



## Clinical trial results:

### A Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Immunogenicity and Safety of Transitioning Subjects With Rheumatoid Arthritis to Biosimilar Rituximab (DRL\_RI) or Continued Treatment With Rituxan® or MabThera®

#### Summary

EudraCT number	2019-002810-37
Trial protocol	HU DE LT PL BG
Global end of trial date	20 April 2022

#### Results information

Result version number	v1 (current)
This version publication date	29 April 2023
First version publication date	29 April 2023

#### Trial information

##### Trial identification

Sponsor protocol code	RI-01-007
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04268771
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Dr. Reddy's Laboratories S.A.
Sponsor organisation address	Elisabethenanlage 11, Basel, Switzerland, CH-4051
Public contact	Dr. Narendra Maharaj, Dr. Reddy's Laboratories Ltd., +91 4044644000, narendramaharaj@drreddys.com
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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	30 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2022
Global end of trial reached?	Yes
Global end of trial date	20 April 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the immunogenicity of transitioning subjects with RA to DRL\_RI (biosimilar rituximab) from US rituximab/EU rituximab to continued treatment with US rituximab/EU rituximab.

To assess the safety of transitioning subjects with RA to DRL\_RI from US rituximab/EU rituximab to continued treatment with US rituximab/EU rituximab.

Protection of trial subjects:

Insured, Investigator care

Background therapy:

Methotrexate

Evidence for comparator:

MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

MabThera has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Actual start date of recruitment	21 January 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Bulgaria: 44
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Lithuania: 10
Worldwide total number of subjects	140
EEA total number of subjects	95

Notes:

<b>Subjects enrolled per age group</b>	
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)	86
From 65 to 84 years	52
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

A total of 140 subjects were randomly assigned to receive DRL\_RI or US-rituximab/EU-rituximab: 70 subjects received DRL\_RI and 70 subjects received US-rituximab (Rituxan, n=22) or EU-rituximab (MabThera, n=48).

### Pre-assignment

Screening details:

Screening period (Days -14 to 0)

### Pre-assignment period milestones

Number of subjects started	224 <sup>[1]</sup>
Number of subjects completed	140

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Eligibility criteria not met: 77
Reason: Number of subjects	Withdrawn consent: 6
Reason: Number of subjects	Eligibility criteria not met and withdrew consent: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 224 subjects were screened of whom 84 failed the screening. The primary reason for screen failure was eligibility criteria not met (77 subjects), 6 subjects had withdrawn consent and 1 had met eligibility criteria & withdrew consent. 140 subjects were enrolled in the study (70 for each treatment group).

### Period 1

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

Blinding implementation details:

The investigators and the subjects were unaware of the treatment assignment. Study center staff involved in study treatment administration and study endpoints assessments, CRO personnel, and the sponsor team including study statistician were blinded. The clinical laboratories analyzing the blood/plasma samples and the concentration/incidence of anti-rituximab antibodies were also blinded.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Arm A - Treatment arm

Arm description:

DRL\_RI

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	DRL_RI
Other name	NIL
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drugs were administered as two 1000-mg IV infusions separated by 2 weeks.

<b>Arm title</b>	Arm B - Reference arm
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Arm description:

US-rituximab or EU-rituximab

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan®, MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drugs were administered as two 1000-mg IV infusions separated by 2 weeks.

<b>Number of subjects in period 1</b>	Arm A - Treatment arm	Arm B - Reference arm
Started	70	70
Completed	66	68
Not completed	4	2
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	-
Subject safety restriction for COVID-19	-	1
Lost to follow-up	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Arm A - Treatment arm
Reporting group description: DRL_RI	
Reporting group title	Arm B - Reference arm
Reporting group description: US-rituximab or EU-rituximab	

Reporting group values	Arm A - Treatment arm	Arm B - Reference arm	Total
Number of subjects	70	70	140
Age categorical Units: Subjects			
Adults (18-64 years)	47	39	86
From 65-84 years	22	30	52
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	59.5	60.1	
standard deviation	± 11.66	± 11.80	-
Gender categorical Units: Subjects			
Female	54	61	115
Male	16	9	25

### Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Full analysis
Subject analysis set description: Safety population: The safety population included all subjects who were randomly assigned and received at least 1 dose of study drug.	
Subject analysis set title	Immunogenicity population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Immunogenicity population: The immunogenicity population included all subjects with at least 1 post-dose ADA assessment result available.	

Reporting group values	Safety population	Immunogenicity population	
Number of subjects	140	137	
Age categorical Units: Subjects			
Adults (18-64 years)	86	85	
From 65-84 years	52	50	
85 years and over	2	2	

Age continuous			
Units: years			
arithmetic mean	59.8	59.75	
standard deviation	± 11.69	± 11.69	
Gender categorical			
Units: Subjects			
Female	115	113	
Male	25	24	

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## End points

### End points reporting groups

Reporting group title	Arm A - Treatment arm
Reporting group description: DRL_RI	
Reporting group title	Arm B - Reference arm
Reporting group description: US-rituximab or EU-rituximab	
Subject analysis set title	Safety population
Subject analysis set type	Full analysis
Subject analysis set description: Safety population: The safety population included all subjects who were randomly assigned and received at least 1 dose of study drug.	
Subject analysis set title	Immunogenicity population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Immunogenicity population: The immunogenicity population included all subjects with at least 1 post-dose ADA assessment result available.	

### Primary: The incidence of ADAs

End point title	The incidence of ADAs <sup>[1]</sup>
End point description: To assess the immunogenicity of transitioning subjects with RA to DRL_RI (biosimilar rituximab) from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab. - The incidence of ADAs - The incidence of Nabs	
End point type	Primary
End point timeframe: The immunogenicity endpoint was measured while on study over up to 12 weeks or until death, regardless of use of prohibited therapies or treatment missed/discontinuation due to any other reasons.	
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: No statistical analysis has been provided, instead all data is included in Descriptive summary statistics.	

End point values	Arm A - Treatment arm	Arm B - Reference arm	Immunogenicity population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	69	68	137	
Units: number	4	2	6	

### Statistical analyses

No statistical analyses for this end point

### Primary: The incidence of Nabs

End point title	The incidence of Nabs <sup>[2]</sup>
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**End point description:**

To assess the immunogenicity of transitioning subjects with RA to DRL\_RI (biosimilar rituximab) from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.

- The incidence of ADAs
- The incidence of Nabs

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End point type	Primary
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**End point timeframe:**

The immunogenicity endpoint was measured while on study over up to 12 weeks or until death, regardless of use of prohibited therapies or treatment missed/discontinuation due to any other reasons.

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**Notes:**

[2] - 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: No statistical analysis has been provided, instead all data is included in Descriptive summary statistics.

<b>End point values</b>	Arm A - Treatment arm	Arm B - Reference arm	Immunogenicity population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	69	68	137	
Units: number	1	0	1	

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Investigators and other site personnel informed, as appropriate, the sponsor's designated safety services of any SAEs that occurred (whether or not attributable to the study drug) in the course of the study within 24 hours of awareness.

Adverse event reporting additional description:

Follow-up information on SAEs and a nonserious AE became serious, this and other relevant follow-up information was also provided to sponsor within 24 hours of awareness. All SAEs were reported. All SAEs were recorded in the CRF. The investigator was responsible for informing the IEC/IRB of the SAEs per local requirements.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

### Reporting groups

Reporting group title	Arm A - Treatment arm
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Reporting group description:

DRL\_RI

Reporting group title	Arm B - Reference arm
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Reporting group description:

US-rituximab or EU-rituximab

Serious adverse events	Arm A - Treatment arm	Arm B - Reference arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 70 (5.71%)	2 / 70 (2.86%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Intestinal resection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic stroke			

subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Enteritis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
COVID-19 pneumonia			
subjects affected / exposed	2 / 70 (2.86%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
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: 3 %

<b>Non-serious adverse events</b>	Arm A - Treatment arm	Arm B - Reference arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 70 (4.29%)	17 / 70 (24.29%)	
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	0 / 70 (0.00%) 0	5 / 70 (7.14%) 5	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 70 (2.86%) 2	5 / 70 (7.14%) 6	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1	4 / 70 (5.71%) 4	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 70 (0.00%) 0	3 / 70 (4.29%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2019	<p>The following is a summary of the major changes implemented with Protocol Amendment 1, Version 2.0, dated 12 Aug 2019:</p> <ul style="list-style-type: none"><li>• Updated exclusion criterion 2 for clarity.</li><li>• Added exclusion criterion 18: Subjects with hypogammaglobulinemia (low IgG) are immunocompromised and more susceptible for both infections and side effects; hence, such subjects should be excluded.</li><li>• Guidance in Section 5.4.1 Packaging was reworded for better clarity. Sentence modified to: "Rituximab concentrate for solution for infusion will be packaged in a carton or kit."</li><li>• Added the following text in Section 6.1 of Schedule of Assessments to clarify data capture at unscheduled visits: "If any unscheduled visits happen at any time during the study, visit details/appropriate data including reason will be captured in the eCRF."</li><li>• Added assessment of IgG (Section 6.1.1) to align with addition of new exclusion criterion 18 to exclude the subjects with low IgG.</li><li>• Added clarification for estimation of rituximab concentration in Section 3.1.2 and Section 6.2.1: time-matched blood samples for estimation of rituximab concentration were added to aid in subsequent data interpretation as and if needed. Relevant procedures (i.e., time-matched blood sample collection and blood loss for estimation of rituximab concentration) were added in Section 6.1.2, Section 6.1.3, Section 6.1.4, Section 6.5, and Appendix 1.</li></ul>
10 July 2020	<p>Summary of the major changes implemented with Protocol Amendment 2, Version 3.0 dated 10 Jul 2020:</p> <ul style="list-style-type: none"><li>• Study was extended to 6 months and included an additional follow-up visit at Week 26 with safety and serum pregnancy test in WOCBP.</li><li>• Reconsent was mandated for additional follow-up.</li><li>• A new Section 3.2 was included for contingency measures to be taken for smooth functioning of the study during the COVID-19 pandemic.</li><li>• Exclusion criterion 6 was revised to update the requirement of historical "severe" hypersensitivity to reference product or any of its excipients.</li><li>• Exclusion criterion 16 was updated to include definition of WOCBP and birth control measures</li><li>• Exclusion criterion 17 was updated to clarify that sexually active male subjects, who do not agree to use one of the highly effective methods of birth control during treatment and for at least 12 months after the last administration of study drug, will be excluded from the study.</li><li>• Section 4.2.2 was revised to emphasize that subjects could take their own independent decision to withdraw from study drug and/or study participation at any time.</li><li>• Section 6.1 and Appendix 1 were updated to include information that complete physical examination was to be performed at all study visits.</li><li>• Information regarding immunological testing in humans was included in Section 6.2.2</li><li>• Detailed definitions of IRRs and hypersensitivity reactions were added in Section 6.3</li><li>• Section 6.3.1.2 was updated to clarify that all ongoing SAEs were to be followed up until resolution or stabilization or until a predefined outcome was reached.</li><li>• Text was clarified regarding the assessment of adverse events outcome in Section 6.3.1.4</li><li>• ANC count was added to Section 6.3.4</li><li>• Clarified requirement of serum FSH testing (Section 6.3.4).</li><li>• A note of clarification was added for HBcAb evaluation in across protocol</li><li>• Clarified that the study sites were advised to follow local or country-specific guidelines while obtaining consent.</li></ul>

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported