Clinical trial results:
PHASE II TRIAL OF RITUXIMAB (MABTHERA®) PLUS LENALIDOMIDE (REVLIMID®) IN PATIENTS WITH LYMPHOMA OF THE MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT)

Summary

EudraCT number	2011-005818-10
Trial protocol	AT
Global end of trial date	28 February 2015

Results information

Result version number	v1
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	AGMT_MALT2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01611259
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	28 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical potential of Rituximab plus Lenalidomide to induce objective/histologic responses in patients with MALT lymphoma

Protection of trial subjects:

Safety was monitored by reporting of clinical adverse events. Patients were assessed regularly and were counselled before each Lenalidomide cycle.
Premedication was recommended for patients at high risk for a thromboembolic event and to prevent tumor lysis syndrome.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	21 May 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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	25

From 65 to 84 years	24
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

50 patients were enrolled in 4 sites in Austria. First patient in was 06-June-2012; last patient in was 26-May-2014.

Pre-assignment

Screening details:

Patients with histologically confirmed MALT lymphoma with measurable disease (stage I – IV) or with first or greater relapse after HP-eradication, radiation or chemotherapy in case of gastric lymphoma. If patients were withdrawn within the first 12 weeks of the study (i.e. before the first response evaluation), they were replaced.

Period 1

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

Blinding implementation details:

None

Arms

Arm title	Treatment

Arm description:

Rituximab (Mabthera®) plus Lenalidomide (Revlimid®)

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab was administered on day 1 of each cycle in a dose of 375 mg/m² (28 day cycle). Restaging should be performed after three cycles. In case of at least stable disease, patients should receive another three courses of therapy. Patients with documented CR after 6 courses stopped therapy/study, while patients with PR or SD were given another two cycles for a maximum of 8 cycles.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dose of lenalidomide for investigation is 20 mg/day, orally on days 1 to 21 followed by 7 days pause (28 day cycle). Restaging should be performed after three cycles. In case of at least stable disease, patients should receive another three courses of therapy. Patients with documented CR after 6 courses stopped therapy/study, while patients with PR or SD were given another two cycles for a maximum of 8 cycles.

Number of subjects in period 1[1]	Treatment
Started	48
Completed	34
Not completed	14
Physician decision	1
Patient decision	7
Adverse event, non-fatal	4
Lack of efficacy	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Two of the enrolled patients withdrew their consents prior to study treatment and did not experience adverse events to other study procedures. These two patients were therefore excluded from intent-to-treat (ITT) and per-protocol (PP) efficacy assessments, safety assessments and listing of baseline characteristics.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description: Rituximab (Mabthera®) plus Lenalidomide (Revlimid®)	

Reporting group values	Treatment	Total	
Number of subjects	48	48	
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	65		
full range (min-max)	33 to 85	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	19	19	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

Rituximab (Mabthera®) plus Lenalidomide (Revlimid®)

Subject analysis set title	Efficacy assessment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

48 patients were included into safety assessment, two of them received treatment but no efficacy assessment was available. Therefore, these two patients were neither included into Intention-to-treat nor Per-protocol efficacy analysis.

Primary: Response

End point title	Response[1]

End point description:

The primary objective of this Phase II study is to evaluate the proportion of patients responding to Lenalidomide and Rituximab. In case of a reponse rate of < 40%, the combination is rejected as ineffective, while an active combination is defined at a minimum response rate of 60% based of findings with rituximab and lenalidomide mono-therapy.

End point type	Primary

End point timeframe:

40 weeks

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.
Response data for ITT was 36/46 = 78.26%, 95%CI (63.64% - 89.05%).
78.3% of the patients showed response to study treatment. The combination of rituximab and lenalidomide met the predefined criteria for efficacy.

End point values	Efficacy assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Patients				
CR	23			
pMRD	2			
PR	10			
rRD	1			
SD	9			
PD	1			

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Serious adverse events	Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 48 (37.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			

subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhea				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Colecystitis				
subjects affected / exposed	1 / 48 (2.08%)			
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 / 48 (4.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				

subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacterial infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Skin infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.17 %

Non-serious adverse events	Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)		
Vascular disorders			
Thrombosis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	9 / 48 (18.75%)		
occurrences (all)	10		
Condition aggravated			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	17 / 48 (35.42%)		
occurrences (all)	20		
Mucositis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Night sweats			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	9		

Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 5 / 48 (10.42%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 11 / 48 (22.92%) 11 3 / 48 (6.25%) 3		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Haemoglobin subjects affected / exposed occurrences (all) Lymphocyte count subjects affected / exposed occurrences (all) Neutrophil count subjects affected / exposed occurrences (all) Platelet count subjects affected / exposed occurrences (all)	 2 / 48 (4.17%) 2 3 / 48 (6.25%) 5 3 / 48 (6.25%) 6 12 / 48 (25.00%) 28 3 / 48 (6.25%) 7		
Injury, poisoning and procedural complications Overdose subjects affected / exposed occurrences (all)	 3 / 48 (6.25%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Insomnia	 6 / 48 (12.50%) 11 		

subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	6		
Tremor			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Vertigo			
subjects affected / exposed	11 / 48 (22.92%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Leucocyte count			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	15		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	10 / 48 (20.83%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	9 / 48 (18.75%)		
occurrences (all)	16		
Dry mouth			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Gastrointestinal pain			

subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Meteorism			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	7 / 48 (14.58%)		
occurrences (all)	10		
Stomatitis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Eyelid oedema			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	23 / 48 (47.92%)		
occurrences (all)	34		
Rash			
subjects affected / exposed	23 / 48 (47.92%)		
occurrences (all)	39		
Skin ulcer			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 4 / 48 (8.33%) 5 6 / 48 (12.50%) 8 11 / 48 (22.92%) 15		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all)	 2 / 48 (4.17%) 2 2 / 48 (4.17%) 2 5 / 48 (10.42%) 6 4 / 48 (8.33%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 3 / 48 (6.25%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2013	New site added, shipment of blood samples clarified in protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: