Clinical trial results:
An open-label Phase II Study of the Efficacy and Safety of the Combination of Fludarabine, Cyclophosphamide, And Rituximab in Patients with Chronic Lymphocytic Leukaemia who are Newly Diagnosed, have Relapsed or are Resistant to First-Line Treatment

Summary

EudraCT number	2008-001250-40
Trial protocol	IE
Global end of trial date	21 November 2019

Results information

Result version number	v1 (current)
This version publication date	13 June 2025
First version publication date	13 June 2025

Trial information

Trial identification

Sponsor protocol code	ICORG07-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00812669
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	RCSI House, 121 St. Stephen's Green, Dublin, Ireland, D02 H903
Public contact	Chief Operations Officer, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie
Scientific contact	Chief Operations Officer, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2019
Global end of trial reached?	Yes
Global end of trial date	21 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•Complete remission rate by NCI Criteria (Appendix 3) and using MRD analysis.

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and SJH/AMNCH Research Ethics Committee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	42
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

52 patients were consented from 7 sites in Ireland from 19Sept2008 to 03Jan2012

Pre-assignment

Screening details:

The target population were males >/= to 18 years of age with High Risk Localised Prostate Carcinoma who must have met all of inclusion and none of the excision criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Patients non blinded

Arms

Arm title	Single Arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion, Tablet
Routes of administration	Oral use, Intravascular use

Dosage and administration details:

Tablet: BSA calculations were used to calculate number of tablets patients should take per day (total daily dose)
Fludarabine tablets can be taken either on an empty stomach or together with food. 40mg/m2/day PO. The tablets have to
be swallowed whole with water; they should not be chewed or broken.
IV: Fludarabine iv should be reconstituted and diluted according to local practice. Dilution in 100ml NaCl 0.9% and administration over 30 minutes is suggested. 25mg/m2/day IV.
Can be taken via IV or PO on Days 1,2 & 3 of a 28 day cycle. Taken for 4 or 6 cycles depending on MRD analysis.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Endoxana
Pharmaceutical forms	Tablet, Powder for solution for injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Cyclophosphamide IV is usually given directly into the tubing of a fast running intravenous infusion. Cyclophosphamide tablets should be swallowed whole with sufficient fluid. The tablets are coated and should not be divided.
250mg/m2/day iv or Po.
Taken on days 1,2 &3

Investigational medicinal product name	Rituxumab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Omit Rituximab in cycle 1.
Dose is 375 mg/m2 IV on Day 1 of the cycle.
When infused for the first time, the infusion should be started at 50mg/hr. The rate can be increased by 50mg/hour increments every 30 minutes to a maximum of 400mg/hr. On second and subsequent infusions, the rate may be set to 100mg/hr, if the infusion was well tolerated previously, and increased in 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.

Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Should be given no sooner than 24 hours post last dose of chemotherapy.
Dose is 6mg subcut on day 4 of a cycle

Number of subjects in period 1	Single Arm
Started	52
Completed	15
Not completed	37
Adverse event, serious fatal	2
Adverse event, non-fatal	6
Other Reasons	4
Progressive Disease	24
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)

Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	52	52	
Age categorical Units: Subjects			
Adults (18-64 years)	42	42	
From 65-84 years	10	10	
Age continuous Units: years			
median	57.5		
standard deviation	± 7.5	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	35	35	

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description: -	
Subject analysis set title	Single Arm
Subject analysis set type	Full analysis

Subject analysis set description:

Arm created so that the study can include statistical analysis even though it is just a one armed study (Error appears unless 2 arms selected for this analysis)

Primary: CR rate

End point title	CR rate

End point description:

The primary response variable (endpoint) is the CR rate achieved using NCI Criteria and MRD analysis. Twenty-nine out of 52, 55.8%, were MRD-ve CR at EOT (95% CI using Wilson's method 42.3% to 68.4%). The lower bound of the CI is above 30% indicating that there is evidence that population percentage of patients achieving MRD-ve CR at the end of treatment is > 30% (as hypothesised in the sample size calculations). This result should be interpreted with caution however, since this is an open-label non-randomised study and there exists a risk of potential sources of bias, particularly selection bias.
In addition to this, 18 out of 52 patients, 34.6%, were MRD-ve CR at the end of cycle 4 (95% CI using Wilson's method 23.2% to 48.2%).

End point type	Primary

End point timeframe:

Measured at end of trial and end of cycle 4

End point values	Single Arm	Single Arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52[1]		
Units: MRD-ve CR				
number (confidence interval 95%)				
EoT	55.8 (42.3 to 68.4)	55.8 (42.3 to 68.4)		
End Cycle 4	34.6 (23.2 to 48.2)	34.6 (23.2 to 48.2)		

Notes:

[1] - This arm was created as a workaround in order to report statistical analysis of a single arm trial

Statistical analyses

Statistical analysis title	Estimation of MRD-ve CR rate at EOT
Comparison groups	Single Arm v Single Arm
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Point estimate (rate)
Point estimate	55.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	42.3
upper limit	68.4

Notes:

[2] - Estimation of MRD-ve CR rate at EOT and 95% confidence interval using Wilson’s method

Secondary: TTF in MRD positive vs negative patients

End point title	TTF in MRD positive vs negative patients

End point description:

No Confidence Intervals for median TTF are presented. All that is presented is the medians and the p-value of 0.0008 for a superiority test. MRD status at EoT was the most significant prognostic factor for TTF in univariate analysis. Patients MRD-negative at EoT experienced prolonged TTF.

End point type	Secondary

End point timeframe:

Median TTF for both sets of patients (MRD negative and positive) was taken at EoT.

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Months				
number (not applicable)				
MRD Positive (Median mths)	59.2			
MRD Negative (Median Mths)	85.3			

Statistical analyses

No statistical analyses for this end point

Secondary: OS at 10 Years

End point title	OS at 10 Years

End point description:

The median overall survival was not reached as there were only 6 deaths, so no further analysis is presented for overall survival. (the 6 deaths occured after median follow up of 62.3 months, 5 from progressive disease and one of t-cell lymphoma)

End point type	Secondary

End point timeframe:

OS was to be calculated from date of enrolment until death or clinical progression

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Patients				

Notes:

[3] - The median OS was not reached as there were only 6 deaths, so no further analysis is presented

Statistical analyses

No statistical analyses for this end point

Secondary: Hypermutation analysis in determining TTF

End point title	Hypermutation analysis in determining TTF

End point description:

Creation of a predictive model for TTF and OS using hypermutation analysis .Originally immunophenotype and FISH analyses were also to be used in determining TTF and OS but it was decided that there was no further information to be gleaned from the study for the secondary objectives apart from the analyses using hypermutation analysis. Patients with mutations in SF3B1 and NOTCH1 experienced significantly shorted TTF than their wild types. There was too little data on overall survival in order to be able to calculate the median OS, so there are no results on OS .
As well, the median TTF for u-IGHV was 67.9 months but wasn't sufficient data to estimate the medianfor m-IGHV, but because the median TTF for all patients was 71.1 months, TTF for m-IGHV must be shorter, though the difference is not statistically significance (p=0.310).

End point type	Secondary

End point timeframe:

TTF was calculated from date of enrollment until death or clinical progression, respectively

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	52[4]			
Units: Months until TTF				
number (not applicable)				
SF3B1 Mutations	38.4			
NOTCH1 mutations	62.4			
SF3Bq Wild-Type	71.1			
NOTCH1 Wild-Type	85.3			

Notes:

[4] - mNOTCH1=17, wild-type NOTCH1-33
mSF3B1=5, wild-type SF3B1 = 47

Statistical analyses

No statistical analyses for this end point

Secondary: Safety profile of modified FCR

End point title	Safety profile of modified FCR

End point description:

Modified Combination of Fludarabine, cyclophosphamide and rituximab.
FCR was modified at cycle 4 or 6 depending on MDR analysis. Patients who were MRD negative and in CR on CT scan stopped therapy after 4 courses of FCR.

Patients with evidence of ongoing disease proceeded to a total of 6 courses of chemotherapy and patients with progressive disease came off trial.
No difference was noted in TTF in MRD-negative patients following FCR4 or FCR6. Interim MRD assessment assists in personalizing therapy and reducing chemotherapy-associated toxicity.

End point type	Secondary

End point timeframe:

Time to Treatment Failure is from time of patient enrollment to time of treatment failure

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	29[5]			
Units: TTF (Months) in MRD-negative patients				
number (not applicable)				
MRD-Negative CR after 6 cycles	85.3			
MRD Negative after 4 cycles	82.2			

Notes:

[5] - 11 MRD negative after 6 cycles (EOT), 18 MRD negative after 4 cycles

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Monitored from Baseline through the study until completion of therapy

Adverse event reporting additional description:

Occurrences causally related to treatment number for individual SAEs was not recorded, therefore in the tables below it is recorded as 0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Single Arm

Reporting group description: -

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 52 (44.23%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Body temperature increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
T-cell lymphoma			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Neurtopenia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia acinetobacter			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Viral Infection			
subjects affected / exposed	1 / 52 (1.92%)		
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	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 52 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Haematoma			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Surgical and medical procedures			
Ear tube insertion			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 52 (50.00%)		
occurrences (all)	35		
Influenza like illness			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Chills			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Peripheral swelling			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Adverse drug reaction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Facial pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	10 / 52 (19.23%)		
occurrences (all)	10		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Menorrhagia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	9		
Dyspnoea			

subjects affected / exposed	6 / 52 (11.54%)			
occurrences (all)	6			
Productive cough				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	5			
Epistaxis				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Oropharyngeal pain				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Rhinorrhoea				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Nasal congestion				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Sinus congestion				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Throat tightness				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Upper-airway cough syndrome				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Wheezing				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	2 / 52 (3.85%)			
occurrences (all)	2			
Localised infection				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences (all)	1			
Pleuritic pain				

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Depressed Mood			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Anxiety			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Mood swings			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Asparate aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood urea increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Fluid intake reduced			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			

Thermal burn subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Taste disorder subjects affected / exposed occurrences (all) Dizziness exertional subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all)	 11 / 52 (21.15%) 12 4 / 52 (7.69%) 4 2 / 52 (3.85%) 2 2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Autoimmune haemolytic anaemia subjects affected / exposed occurrences (all)	 3 / 52 (5.77%) 4 2 / 52 (3.85%) 3 1 / 52 (1.92%) 1 3 / 52 (5.77%) 3		
Ear and labyrinth disorders			

Deafness			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	14 / 52 (26.92%)		
occurrences (all)	19		
Abdominal pain			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Tongue coated			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Abdominal Discomfort			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Abdominal symptom			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gingival bleeding			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tongue blistering			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	10 / 52 (19.23%)		
occurrences (all)	12		
Pruritus			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	8		
Rash maculo-papular			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Rash macular			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood blister			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Onychoclasis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		

Haematuria			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Renal impairment			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	7		
Bone pain			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Limb discomfort			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Metatarsalgia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Pain in jaw			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gamma glutamyltransferase increased			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Infections and infestations			
Herpes Simplex			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Oral candidiasis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tooth Abscess			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 52 (25.00%)		
occurrences (all)	18		
Gout			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2008	Protocol V3.0 was the first Approved by the Irish EC. Updated to Protocol V4.0 19-Jun-2008 due to admin changes and additional investigators added to the studu
30 September 2008	Protocol V5.0 24-Sept-2008: Updates include clarifications and admin changes.
20 July 2010	Protocol V6.0 04May2010: a) To align the protocol and Patient Information Leaflet with the new ICORG SOP for Protocol Development and Preparation of PIL and Consent Form, b) To decrease required patient's accrual number, c) Additional clarification edits.
04 October 2012	Protocol v7 02May2012: Chane to statistical analysis section to include analysis conducted through the study (for toxicity to be reviewed every 6 months and efficacy to be reviewed annually).
11 June 2019	Protocol V8 08Feb2019: The main change in the updated Protocol v8 08-Feb-2019 is the shortened timelines for patient follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported