



## Clinical trial results:

**Tratamiento con inmunoglobulinas y rituximab en el rechazo crónico humoral en el trasplante renal: estudio multicéntrico, prospectivo, randomizado y controlado con placebo.**

**Treatment with intravenous immunoglobulins and rituximab in renal transplant recipients with chronic humoral rejection: a multicentre, prospective, randomized, placebo-controlled study.**

### Summary

EudraCT number	2010-023746-67
Trial protocol	ES
Global end of trial date	30 December 2016

### Results information

Result version number	v1 (current)
This version publication date	04 December 2021
First version publication date	04 December 2021

### Trial information

#### Trial identification

Sponsor protocol code	TRITON
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, joaquin.lopez.soriano@vhir.org
Scientific contact	Francesc Moreso, VHIR, fjmoreso@vhebron.net

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	13 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of intravenous immunoglobulins (IVIG) combined with rituximab (RTX)

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and is consistent with the Principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.  
Patients with proteinuria >0.5 g/day received an angiotensin converting enzyme inhibitor/angiotensin II receptor blocker.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	25
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients eligible for the study were renal transplants with biopsy-proven chronic ABMR diagnosed less than 6 months before randomization.

Other inclusion criteria were age  $\geq 18$  years, stability of renal function defined as a decrease of eGFR  $< 15\%$  between the time of the diagnostic biopsy and the inclusion.

1 patient withdrew each group

### 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

Blinding implementation details:

A central blocked computerized random-generator was utilized to allocate patients to each group. Study drugs and placebo were wrapped to assure the double-blind procedure

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	IG + RTX

Arm description:

In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.

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

Dosage and administration details:

375 mg/m<sup>2</sup> 1 dose, 1 week after IG treatment

Investigational medicinal product name	Immunoglobulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.5 g/kg intravenous, four consecutive doses every 3 weeks

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

Arm type	Placebo
Investigational medicinal product name	Saline 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

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Dosage and administration details:

The control group received an isovolumetric saline solution, following the same schedule

<b>Number of subjects in period 1</b>	IG + RTX	Placebo
Started	12	13
Completed	11	12
Not completed	1	1
Consent withdrawn by subject	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	IG + RTX
Reporting group description:	
In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	IG + RTX	Placebo	Total
Number of subjects	12	13	25
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	47	49	
standard deviation	± 13	± 15	-
Gender categorical			
Units: Subjects			
Female	4	6	10
Male	8	7	15

## End points

### End points reporting groups

Reporting group title	IG + RTX
Reporting group description: In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.	
Reporting group title	Placebo
Reporting group description: -	

### Primary: Decline of eGFR

End point title	Decline of eGFR
End point description:	
End point type	Primary
End point timeframe: One year	

End point values	IG + RTX	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: ml/min				
median (standard deviation)	-4.2 ( $\pm$ 14.4)	-6.6 ( $\pm$ 12.0)		

### Statistical analyses

Statistical analysis title	EGFR decline
Comparison groups	IG + RTX v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.475
Method	t-test, 2-sided

### Secondary: Proteinuria Increase

End point title	Proteinuria Increase
End point description:	
End point type	Secondary

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End point timeframe:

1 year

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End point values	IG + RTX	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: gram/day				
arithmetic mean (standard error)	0.9 (± 2.1)	0.9 (± 2.1)		

### Statistical analyses

Statistical analysis title	Proteinuria
Comparison groups	IG + RTX v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.378
Method	t-test, 2-sided



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All the study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	IG + RTX
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Reporting group description:

In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	IG + RTX	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	4 / 13 (30.77%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Acute gastroenteritis with acute renal failure		
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagus perforation			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract neoplasm			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	IG + RTX	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	11 / 13 (84.62%)	
Nervous system disorders			
Memory impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Venous thrombosis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Leukopenia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Coagulation time abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Discomfort subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 13 (7.69%) 1	
Odynophagia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Pancreatic pseudocyst subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Respiratory, thoracic and mediastinal disorders			
Mucus subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Cold burn subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Cough			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Pulmonar thromboembolism subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Oedema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Rash subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 13 (7.69%) 1	
Graft complication subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Renal transplant subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Endocrine disorders Adenopathy submandibular subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Hyperparathyroidism subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 13 (15.38%) 2	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	

Hip pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Lumbar pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Malleolar oedema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 13 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 13 (15.38%) 2	
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Acidosis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	3 / 13 (23.08%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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 absence of any effect on circulating donor specific antibodies suggests that this treatment may also be not efficient in patients with chronic ABMR diagnosed at earlier stages
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28949089>