Clinical trial results:
Fludarabine/Rituximab combined with escalating doses of Lenalidomide followed by Rituximab/Lenalidomide in untreated chronic lymphocytic leukemia (CLL) – a dose-finding study with concomitant evaluation of safety and efficacy

Summary

EudraCT number	2008-001430-27
Trial protocol	AT
Global end of trial date	16 January 2012

Results information

Result version number	v1 (current)
This version publication date	30 July 2016
First version publication date	30 July 2016

Trial information

Trial identification

Sponsor protocol code	CLL-5 RevliRit

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00738829
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/20, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, 0043 6626404411, d.wolkersdorfer@agmt.at
Scientific contact	Richard Greil, AGMT, 0043 5725525801, r.greil@salk.at

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 January 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this dose-finding study is to determine the maximum tolerated dose of lenalidomide in combination with fludarabine/rituximab therapy.

Protection of trial subjects:

Safety assessments were done regularly.
Premedication prior to each infusion of rituximab and prophylactic anti-thrombotic therapy during study therapy was given. The study was designed to have a reduced dose fludarabine/rituximab debulking step and slow dose escalation for lenalidomide in order to minimize the risk of tumor lysis syndrome.

Background therapy:

In this study lenalidomide was combined with a backbone of FR (taken from the FCR regimen) for an initial 6 months treatment and dose-finding phase and followed by a 6 month course of lenalidomide in combination with rituximab maintenance.

Evidence for comparator:

Lenalidomide has been shown to be synergistic with rituximab in vitro, thus arguing for trials of a combination therapy. In mantle cell lymphoma a phase I/II trial combining lenalidomide with rituximab has shown promising results.

Actual start date of recruitment	30 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	Austria: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	19
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 30-Sep-2008 and 29-Nov-2010 45 patients were enrolled at 7 sites in Austria.

Pre-assignment

Screening details:

Patients with untreated CLL with treatment indication according to NCI criteria, age 18 or older, ECOG 0-2 were enrolled.

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	FLR Induction

Arm description:

Fludarabine-rituximab backbone with escalating lenalidomide doses

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide: day 8-21 of cycle 1; day 1-21 of cycles 2-6
Starting Dose: 2,5mg
Lenalidomide dose was increades via dose levels 5/10/15/20/25mg/d every 28 days in the absence of grade 3/4 infection or prolonged cytopenia (not due to bone marrow infiltration by CLL), as well as in the absence of Grade 3/4 non hematologic toxicities.
In case of limiting toxicity (serious infection or limiting grade 3 to 4 toxicity other than neutropenia) treatment should be continued at last tolerated dose (1 dose level below).

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera(R)
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab q4w
375mg/m2 iv day 4 on cycle 1
500mg/m2 iv day 1 on cycles 2-6

Number of subjects in period 1	FLR Induction
Started	45
Completed	40
Not completed	5
Consent withdrawn by subject	2

Adverse event, non-fatal	2
Lack of efficacy	1

Period 2	
Period 2 title	Maintenance
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LR Maintenance

Arm description:

Rituximab-lenalidomide maintenance

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide day 1-28 of 28 day cycles for 6 months at the maximal dose level reached individually in induction phase

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera(R)
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375mg/m2 iv 2/4/6 months after end of induction phase

Number of subjects in period 2	LR Maintenance
Started	40
Completed	39
Not completed	1
Physician decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Induction

Reporting group description: -

Reporting group values	Induction	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	66		
full range (min-max)	43 to 79	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	26	26	

End points

End points reporting groups

Reporting group title	FLR Induction
Reporting group description:	
Fludarabine-rituximab backbone with escalating lenalidomide doses	
Reporting group title	LR Maintenance
Reporting group description:	
Rituximab-lenalidomide maintenance	

Primary: Achieved lenalidomide dose at end of 6 cycles

End point title	Achieved lenalidomide dose at end of 6 cycles[1]
End point description:	
Individual dose of lenalidomide achieved at cycle 6 of FLR induction treatment	
End point type	Primary
End point timeframe:	
6 cycles of FLR induction treatment	

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: No statistical analysis is provided as this is an one armed, open label, non-comperative study.

End point values	FLR Induction			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Patients				
25 mg	15			
20 mg	3			
15 mg	6			
10 mg	5			
5 mg	5			
2,5 mg	3			
0 mg	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for adverse events for 28 days after discontinuing study treatment or completion of study treatment.

Adverse event reporting additional description:

All adverse events grade 2 or greater including all SAEs and all AEs resulting in IMP dose modifications were collected. Laboratory test value abnormalities were not reported as AEs unless there was an associated clinical condition for which the patient was given treatment or treatment altered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	All enrolled patients

Reporting group description: -

Serious adverse events	All enrolled patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 45 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hydrocele operation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Face oedema			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Guillain-Barre syndrome			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dry skin			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteremia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.4 %

Non-serious adverse events	All enrolled patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 45 (91.11%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Thrombophlebitis			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	16		
Neutropenia			
subjects affected / exposed	28 / 45 (62.22%)		
occurrences (all)	57		
Thrombocytopenia			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Pain			

subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3 6 / 45 (13.33%) 6		
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all) Hypersensitivity subjects affected / exposed occurrences (all)	 5 / 45 (11.11%) 5 2 / 45 (4.44%) 2		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 2 6 / 45 (13.33%) 7 2 / 45 (4.44%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 4 / 45 (8.89%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 3 7 / 45 (15.56%) 9		
Psychiatric disorders Anxiety			

subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Osteoarthritis			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Herpes zoster			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Metabolism and nutrition disorders			

Hyperuricaemia subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2009	The amendment was concerning administrational issues as well as a safety issue: a new thrombose prophylaxis was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported