sclerosis greater than 50%.</p> <p>In relation to concomitant treatments, the antiproteinuric drugs and the regimen with which they are administered are modified.</p> <p>The latest changes are related to an update of the study's procedural schedule.</p>
29 January 2013	<p>This version clarified the withdrawal criterion related to loss to follow-up. To this end, the number of visits the patient should not attend in order to be considered as a loss to follow-up was specified.</p> <p>In relation to visits, the window period in which visits can take place was specified.</p> <p>Finally, the serious adverse event reporting form was eliminated as a specific form was designed for the study.</p>
03 June 2013	<p>A modification was made to the primary study criteria by extending the time periods to be taken into account for the assessment of efficacy in obtaining remission.</p> <p>The first exclusion criterion was modified to adapt it to the patients assessed in routine clinical practice. To this end, the restriction that patients had been treated with cyclophosphamide and mycophenolate was eliminated, and patients who had received at least one of the treatments could be included. Likewise, exclusion criterion 6 was modified to exclude prophylactic treatments.</p> <p>Data collection on the need for methotrexate treatment was added to the secondary variables.</p>

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.

In relation to database development and statistical analysis, given the number of patients recruited and patients withdrawn, the exploitation of the data was considered meaningless as it could not provide any data with statistical significance.

Notes: