Clinical trial results:
A prospective multicenter Phase 2 Study of the Chemotherapy-free Combination of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib) in Combination with Obinutuzumab (GA 101) in Patients with Previously Untreated Follicular Lymphoma (FL) and a High Tumor Burden

Summary

EudraCT number	2014-005164-15
Trial protocol	DE
Global end of trial date	21 June 2022

Results information

Result version number	v1 (current)
This version publication date	28 February 2025
First version publication date	28 February 2025

Trial information

Trial identification

Sponsor protocol code	ALTERNATIVE

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LMU Klinikum
Sponsor organisation address	Marchioninistr 15, München, Germany, 81377
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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	31 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2022
Global end of trial reached?	Yes
Global end of trial date	21 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of the chemotherapy-free combination of ibrutinib and obinutuzumab (GA 101) in patients with previously untreated follicular lymphoma (FL) and a high tumor burden. Primary endpoint is the rate of progression free survival one year after registration. Progression-free survival (PFS) is chosen as primary endpoint since it represents besides overall survival the most relevant parameter for patients. PFS is defined as the time from registration to lymphoma progression or death from any cause.

Protection of trial subjects:

The study was reviewed by an independent ethics committee and accepted from an ethical point of view. Each interventional measure could be individually rejected by the patients. Patients could withdraw from the study at any time without having to give reasons.

Background therapy:

No background therapy

Evidence for comparator:

No comparator used in this trial.

Actual start date of recruitment	14 March 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	Germany: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 1 April 2016, last patient in: 8 May 2017

Pre-assignment

Screening details:

Subjects must fulfill all the inclusion criteria defined in the study protocol. If any of the exclusion criteria apply, subjects are not included in the study.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ibrutinib + Obinutuzumab

Arm description:

Six 21-day cycles of ibrutinib plus obinutuzumab, followed by 12 additional 2 months cycles of ibrutinib plus obinutuzumab maintenance in patients with at least a partial remission at the end of induction.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	L01EL01
Other name	IMBRUVICA
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Induction: orally at a dose of 560 mg approximately 30 minutes before or approximately 2 hours after a meal once daily every day until the start of maintenance for a total of 24 weeks.
Maintenance: orally at a dose of 560 mg approximately 30 minutes before or approximately 2 hours after a meal once daily every day for another 24 months.

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	GAZYVARO
Pharmaceutical forms	Powder for concentrate for dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction: 1000 mg by intravenous infusion on days d 1, 8, 15 of cycle 1 and on day 1 of cycles 2-6 to be given every 21 days.
Maintenance: 1000 mg by intravenous infusion every 2 months for a total of 24 months.

Number of subjects in period 1	Ibrutinib + Obinutuzumab
Started	98
Completed	98

Baseline characteristics

Reporting groups	
Reporting group title	Overall period
Reporting group description:	
All registered patients	

Reporting group values	Overall period	Total	
Number of subjects	98	98	
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)	61	61	
From 65-84 years	37	37	
85 years and over	0	0	
Age continuous Units: years			
median	59		
full range (min-max)	29 to 81	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	59	59	
Histology Units: Subjects			
FL grade 1	24	24	
FL grade 2	59	59	
FL grade 3A	14	14	
Hodgkin's Lymphoma	1	1	
Ann Arbor stage Units: Subjects			
Stage I	1	1	
Stage II	9	9	
Stage III	34	34	
Stage IV	54	54	
LDH Units: Subjects			
> upper normal limit	34	34	
<= upper normal limit	64	64	
Hemoglobin Units: Subjects			
< 12g/dL	14	14	

>= 12g/dL	84	84	
Involved nodal areas Units: Subjects			
> 4	42	42	
<= 4	56	56	
Number of FLIPI risk factors Units: Subjects			
n = 0	4	4	
n = 1	14	14	
n = 2	40	40	
n = 3	27	27	
n = 4	11	11	
n = 5	2	2	
ECOG performance status Units: Subjects			
ECOG = 0	71	71	
ECOG = 1	25	25	
ECOG = 2	1	1	
Missing	1	1	

End points

End points reporting groups

Reporting group title	Ibrutinib + Obinutuzumab
Reporting group description:	
Six 21-day cycles of ibrutinib plus obinutuzumab, followed by 12 additional 2 months cycles of ibrutinib plus obinutuzumab maintenance in patients with at least a partial remission at the end of induction.	
Subject analysis set title	Full Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Full analysis of all ranomized patients	

Primary: 1-year progression free survival

End point title	1-year progression free survival[1]
End point description:	
The rate of patients achieving a progression free survival of more than one year after registration. Progression-free survival is defined as the time from registration to lymphoma progression or death from any cause.	
End point type	Primary
End point timeframe:	
From registration to one year after registration	
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: Reporting mask does not support entering a statistics for one-arm-trials. According to FAQ and EMA support team we deleted this section.	

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: subjects				
PFS event within 1 year from registration	19			
No PFS event within 1 year from registration	76			

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year progression-free survival

End point title	2-year progression-free survival
End point description:	
2-year progression-free survival as estimated by the Kaplan-Meier method.	
End point type	Secondary
End point timeframe:	
From registration to two years after registration.	

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Subjects				
number (confidence interval 95%)	69.8 (61.2 to 79.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year progression-free survival

End point title	3-year progression-free survival

End point description:

3-year progression-free survival as estimated by the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From registration to three years after registration.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Subjects				
number (confidence interval 95%)	63.5 (54.6 to 73.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year overall survival

End point title	1-year overall survival

End point description:

One-year overall survival as estimated by the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From registration to one year after registration.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Subjects				
number (confidence interval 95%)	96.9 (93.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year overall survival

End point title	2-year overall survival

End point description:

Two-year overall survival as estimated by the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From registration to two years after registration.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Subjects				
number (confidence interval 95%)	95.8 (91.9 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year overall survival

End point title	3-year overall survival

End point description:

Three-year overall survival as estimated by the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From registration to three years after registration.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Subjects				
number (confidence interval 95%)	93.7 (89.0 to 98.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year response duration

End point title	1-year response duration

End point description:

For patients with CR or PR at the end of induction, duration of response was calculated as the time from the end of induction visit to progression or death from any cause.

End point type	Secondary

End point timeframe:

From end of induction to 1 year after end of induction.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: Subjects				
number (confidence interval 95%)	86.0 (79.0 to 93.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year response duration

End point title	2-year response duration

End point description:

End point type	Secondary

End point timeframe:

From end of induction to 2 years after end of induction.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: Subjects				
number (confidence interval 95%)	73.2 (64.4 to 83.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year response duration

End point title	3-year response duration

End point description:

End point type	Secondary

End point timeframe:

From end of induction to 3 years after end of induction.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: Subjects				
number (confidence interval 95%)	66.1 (56.8 to 77.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment outcome after induction

End point title	Treatment outcome after induction

End point description:

End point type	Secondary

End point timeframe:

From registration to the end of induction.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Subjects				
Complete remission (CR)	5			
Partial remission (PR)	82			
Stable disease (SD)	5			
Progression of disease (PD)	5			
Missing	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment outcome after 1 year

End point title	Treatment outcome after 1 year

End point description:

End point type	Secondary

End point timeframe:

From registration to one year after registration.

End point values	Ibrutinib + Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	95			
Units: Subjects				
CR	11			
PR	62			
SD	3			
PD	18			
Death	1			
Missing	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From registration to end of study	
Adverse event reporting additional description:	
There were 1429 adverse events in total, 95 of which were serious adverse events.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	4.03

Reporting groups	
Reporting group title	Safety populaion
Reporting group description:	
All patients who started therapy with Ibrutinib or Obinutuzumab.	

Serious adverse events	Safety populaion		
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 97 (53.61%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal adenocarcinoma			

subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cervix carcinoma stage 0				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Capillary leak syndrome				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	4 / 97 (4.12%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 97 (4.12%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Sarcoidosis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cytokine release syndrome				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chylothorax				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper-airway cough syndrome				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Suicidal ideation				

subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Panic disorder				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Hepatic enzyme increased				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Subdural haematoma				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Iritis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal haemorrhage			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage urinary tract			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 0		
Herpes dermatitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis fungal			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Sepsis				
subjects affected / exposed	3 / 97 (3.09%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 1			
Gastroenteritis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	3 / 97 (3.09%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vulval abscess				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety populaion		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 97 (98.97%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 97 (17.53%)		
occurrences (all)	23		
Haematoma			

subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	26		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	27 / 97 (27.84%)		
occurrences (all)	42		
Pyrexia			
subjects affected / exposed	14 / 97 (14.43%)		
occurrences (all)	18		
Asthenia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	16		
Oedema			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	10		
Chest pain			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Mucosal inflammation			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 97 (29.90%)		
occurrences (all)	35		
Dyspnoea			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	15		
Epistaxis			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	8		
Dyspnoea exertional			

subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Pleural effusion			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	13		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	10		
Depression			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Investigations			
Blood uric acid increased			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Platelet count decreased			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	7		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 97 (14.43%)		
occurrences (all)	16		
Headache			

subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	14		
Polyneuropathy			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	7		
Paraesthesia			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	15		
Thrombocytopenia			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	17		
Anaemia			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	8		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	38 / 97 (39.18%)		
occurrences (all)	59		
Vomiting			
subjects affected / exposed	16 / 97 (16.49%)		
occurrences (all)	17		
Abdominal pain upper			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	17		
Nausea			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	16		
Dyspepsia			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	13		
Abdominal pain			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 11 7 / 97 (7.22%) 7 6 / 97 (6.19%) 7		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Onychoclasis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Petechiae subjects affected / exposed occurrences (all) Skin fissures subjects affected / exposed occurrences (all) Skin disorder subjects affected / exposed occurrences (all)	 28 / 97 (28.87%) 40 12 / 97 (12.37%) 14 9 / 97 (9.28%) 9 8 / 97 (8.25%) 8 8 / 97 (8.25%) 9 5 / 97 (5.15%) 5 5 / 97 (5.15%) 5 5 / 97 (5.15%) 6		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	16 / 97 (16.49%) 22			
Back pain subjects affected / exposed occurrences (all)	15 / 97 (15.46%) 18			
Muscle spasms subjects affected / exposed occurrences (all)	12 / 97 (12.37%) 14			
Musculoskeletal pain subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 9			
Myalgia subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 10			
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	24 / 97 (24.74%) 36			
Bronchitis subjects affected / exposed occurrences (all)	11 / 97 (11.34%) 15			
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 97 (10.31%) 23			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 11			
Infection subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 10			
Pneumonia subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 8			
Respiratory tract infection				

subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Influenza			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	10		
Herpes zoster			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Sinusitis			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Cystitis			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	9		
Conjunctivitis			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Viral infection			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Vitamin D deficiency			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2017	Adaptation of the CTP to the new IB of the IMPs.
23 April 2018	Adaptation of the CTP to the new IB of the IMPs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported