



Clinical trial results:

CLINICAL TRIAL WITH PROPHYLACTIC TENOFOVIR FOR HAEMATOLOGICAL CANCER PATIENTS SHOWING A HBc-Ab POSITIVE AND HBs-Ag PATTERN AND TO BE TREATED WITH RITUXIMAB (PREBLIN STUDY)

Summary

EudraCT number	2011-000905-30
Trial protocol	ES
Global end of trial date	23 July 2015

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	REM-TEN-2011-01
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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	PORIB, Pharmacoeconomics & Outcomes Research Iberia, 34 917159147, MA_casado@porib.com

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	23 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare in HBcAb- positive and HBsAg-negative haematological cancer patients, the prophylactic use of TDF versus observation assessed as the percentage of patients who experienced HBV reactivation (seroreversion or reappearance of the HBsAg) in plasma and/or an increase of HBV DNA levels $\geq 1 \log_{10}$ IU/mL compared with the baseline value during the 18 months after the starting of treatment with rituximab

Protection of trial subjects:

Patients were excluded during the study for any of the following reasons: Pregnancy during the treatment. Serious adverse reaction requiring the definitive discontinuation of the study treatment. Discontinuation of the treatment with the study drug for more than 2 weeks. At the patient's request. Patients with adverse events were monitored through clinical assessments and pertinent laboratory analyses, as indicated by the supervising physician. All adverse events were monitored until they were satisfactorily resolved or have stabilized

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	10
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with hematological malignancy receiving RTX either as monotherapy or in combination with chemotherapy were eligible. Inclusion criteria were age 18 years, prior serologic evidence of HBV exposure (anti-HBc positive), HBsAg-negative status, undetectable HBV viral load (<lower limit of quantification), signed informed consent.

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, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	RTX+TDF

Arm description: -

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

Dosage and administration details:

100 mg each perfusion. 5-1 cycles, according to protocol

Investigational medicinal product name	Tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg once daily, orally

Arm title	RTX alone
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Arm description: -

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

Dosage and administration details:

100 mg each perfusion. 5-1 cycles, according to protocol

Number of subjects in period 1	RTX+TDF	RTX alone
Started	33	28
Completed	33	28

Baseline characteristics

Reporting groups

Reporting group title	RTX+TDF
Reporting group description: -	
Reporting group title	RTX alone
Reporting group description: -	

Reporting group values	RTX+TDF	RTX alone	Total
Number of subjects	33	28	61
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			
arithmetic mean	69.9	71.0	
standard deviation	± 13.3	± 9.0	-
Gender categorical Units: Subjects			
Female	15	10	25
Male	18	18	36

End points

End points reporting groups

Reporting group title	RTX+TDF
Reporting group description: -	
Reporting group title	RTX alone
Reporting group description: -	

Primary: Undetectable HBV DNA levels

End point title	Undetectable HBV DNA levels
End point description: The primary endpoint was the percentage of RTX-treated patients in the 2 groups with undetectable HBV-DNA levels (Group I and Group II) showing HBV reactivation within the 18 months of follow-up. Reactivation was defined by HBsAg and/or HBV DNA detection, or a confirmed 1 log ₁₀ IU/mL increase in HBV DNA levels from baseline	
End point type	Primary
End point timeframe: 18 months of follow-up	

End point values	RTX+TDF	RTX alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	28		
Units: percent				
number (not applicable)	0	3		

Statistical analyses

Statistical analysis title	HBV levels
Comparison groups	RTX alone v RTX+TDF
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.091
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 months of follow-up

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	RTX + TDF
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Reporting group description: -

Reporting group title	RTX alone
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Reporting group description: -

Serious adverse events	RTX + TDF	RTX alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 31 (25.81%)	7 / 28 (25.00%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Asthenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematologic toxicity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 31 (0.00%)	3 / 28 (10.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Mucositis			

subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	4 / 31 (12.90%)	4 / 28 (14.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RTX + TDF	RTX alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)	10 / 28 (35.71%)	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	3 / 31 (9.68%)	3 / 28 (10.71%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Vomiting			
subjects affected / exposed	2 / 31 (6.45%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Asthenia			

subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 28 (0.00%) 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 31 (9.68%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Infection			
subjects affected / exposed	2 / 31 (6.45%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	2 / 31 (6.45%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	

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 difference in the HBV reactivation rate between patients receiving TDF and those under close monitoring was not statistically significant. The calculated sample size was not reached.
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28898281>