Clinical trial results:
A Randomized, Double-blind Study Evaluating the Efficacy, Safety, and Immunogenicity of ABP 798 Compared with Rituximab in Subjects with CD20 Positive B-cell Non-Hodgkin Lymphoma (NHL)

Summary

EudraCT number	2013-005542-11
Trial protocol	DE CZ RO IT ES FR BG PL GR
Global end of trial date	28 June 2019

Results information

Result version number	v1 (current)
This version publication date	12 July 2020
First version publication date	12 July 2020

Trial information

Trial identification

Sponsor protocol code	20130109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02747043
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	28 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to evaluate the efficacy of ABP 798 compared with rituximab.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2016
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	Italy: 50
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Georgia: 9
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	India: 16
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 7

Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Japan: 15
Worldwide total number of subjects	256
EEA total number of subjects	151

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)	169
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 380 subjects were screened and 256 participants (128 in the ABP 798 treatment group and 128 in the rituximab treatment group) were randomized at 91 centers across 20 countries.

Pre-assignment

Screening details:

Participants were randomized centrally to receive either ABP 798 or rituximab in a 1:1 manner. The randomization was stratified based on geographic region (Europe, Americas, Japan, Asia Pacific – Other) and age group (> 60 years of age, ≤ 60 years of age).

Period 1

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

Blinding implementation details:

Since the investigational product containers were different for ABP 798 and rituximab, investigational product (ABP 798 or rituximab) was prepared by an unblinded pharmacist or designee, into a common IV preparation, for administration to the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	ABP 798

Arm description:

ABP 798 was administered at a dose of 375 mg/m^2 as an intravenous (IV) infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.

Arm type	Experimental
Investigational medicinal product name	ABP 798
Investigational medicinal product code	
Other name	biosimilar to Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ABP 798 was supplied as a sterile, preservative-free liquid concentrate for IV infusion at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-dose vials. Subjects were to receive premedications before each infusion. Premedications were to be given according to local practice for administration of rituximab therapy.

Arm title	Rituximab

Arm description:

Rituximab was administered at a dose of 375 mg/m^2 as an IV infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.

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

Dosage and administration details:

Rituximab was procured from commercial supplies in the US and was supplied as a sterile, clear, colorless, preservative-free liquid concentrate for IV infusion at a concentration of 10 mg/mL in either 100-mg/10 mL or 500-mg/50 mL single-dose vials. Subjects were to receive premedications before

each infusion. Premedications were to be given according to local practice for administration of rituximab therapy.

Number of subjects in period 1	ABP 798	Rituximab
Started	128	128
Treated	128	126
Completed	118	123
Not completed	10	5
Consent withdrawn by subject	1	1
Physician decision	1	1
Disease progression	4	-
Adverse event, non-fatal	3	1
not specified	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ABP 798
Reporting group description:	
ABP 798 was administered at a dose of 375 mg/m^2 as an intravenous (IV) infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.	
Reporting group title	Rituximab
Reporting group description:	
Rituximab was administered at a dose of 375 mg/m^2 as an IV infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.	

Reporting group values	ABP 798	Rituximab	Total
Number of subjects	128	128	256
Age Categorical Units:			
<= 60 years	71	70	141
> 60 years	57	58	115
Age Continuous Units: years			
arithmetic mean	57.6	58.2	
standard deviation	± 12.72	± 12.20	-
Sex: Female, Male Units:			
Female	68	62	130
Male	60	66	126
Race/Ethnicity, Customized Units: Subjects			
White	102	101	203
Asian, Non-Japanese	17	14	31
Asian, Japanese	7	8	15
Missing	1	2	3
Other	0	2	2
American Indian or Alaska Native	1	0	1
White, Asian-Non-Japanese	0	1	1
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	119	119	238
Hispanic or Latino	8	7	15
Not allowed to collect	1	2	3
Eastern Cooperative Oncology Group (ECOG) Status			
Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	107	110	217
Grade 1	21	18	39

Region of Enrollment Units: Subjects			
Europe	88	86	174
Asia Pacific - Other	23	23	46
Americas	10	11	21
Japan	7	8	15
Previous Radiation Treatment Units: Subjects			
Yes	3	3	6
No	125	125	250
Weight Units: kg			
arithmetic mean	75.29	75.19	
standard deviation	± 19.135	± 16.981	-
Height Units: cm			
arithmetic mean	166.81	167.64	
standard deviation	± 10.737	± 10.292	-
Time Since Original Diagnosis Units: months			
arithmetic mean	6.31	5.17	
standard deviation	± 16.325	± 10.181	-

End points

End points reporting groups

Reporting group title	ABP 798
Reporting group description:	
ABP 798 was administered at a dose of 375 mg/m^2 as an intravenous (IV) infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.	
Reporting group title	Rituximab
Reporting group description:	
Rituximab was administered at a dose of 375 mg/m^2 as an IV infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.	

Primary: Percentage of Participants Who Responded (Overall Response Rate - ORR) by Week 28 Based on Independent Central Assessment of Disease

End point title	Percentage of Participants Who Responded (Overall Response Rate - ORR) by Week 28 Based on Independent Central Assessment of Disease

End point description:

Overall response within the first treatment cycle was assessed according to International Working Group – Non-Hodgkin Lymphoma criteria (IWG-NHL criteria [Cheson et al, 1999]) by a central reader. Response was evaluated using computerized tomography (CT) scans and positron emission tomography (PET) (to assess nodal disease/organ enlargement), and bone marrow biopsy (to assess bone marrow infiltration). ORR was the percentage of participants with a best overall response of complete response (CR), unconfirmed complete response (CRu) or partial response (PR). Participants that do not meet the criteria for response were considered non-responders.

CR was defined as no evidence of disease.
CRu showed nodes in the original sum of the products (SPD) regressed by >75% and/or indeterminate bone marrow results.
PR was a ≥ 50% decrease in SPD of the six largest dominant nodes; >=50% decrease in liver and spleen nodes, and no increase in size of other nodes nor any new sites of disease.

End point type	Primary

End point timeframe:

Post treatment up to Week 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123[1]	124[2]		
Units: percentage of participants				
number (not applicable)	78.0	70.2		

Notes:

[1] - The modified full analysis set (mFAS) includes subjects with evidence of disease at baseline

[2] - mFAS

Statistical analyses

Statistical analysis title	Risk Difference analysis of ORR by Week 28: 90% CI

Statistical analysis description:

Clinical equivalence of the primary endpoint will first be demonstrated by comparing the 1-sided 95% lower confidence limit of the RD of ORR by week 28 between ABP 798 and rituximab with a noninferiority margin of -15%. If this is successful, the 1-sided upper 95% confidence limit of the RD of

ORR by week 28 will be compared with a nonsuperiority margin of +35.5%.

Comparison groups	Rituximab v ABP 798
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	7.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.4
upper limit	16.8

Statistical analysis title	Risk Difference analysis of ORR by Week 28: 95% CI

Statistical analysis description:

2-sided 95% confidence interval will be evaluated against a symmetrical margin of 15% for noninferiority and nonsuperiority

Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	18.6

Secondary: Percentage of Participants Who Responded (Overall Response Rate - ORR) at Week 12 Based on Independent Central Assessment of Disease

End point title	Percentage of Participants Who Responded (Overall Response Rate - ORR) at Week 12 Based on Independent Central Assessment of Disease

End point description:

Overall response within the first treatment cycle was assessed according to International Working Group – Non-Hodgkin Lymphoma criteria (IWG-NHL criteria [Cheson et al, 1999]) by a central reader. Response was evaluated using computerized tomography (CT) scans and positron emission tomography (PET) (to assess nodal disease/organ enlargement), and bone marrow biopsy (to assess bone marrow infiltration). ORR was the percentage of participants with a best overall response of complete response (CR), unconfirmed complete response (CRu) or partial response (PR). Participants that do not meet the criteria for response were considered non-responders.

CR was defined as no evidence of disease.
CRu showed nodes in the original sum of the products (SPD) regressed by >75% and/or indeterminate bone marrow results.
PR was a ≥ 50% decrease in SPD of the six largest dominant nodes; >=50% decrease in liver and spleen nodes, and no increase in size of other nodes nor any new sites of disease.

End point type	Secondary

End point timeframe:
Week 12

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123[3]	124[4]		
Units: percentage of participants				
number (not applicable)	59.3	58.1		

Notes:
[3] - The modified full analysis set (mFAS) includes subjects with evidence of disease at baseline
[4] - mFAS

Statistical analyses

Statistical analysis title	ORR at Week 12 90% CI

Statistical analysis description:
The 2-sided 90% confidence limits of the risk difference (RD) of ORR at week 12 used a generalized linear model adjusted for the stratification factors (geographic region and age group).

Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.3
upper limit	11.2

Statistical analysis title	ORR Week 12 95% CI

Statistical analysis description:
The 2-sided 95% confidence limits of the risk difference (RD) of ORR at week 12 used a generalized linear model adjusted for the stratification factors (geographic region and age group).

Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	13.2

Secondary: Pharmacokinetic Serum Concentrations by Visit

End point title	Pharmacokinetic Serum Concentrations by Visit

End point description:

Pharmacokinetic serum samples were analyzed by a central lab. Participants with PK concentrations below the lower limit of quantification (LLOQ) were excluded from these analyses.

End point type	Secondary

End point timeframe:

Weeks 2, 3, 4, 12 and 20

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	126		
Units: microgram/mL				
geometric mean (geometric coefficient of variation)				
Week 2 (predose) (n=123, 125)	58.66 (± 50.4)	58.63 (± 76.9)		
Week 3 (predose) (n=125, 126)	105.39 (± 37.8)	108.77 (± 59.1)		
Week 4 (predose) (n=126, 121)	132.70 (± 42.6)	140.23 (± 57.9)		
Week 12 (predose) (n=121, 124)	21.86 (± 156.1)	20.55 (± 194.1)		
Week 12 (postdose) (n=113, 117)	207.05 (± 58.1)	209.14 (± 66.8)		
Week 20 (predose) (n=118, 122)	13.37 (± 138.7)	16.45 (± 115.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Complete Depletion of Clusters of Differentiation 19-Positive (CD19+) Cell Count From Baseline to Day 8

End point title	Percentage of Participants with Complete Depletion of Clusters of Differentiation 19-Positive (CD19+) Cell Count From Baseline to Day 8

End point description:

Complete depletion of CD19+ cell count at any postdose time was defined as CD19+ cell counts < 20 cell/µL (0.02 * 10^9 cell/L). Participants with missing CD19+ cell count at baseline or participants with CD19+ cell count < 20 cell/µL at baseline were to be excluded
from the derivation of complete depletion of CD19+ cell count.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Study Day 8

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: percentage of participants				
number (not applicable)	98.3	98.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Immunoglobulin G (IgG) Results by Visit

End point title	Total Immunoglobulin G (IgG) Results by Visit

End point description:

Samples were analyzed by a central lab.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 8 (Week 2), Weeks 3, 4, 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	128		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Baseline (n=127, 123)	9.740 (± 2.5988)	10.570 (± 2.5970)		
Day 8 (Week 2) (n=122, 123)	9.790 (± 2.5719)	10.486 (± 2.4916)		
Week 3 (n=122, 123)	9.545 (± 2.5933)	10.374 (± 2.3214)		
Week 4 (n=124, 121)	9.744 (± 2.5805)	10.196 (± 2.2842)		
Week 28 (n=103, 104)	9.846 (± 2.6316)	10.281 (± 2.3617)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Immunoglobulin M (IgM) Results by Visit

End point title	Total Immunoglobulin M (IgM) Results by Visit

End point description:

Samples were analyzed by a central lab.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 8 (Week 2), Weeks 3, 4, 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	128		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Baseline (n=127, 123)	1.021 (± 1.0072)	1.247 (± 3.4018)		
Day 8 (Week 2) (n=122, 123)	1.004 (± 1.0300)	1.280 (± 3.7292)		
Week 3 (n=122, 122)	1.001 (± 1.0564)	1.370 (± 5.0250)		
Week 4 (n=124, 120)	0.985 (± 1.0459)	1.385 (± 5.3266)		
Week 28 (n=103, 104)	0.816 (± 0.8505)	1.127 (± 3.6752)		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Treatment-Emergent Adverse Events

End point title	Participants with Treatment-Emergent Adverse Events

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial participant. The event does not necessarily have a causal relationship with study treatment. Each AE was graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, where Grade 1 = Mild AE Grade 2 = Moderate AE Grade 3 = Severe AE Grade 4 = Life-threatening or disabling AE Grade 5 = Death related to AE. Serious adverse events include any event that is fatal, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other significant medical hazard.
IP = investigational product

End point type	Secondary

End point timeframe:

Day 1 (post treatment) to Week 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	126		
Units: participants				
Any AE	107	95		
Any grade >=3 AE	14	13		
Any fatal AE	0	0		
Any serious AE	5	5		
Any AE leading to discontinuation of IP	4	1		
Any AE leading to dose delay/withheld IP	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Treatment-emergent Adverse Events of Interest (AEOIs)

End point title	Percentage of Participants with Treatment-emergent Adverse Events of Interest (AEOIs)

End point description:

The AEOIs prespecified for this study were infusion reactions including hypersensitivity, cardiac disorders, serious infections, progressive multifocal leukoencephalopathy, hematological reactions, hepatitis B reactivation, opportunistic infections, severe mucocutaneous reactions, tumor lysis syndrome, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome. Infusion reactions including hypersensitivity adverse events of interest must have start date the same as, or one day after, an investigational product administration start date.

End point type	Secondary

End point timeframe:

Day 1 (post treatment) to Week 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	126		
Units: percentage of participants				
number (not applicable)				
Any AEOI	49.2	45.2		
Infusion reactions including hypersensitivity	43.0	42.9		
Hematological reactions	5.5	4.8		
Cardiac disorders	2.3	1.6		
Serious infections	1.6	0		
Severe mucocutaneous reactions	0.8	0		
Gastrointestinal perforation	0	0		
Hepatitis B reactivation	0	0		
Opportunistic infection	0	0		
Progressive multifocal leukoencephalopathy	0	0		

Reversible posterior leukoencephalopathy	0	0		
Tumor lysis syndrome	0	0		

Statistical analyses

Statistical analysis title	Risk Difference: Any AEOI
Statistical analysis description:	
Risk difference (ABP 798 – Rituximab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.	
Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	16.3

Statistical analysis title	Risk Difference: Infusion Reactions
Statistical analysis description:	
Risk difference (ABP 798 – Rituximab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.	
Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	12.3

Statistical analysis title	Risk Difference: Hematological Reactions
Statistical analysis description:	
Risk difference (ABP 798 – Rituximab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.	
Comparison groups	ABP 798 v Rituximab

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	13

Statistical analysis title	Risk Difference: Cardiac Disorders

Statistical analysis description:

Risk difference (ABP 798 – Rituximab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.

Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	13.2

Statistical analysis title	Risk Difference: Serious Infections

Statistical analysis description:

Risk difference (ABP 798 – Rituximab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.

Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	14

Statistical analysis title	Risk Difference: Severe Mucocutaneous Reactions

Statistical analysis description:

Risk difference (ABP 798 – Rituximab) and CIs were estimated by Wald asymptotic confidence limits, or exact confidence limits if n < 25 for either treatment.

Comparison groups	ABP 798 v Rituximab
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	13.2

Secondary: Number of Participants Who Developed Anti-drug Antibodies

End point title	Number of Participants Who Developed Anti-drug Antibodies

End point description:

Samples were first tested in an electrochemiluminescence (ECL)-based bridging immunoassay to detect antibodies capable of binding to ABP 798/rituximab (Binding Antibody Assay). Samples confirmed to be positive for binding antibodies were subsequently tested in a cell-based assay to determine neutralizing activity against ABP 798/rituximab (Neutralizing Antibody Assay).
Developing antibody incidence was defined as participants with a negative or no binding antibody result at baseline and a positive antibody result at any post-baseline time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 12, 20 and 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126[5]	123[6]		
Units: participants				
Binding antibody positive postbaseline	3	1		
Neutralizing antibody positive postbaseline	1	1		

Notes:

[5] - Subjects with a binding antibody negative or no result at baseline and a post baseline result.

[6] - Subjects with a binding antibody negative or no result at baseline and a post baseline result.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants' Progression-Free Survival (PFS) Status Based on the Independent Central Assessment of Disease

End point title	Participants' Progression-Free Survival (PFS) Status Based on the Independent Central Assessment of Disease

End point description:

PFS was based on disease assessments determined by the central, independent, blinded radiologists'

and oncologist’s review.

End point type	Secondary

End point timeframe:

Day 1 up to Week 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	126		
Units: percentage of participants				
number (not applicable)				
Participants with disease progression or death	3.1	2.4		
Participants alive and progression-free	96.9	97.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Survived -- Overall Survival (OS)

End point title	Percentage of Participants Who Survived -- Overall Survival (OS)

End point description:

Percentage of participants who were alive at the end of the study.

End point type	Secondary

End point timeframe:

Day 1 up to Week 28

End point values	ABP 798	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	126		
Units: percentage of participants	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 (post treatment) to Week 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	ABP 798
Reporting group description: ABP 798 was administered at a dose of 375 mg/m^2 as an intravenous (IV) infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.	
Reporting group title	Rituximab
Reporting group description: Rituximab was administered at a dose of 375 mg/m^2 as an IV infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.	

Serious adverse events	ABP 798	Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 128 (3.91%)	5 / 126 (3.97%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Erectile dysfunction			

subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (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 %

Non-serious adverse events	ABP 798	Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 128 (46.09%)	61 / 126 (48.41%)	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 128 (11.72%)	12 / 126 (9.52%)	
occurrences (all)	18	24	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	12 / 128 (9.38%)	6 / 126 (4.76%)	
occurrences (all)	14	9	
Fatigue			
subjects affected / exposed	13 / 128 (10.16%)	12 / 126 (9.52%)	
occurrences (all)	20	23	
Pyrexia			
subjects affected / exposed	8 / 128 (6.25%)	8 / 126 (6.35%)	
occurrences (all)	9	13	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 128 (3.13%)	9 / 126 (7.14%)	
occurrences (all)	4	16	
Diarrhoea			
subjects affected / exposed	3 / 128 (2.34%)	9 / 126 (7.14%)	
occurrences (all)	3	11	
Nausea			
subjects affected / exposed	6 / 128 (4.69%)	14 / 126 (11.11%)	
occurrences (all)	7	22	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	9 / 128 (7.03%)	8 / 126 (6.35%)	
occurrences (all)	10	12	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 128 (4.69%)	12 / 126 (9.52%)	
occurrences (all)	6	16	
Rash			
subjects affected / exposed	9 / 128 (7.03%)	6 / 126 (4.76%)	
occurrences (all)	12	7	
Urticaria			
subjects affected / exposed	7 / 128 (5.47%)	2 / 126 (1.59%)	
occurrences (all)	7	6	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 128 (5.47%)	1 / 126 (0.79%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	modified subject inclusion/exclusion criteria specified CT of the neck (if palpable lymph node > 1.0 cm or if performed at baseline) chest, abdomen, and pelvis at week 12 and week 28 added standard 12-lead ECG to the week-28 (EOS) procedures added reference to possible follow-up testing for subjects testing positive for neutralizing antibodies at the final scheduled study visit clarified that disease progression should not be reported as an adverse event, but that symptoms of progression should be reported removed end-of-infusion PK sampling at week 4 and week 20
07 January 2016	- corrected sample size power
24 June 2016	- modified subject inclusion criteria - specified that the dose of ABP 798/rituxima would be calculated based on height and weight obtained at baseline, and that the dose would remain the same throughout the study - added stopping criteria for infusion-related reactions - added additional monitoring requirements for infusion-related hypersensitivity reactions - specified that clinical disease assessments should be performed by investigator or sub-investigator
17 July 2017	- added details regarding optional additional PK sampling visit - modified subject inclusion/exclusion criteria - specified visits for physical examination and PK sapling procedures - clarified that the end of study (EOS) biopsies for complete response confirmation were required if bone marrow involvement was identified at baseline, and if not obtained then complete response subjects were to be classified as partial responders

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported