Clinical trial results:
Bortezomib in late antibody-mediated kidney transplant rejection (BORTEJECT Study)

Summary

EudraCT number	2012-002857-41
Trial protocol	AT
Global end of trial date	23 January 2017

Results information

Result version number	v1 (current)
This version publication date	20 March 2020
First version publication date	20 March 2020

Trial information

Trial identification

Sponsor protocol code	BORTEJECT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01873157
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Abt. für Nephrologie und Dialyse, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, 0043 014040043630, georg.boehmig@meduniwien.ac.at
Scientific contact	Abt. für Nephrologie und Dialyse, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, 0043 014040043630, georg.boehmig@meduniwien.ac.at

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	01 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the planned non-commercial investigator-initiated and -driven study is to assess the efficiency of the innovative concept of proteasome inhibition in the treatment of late AMR. Our primary hypothesis is that, by inhibiting alloantibody production bortezomib halts the progression of ongoing graft injury and dysfunction.

Protection of trial subjects:

The study was conducted in conformance with Good Clinical Practice standards and local statutes and regulations regarding ethical committee review. Safety evaluation included a monitoring of all adverse events that occurred throughout the 24-month study period, as defined by the International Conference on Harmonization guidelines and World Health Organization Good Clinical Practice guidelines. The following measures were repeatedly assessed throughout the course of the study to monitor subject safety: assessment of adverse events, clinical laboratory tests, medical history, and vital signs assessment. An independent data and safety monitoring board (DSMB) monitored all safety issues and reviewed data at the interim analyses. Interim analyses were performed after completion of 10 and 20 cases.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2013
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	Austria: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	36
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at the outpatient ward (in the context of routine visits) of the Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Austria (Between Oct 2013 and Feb 2015: 1165 patients registered; 741 subjected to ABMR screening), according to HLA antibody/ABMR screening results.

Pre-assignment

Screening details:

Screening included 1076 kidney transplant recipients registered between Oct 2013 and Feb 2014 (age >18 years, ≥180 days post-transplantation, eGFR >20 ml/min/1.73 m2); 741 patients were subjected to serological DSA screening. Of those 86 DSA+ patients underwent biopsies and 45 were eligible. 44 patients entered the RCT (1 withdrawal after randomiza

Period 1

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

Blinding implementation details:

Randomisation was conducted by members of the pharmacy of the General Hospital of Vienna, using a password-protected web based system (web-based randomizer of the Medical University of Vienna. Patients were randomised on a 1:1 ratio to either Velcade or Placebo. The study was double-blind (subjects, investigators, monitor, data analysis).

Arms

Are arms mutually exclusive?	Yes
Arm title	Bortezomib

Arm description:

Bortezomib

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	ATC group: L01XX32
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Patients received two cycles of bortezomib. Each treatment cycle consisted of bortezomib at 1.3 mg/m2, administered intravenously twice weekly on days 1, 4, 8 and 11.

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

A 0.9% sodium chloride solution (normal saline solution) was used as placebo.

Number of subjects in period 1	Bortezomib	Placebo
Started	21	23
Completed	21	23

Baseline characteristics

Reporting groups	
Reporting group title	RCT

Reporting group description: -

Reporting group values	RCT	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	36	
From 65-84 years	8	8	
85 years and over	0	0	
Age continuous			
Median age (IQR)			
Units: years			
median	55.7		
inter-quartile range (Q1-Q3)	43.3 to 60.9	-	
Gender categorical			
Proportion of female reccipients			
Units: Subjects			
Female	26	26	
Male	18	18	
DSA positive			
Luminex single antigen test-based detection of DSA against the organ donor.			
Units: Subjects			
DSA-positive	44	44	
ABMR-specific features on biopsy			
Detection of ABMR-specific features on biopsy			
Units: Subjects			
ABMR features	44	44	

End points

End points reporting groups

Reporting group title	Bortezomib
Reporting group description: Bortezomib	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Slope of the estimated glomerular filtration rate

End point title	Slope of the estimated glomerular filtration rate
End point description: The eGFR was calculated according to the Mayo equation.	
End point type	Primary
End point timeframe: The slope of eGFR was computed from measurements at 0, 6, 12, 18 and 24 months.	

End point values	Bortezomib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: ml/min/1.73 m2 per year				
arithmetic mean (confidence interval 95%)	-4.7 (-8.6 to -0.8)	-5.2 (-8.9 to -1.4)		

Statistical analyses

Statistical analysis title	Linear mixed model for eGFR slope comparison
Statistical analysis description: GFR trajectories were analyzed using a mixed linear model with eGFR values from 0 to 24 months as dependent, and time and the interaction of treatment and time, as fixed effects. Furthermore, patient-specific random effects for intercept and slope were specified. The covariance structure was specified as an autoregressive model of the first order. The null hypothesis that the coefficient of the interaction term treatment and time is zero was tested at a two-sided significance level of 5%.	
Comparison groups	Placebo v Bortezomib
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.86
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.81
upper limit	5.75

Notes:

[1] - Linear mixed model

Secondary: HLA antibody levels

End point title	HLA antibody levels

End point description:

Median of the mean fluorescence intinsity of the immunodominant DSA at 24 months

End point type	Secondary

End point timeframe:

Measurement at month 24

End point values	Bortezomib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: no unit				
median (inter-quartile range (Q1-Q3))				
DSA-MFI	5365 (1728 to 11812)	2255 (1075 to 11697)		

Statistical analyses

Statistical analysis title	Group comparison for DSA-MFI

Statistical analysis description:

Mann Whitney U test

Comparison groups	Placebo v Bortezomib
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.49
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Mann Whitney U test

Secondary: Death-censored graft loss

End point title	Death-censored graft loss

End point description:

Death censored graft survival

End point type	Secondary

End point timeframe:

Until the end-of follow-up at 24 months

End point values	Bortezomib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: Number				
Graft loss	3	1		

Statistical analyses

Statistical analysis title	Kaplan Meier analysis for survival assessment
Statistical analysis description: The log rank test was used for group comparison.	
Comparison groups	Placebo v Bortezomib
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Logrank

Secondary: Measured GFR

End point title	Measured GFR
End point description: Clearance of chromium-51 ethylenediaminetetraacetic acid based on the slope-intercept method	
End point type	Secondary
End point timeframe: Measurement at 24 months	

End point values	Bortezomib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: ml/min/1.73 m2				
median (inter-quartile range (Q1-Q3))	33 (28 to 39)	42 (23 to 49)		

Statistical analyses

Statistical analysis title	Group comparison for mGFR
Statistical analysis description: For group comparison the Mann Whitney U test was used	

Comparison groups	Bortezomib v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.31
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - For group comparison the Mann Whitney U test was used.

Secondary: Microcirculation inflammation

End point title	Microcirculation inflammation

End point description:

Sum of g and ptc Banff scores

End point type	Secondary

End point timeframe:

Measurement in biopsies performed at the end of follow-up at 24 months.

End point values	Bortezomib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
median (inter-quartile range (Q1-Q3))	4 (0 to 5)	2 (1 to 5)		

Statistical analyses

Statistical analysis title	Group comparison for microcirculation inflammation

Statistical analysis description:

For group comparison with respect to microcirculation inflammation the Mann Whitney U test was used.

Comparison groups	Bortezomib v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.87
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - For group comparison the Mann Whitney U test was used.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the baseline visit untel the end-of the study period at 24 months.

Assessment type	Systematic

Dictionary used

Dictionary name	as reported
Dictionary version	1

Reporting groups

Reporting group title	Bortezomib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Bortezomib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	3 / 23 (13.04%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: NSTEMI		
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (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			
Neuropathy peripheral			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal cancer metastatic			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypoglycaemia			

subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
LUMBAR syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (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: 1 %

Non-serious adverse events	Bortezomib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 21 (90.48%)	21 / 23 (91.30%)	
Vascular disorders			
Oedema			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Cardiac disorders			
Cardiovascular disease			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Arrhythmia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	2 / 21 (9.52%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Restless legs syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	0	
Headache			

subjects affected / exposed	2 / 21 (9.52%)	3 / 23 (13.04%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	6 / 21 (28.57%)	3 / 23 (13.04%)	
occurrences (all)	6	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 21 (19.05%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Dysphagia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	13 / 21 (61.90%)	5 / 23 (21.74%)	
occurrences (all)	13	5	
Obstipation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pancreatitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
lip carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Basal cell carcinoma			

subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Actinic keratosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Stasis dermatitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Prostate cancer			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Hyperthyreosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
LUMBAR syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	8 / 21 (38.10%)	12 / 23 (52.17%)	
occurrences (all)	8	12	

Pneumonia			
subjects affected / exposed	2 / 21 (9.52%)	4 / 23 (17.39%)	
occurrences (all)	2	4	
Urinary tract infection			
subjects affected / exposed	5 / 21 (23.81%)	2 / 23 (8.70%)	
occurrences (all)	5	2	
dental infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Cytomegalovirus infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Polyomavirus-associated nephropathy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

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.

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29242250