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

Summary

EudraCT number	2011-004912-43
Trial protocol	AT
Global end of trial date	15 January 2015
Results information	
Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification	
Sponsor protocol code	AGMT_CLL-9
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01703364
WHO universal trial number (UTN)	-
Other trial identifiers	Celgene: RV-CLL-AGMT-0710

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	15 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Tolerability of escalated starting dose
The first 5 patients will start with dose level 5 mg Lenalidomide and further escalating dose. After the fifth patient is included in the study, enrolment will be interrupted until this patient has finished his first treatment cycle. A safety board will evaluate the toxicities of the first 5 patients. If there are more than 2 patients experiencing a DLT in the first treatment cycle, the starting dose will not be escalated and further 5 patients will be enrolled with a starting dose of 5 mg Lenalidomide. If only 2 or less patients experience a DLT in the first treatment cycle, the next 5 patients will start the treatment with 10 mg Lenalidomide. If more than 4 DLTs occur in the first treatment cycle of the first 5 patients the trial will be stopped.

Protection of trial subjects:

Safety assessments were done on cycle 1 day 1, 5 and 10 and day 1 of every further cycle (cycles 2 – 6).
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. The patients were counselled before each cycle of Lenalidomide e.g. about pregnancy precautions and the potential risks of fetal exposure to Lenalidomide.

Background therapy:

Fludarabine 25 mg/m² iv d1-3 or 40 mg/m² po d1-3; repeat every 28 days
Rituximab 375 mg/m² iv day 4 on cycle 1; 500 mg/m² iv day 1 on cycles 2 – 6; repeat every 28 days

Evidence for comparator: -

Actual start date of recruitment	13 August 2012
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: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	6
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between August 2012 and June 2014 12 patients were recruited at two sites in Austria.

Pre-assignment

Screening details:

Patients with untreated CLL with treatment indication according to NCI criteria were enrolled.
2 subjects, who did not complete the first 3 treatment cycles including staging I were replaced according to protocol.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Starting dose 5 mg lenalidomide

Arm description:

Lenalidomide with a backbone of FR for 6 cycles. Patients started with dose level 5 mg lenalidomide and further escalating dose. Lenalidomide was increased by dose steps of 5 mg every 28 days in the absence of limiting toxicity. If dose limiting toxicity ensues the patients was treated with last tolerable dose for the remainder of the 6 treatment cycles.

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

Dosage and administration details:

Cycle 1: day 8-21
Cycles 2-6: day 1-21
Starting Dose: 5 mg; lenalidomide dose increased via dose levels 10/15/20/25 mg/d every 28 days if no limiting toxicity occurs

Arm title	Starting dose 10 mg lenalidomide

Arm description:

Lenalidomide with a backbone of FR for 6 cycles. Patients started with dose level 10 mg lenalidomide and further escalating dose. Lenalidomide was increased by dose steps of 5 mg every 28 days in the absence of limiting toxicity. If dose limiting toxicity ensues the patients was treated with last tolerable dose for the remainder of the 6 treatment cycles.

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

Dosage and administration details:

Cycle 1: day 8-21
Cycles 2-6: day 1-21
Starting Dose: 10 mg; lenalidomide dose increased via dose levels 10/15/20/25 mg/d every 28 days if no limiting toxicity occurs

Number of subjects in period 1	Starting dose 5 mg lenalidomide	Starting dose 10 mg lenalidomide
Started	5	7
Completed	4	5
Not completed	1	2
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	12	12	
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)	6	6	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	5	
Male	7	7	

End points

End points reporting groups

Reporting group title	Starting dose 5 mg lenalidomide

Reporting group description:

Lenalidomide with a backbone of FR for 6 cycles. Patients started with dose level 5 mg lenalidomide and further escalating dose. Lenalidomide was increased by dose steps of 5 mg every 28 days in the absence of limiting toxicity. If dose limiting toxicity ensues the patients was treated with last tolerable dose for the remainder of the 6 treatment cycles.

Reporting group title	Starting dose 10 mg lenalidomide

Reporting group description:

Lenalidomide with a backbone of FR for 6 cycles. Patients started with dose level 10 mg lenalidomide and further escalating dose. Lenalidomide was increased by dose steps of 5 mg every 28 days in the absence of limiting toxicity. If dose limiting toxicity ensues the patients was treated with last tolerable dose for the remainder of the 6 treatment cycles.

Primary: Tolerability of escalated starting dose

End point title	Tolerability of escalated starting dose[1]

End point description:

DLT is defined as:

Occurrence of any grade III/IV non hematologic toxicity, except the following:
grade III nausea or grade III vomiting, grade III diarrhea, fatigue, alopecia, grade III dehydration, grade III acidosis or alkalosis, grade III hypercholeresterolemia, grade III hypertriglyceridemia, occurrence of isolated grade III elevation of liver function tests (LFTs) without associated clinical symptoms lasting for ≤ 5 days in duration, isolated grade III elevation of Amylase, grade III hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia

Hematologic grade IV toxicities that fail to recover to at least grade III within 14 days of last treatment

Severe infection requiring antibiotic or antifungal treatment exceeding expected severity observed in other CLL treatment

End point type	Primary

End point timeframe:

28 days
End of cycle 1 of each patient

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: Definition of tolerability of escalated starting dose: 2 or less patients of the first 5 patients (starting dose 5 mg Lenalidomide) experience a dose limiting toxicity (DLT) in the first treatment cycle. No DLT occured during cycle 1 in the first 5 patients and starting dose of Lenalidomide was escalated to 10 mg.

End point values	Starting dose 5 mg lenalidomide	Starting dose 10 mg lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Patients				
DLT in cycle 1	0	1		
No DLT in cycle 1	5	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of study medication.

Adverse event reporting additional description:

- All grades III and IV AEs were documented.

Additionally all of the following AEs were documented:

- AEs of all grades during the first two cycles
- AEs which lead to dose modification
- AEs that are associated with a SAE
- AEs that are considered relevant by the Investigator

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 12 (8.33%)		
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 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic infarction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		

Thrombophlebitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	9		
Spinal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast swelling			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Body temperature increased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
C-reactive protein increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pulse abnormal			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Trigeminal nerve disorder			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haemolysis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	21		
Lymphopenia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	18		
Neutropenia			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	39		
Thrombocytopenia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	8		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Diarrhoea			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Tooth disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hyperkeratosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	5		
Rash papular			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Bursitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Joint pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Appetite disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hyponatremia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Bone pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported