Clinical trial results:
A two-part, multicentre, international phase I and II trial assessing the safety and efficacy of the Hsp90 inhibitor ganetespib in combination with paclitaxel weekly in women with high-grade serous, high-grade endometrioid, or undifferentiated, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer

Summary

EudraCT number	2013-003868-31
Trial protocol	AT DE BE
Global end of trial date	04 December 2017

Results information

Result version number	v1 (current)
This version publication date	28 June 2019
First version publication date	28 June 2019
Summary attachment (see zip file)	Summary GANNET53 (Update_2019-04-01.pdf)

Trial information

Trial identification

Sponsor protocol code	GANNET53

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02012192
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Innsbruck
Sponsor organisation address	Anichstraße 35, Innsbruck, Austria,
Public contact	Project Manager, AGO Studienzentrale, 0043 51250424132, ago.studienzentrale@i-med.ac.at
Scientific contact	Project Manager, AGO Studienzentrale, 0043 51250424132, ago.studienzentrale@i-med.ac.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	04 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2017
Global end of trial reached?	Yes
Global end of trial date	04 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to determine efficacy of ganetespib + paclitaxel weekly vs. paclitaxel weekly alone

Protection of trial subjects:

- Adherence to good clinical practice (GCP) and applicable law
- Definition of Inclusion/Exclusion criteria (the criteria were adapted during the conduct of the trial when new safety information was available)
- Safety assessments consisted of monitoring and recording of adverse events (including serious adverse events); measurement of protocol-specified vital signs
- Safety Data were evaluated regularly by the IDMC

Background therapy: -

Evidence for comparator:

Paclitaxel, as being part of the taxane family of medication, was chosen as active comparator. Paclitaxel given as single agent on a weekly basis at a dose of 80-90 mg/m2/week, proved to be one of the most effective regimens in this situation, with response rates in the range of 20-60% (Lortholary et al, Ann Oncol 23:346-52, 2012; Richard et al, Nature Reviews Clinical Oncology 7:575-82, 2010).

The combination of ganetespib and paclitaxel resulted in synergistic, anti-proliferative effects in vitro and in vivo. Concurrent treatment with both drugs resulted in a significant enhancement of antitumor activity compared to either agent alone (Proia et al, Invest New Drugs 6: 2210-9, 2012)

Clinical evidence for the combination of a taxane and ganetespib was provided by trials which have evaluated the combination of docetaxol and ganetespib. As of 21 September 2015, 408 patients were treated with this combination. These trials have shown well tolerance, a lack of drug-drug interactions in phase I trials, a similar safety profile in phase IIb/III trials compared to single agent use and promising preliminary efficacy in patients with advanced adenocarcinoma of the lung.

Actual start date of recruitment	01 April 2015
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	Austria: 2
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 47
Worldwide total number of subjects	133
EEA total number of subjects	133

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)	82
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period:
Part II: 13.04.2015 - 21.09.2016

Pre-assignment

Screening details:

The following study screening assessments are to be completed within 4 weeks (28 days) prior to study entry.
- Signed and dated informed consent
- Verification of in- and exclusion criteria
- High-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer.

Period 1

Period 1 title	Phase II: randomized, open-label,two-arm (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm P

Arm description:

Patients received a standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause.

Arm type	Active comparator
Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received a standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause.

Arm title	Arm P+G

Arm description:

Patients received 150 mg/m2 ganetespib (dose established in Part I) in combination with the standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause. After at least six cycles of ganetespib combination therapy the physician was allowed to discontinue paclitaxel and to continue maintenance with ganetespib at the dose level previously used in the combination or re-escalated to the ganetespib dose level 0.

Arm type	Experimental
Investigational medicinal product name	Ganetespib
Investigational medicinal product code	PR2
Other name	STA-9090
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

150 mg/m2

Number of subjects in period 1	Arm P	Arm P+G
Started	43	90
Completed	43	86
Not completed	0	4
Consent withdrawn by subject	-	1
Physician decision	-	3

Baseline characteristics

Reporting groups

Reporting group title	Arm P

Reporting group description:

Patients received a standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause.

Reporting group title	Arm P+G

Reporting group description:

Patients received 150 mg/m2 ganetespib (dose established in Part I) in combination with the standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause. After at least six cycles of ganetespib combination therapy the physician was allowed to discontinue paclitaxel and to continue maintenance with ganetespib at the dose level previously used in the combination or re-escalated to the ganetespib dose level 0.

Reporting group values	Arm P	Arm P+G	Total
Number of subjects	43	90	133
Age categorical Units: Subjects			
Adults (18-64 years)	25	57	82
From 65-84 years	18	33	51
Age continuous Units: years			
median	62	61	
full range (min-max)	46 to 81	40 to 79	-
Gender categorical Units: Subjects			
Female	43	90	133
Male	0	0	0

Subject analysis sets

Subject analysis set title	Arm P / Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety will include all patients who received at least one dose of study drug. In the safety analyses, patients will be included in the arm into which they have actually been randomized.

Subject analysis set title	Arm P / ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all randomized patients. Analyses of this population assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Subject analysis set title	Arm P / PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population includes all patients who received at least one dose of study treatment without major protocol deviations.

Subject analysis set title	Arm P+G / ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all randomized patients. Analyses of this population assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Subject analysis set title	Arm P+G / Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety will include all patients who received at least one dose of study drug. In the safety analyses, patients will be included in the arm into which they have actually been randomized.

Subject analysis set title	Arm P+G / PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population includes all patients who received at least one dose of study treatment without major protocol deviations.

Reporting group values	Arm P / Safety	Arm P / ITT	Arm P / PP
Number of subjects	43	43	42
Age categorical Units: Subjects			
Adults (18-64 years)	25	25	24
From 65-84 years	18	18	18
Age continuous Units: years			
median	62	62	62
full range (min-max)	46 to 81	46 to 81	46 to 81
Gender categorical Units: Subjects			
Female	43	43	42
Male	0	0	0

Reporting group values	Arm P+G / ITT	Arm P+G / Safety	Arm P+G / PP
Number of subjects	90	90	86
Age categorical Units: Subjects			
Adults (18-64 years)	57	57	54
From 65-84 years	33	33	32
Age continuous Units: years			
median	61	61	61
full range (min-max)	40 to 79	40 to 79	40 to 79
Gender categorical Units: Subjects			
Female	90	90	86
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm P

Reporting group description:

Patients received a standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause.

Reporting group title	Arm P+G

Reporting group description:

Patients received 150 mg/m2 ganetespib (dose established in Part I) in combination with the standard dose of 80 mg/m2 paclitaxel weekly.
Patients received the therapy until disease progression or EoT due to any other cause. After at least six cycles of ganetespib combination therapy the physician was allowed to discontinue paclitaxel and to continue maintenance with ganetespib at the dose level previously used in the combination or re-escalated to the ganetespib dose level 0.

Subject analysis set title	Arm P / Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety will include all patients who received at least one dose of study drug. In the safety analyses, patients will be included in the arm into which they have actually been randomized.

Subject analysis set title	Arm P / ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all randomized patients. Analyses of this population assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Subject analysis set title	Arm P / PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population includes all patients who received at least one dose of study treatment without major protocol deviations.

Subject analysis set title	Arm P+G / ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all randomized patients. Analyses of this population assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Subject analysis set title	Arm P+G / Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety will include all patients who received at least one dose of study drug. In the safety analyses, patients will be included in the arm into which they have actually been randomized.

Subject analysis set title	Arm P+G / PP
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population includes all patients who received at least one dose of study treatment without major protocol deviations.

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS was defined as the days between randomization and the date of documented progression or death of any cause. For patients whose progression status could not be determined, their PFS data was censored at the last assessment date that the patient was confirmed to have no progression.
Progression was evaluated according to RECIST 1.1 (therefore scans were performed of the chest (by X-ray or preferably by CT scan), abdomen and pelvis by CT scan (or MRI scans)) or by CA-125 as well as by the investigator on the basis of physical and/or gynecological examinations. Evidence of progressive disease was considered clear radiological, clinical, or symptomatic evidence. CA-125 evaluation alone

was not defined as disease progression.

End point type	Primary

End point timeframe:

Patients were assessed for disease response and progressive disease throughout the trial.
Baseline assessment: 28 days before first dose of study drug
Post baseline assessment: every 8 weeks (+/- 1 week) from date of randomization

End point values	Arm P	Arm P+G	Arm P / ITT	Arm P / PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	43	90	43	42
Units: Months				
median (confidence interval 95%)	5.329 (4.006 to 6.652)	3.454 (3.092 to 3.882)	5.329 (4.006 to 6.652)	5.329 (4.002 to 6.636)

End point values	Arm P+G / ITT	Arm P+G / PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	86		
Units: Months				
median (confidence interval 95%)	3.487 (3.092 to 3.882)	3.454 (2.681 to 4.226)		

Statistical analyses

Statistical analysis title	PFS in ITT population
Comparison groups	Arm P / ITT v Arm P+G / ITT
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.304
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.897
upper limit	1.895

Statistical analysis title	PFS in PP population
Comparison groups	Arm P / PP v Arm P+G / PP

Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.911
upper limit	1.943

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the days between randomization and the date of documented death from any cause. For patients whose survival status could not be determined, their OS data was censored at the last documented date that the patient is confirmed to be alive.

End point type	Secondary

End point timeframe:

Survival status was observed throughout the study by regular visits of the patient. After the treatment period, the patient had regular long-term follow-ups in three-monthly intervals (+/- 14 days) where the survival status was recorded.

End point values	Arm P / ITT	Arm P / PP	Arm P+G / ITT	Arm P+G / PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	42	90	86
Units: Months				
median (confidence interval 95%)	14.901 (7.585 to 22.218)	12.336 (5.274 to 19.397)	10.954 (9.190 to 12.718)	10.658 (8.690 to 12.626)

Statistical analyses

Statistical analysis title	OS in ITT population
Comparison groups	Arm P+G / ITT v Arm P / ITT
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.399

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.902
upper limit	2.171

Statistical analysis title	OS in PP population
Comparison groups	Arm P / PP v Arm P+G / PP
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.402
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.897
upper limit	2.192

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

ORR was estimated as the proportion of responders, defined as a patient whose best overall response is partial response (PR) or complete response (CR) during the treatment period (best ORR). ORR was considered confirmed when the result was repeated in the following efficacy assessment, no less than four weeks later (confirmed ORR). Response was evaluated according to RECIST 1.1 (therefore scans were performed of the chest (by X-ray or preferably by CT scan), abdomen and pelvis by CT scan (or MRI scans)) or by CA-125 as well as by the investigator on the basis of physical and/or gynecological examinations. An objective response was confirmed by repeated assessment not earlier than 4 weeks after initial documentation (e.g. CA-125 measurement) or at the next scheduled tumor assessment if it was to occur more than 4 weeks after the initial response.

End point type	Secondary

End point timeframe:

Patients were assessed for disease response and progressive disease throughout the trial
Baseline assessment: within a maximum of 28 days before first dose of study drug
Post-baseline assessments: every 8 weeks (+/- 1 week) from date of randomization

End point values	Arm P / ITT	Arm P / PP	Arm P+G / ITT	Arm P+G / PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	42	90	86
Units: Percentage of patients [%]				
Best objective response rate (best ORR)	40	38	26	26
Confirmed best ORR	28	29	14	14

Statistical analyses

Statistical analysis title	Phase II: Best ORR in ITT
Comparison groups	Arm P / ITT v Arm P+G / ITT
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Mantel-Haenszel

Statistical analysis title	Phase II: Best ORR in PP
Comparison groups	Arm P / PP v Arm P+G / PP
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155
Method	Mantel-Haenszel

Statistical analysis title	Phase II: Confirmed best ORR in ITT
Comparison groups	Arm P / ITT v Arm P+G / ITT
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394
Method	Mantel-Haenszel

Statistical analysis title	Phase II: Confirmed best ORR in PP
Comparison groups	Arm P / PP v Arm P+G / PP
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety was assessed for each patient at each patient contact throughout the trial.

Adverse event reporting additional description:

Assessment started after informed consent had been obtained and events were reported until safety follow-up or EoT, event resolutaion to baseline, event was assessed as stable, patient is lost to FU or withdrew consent.
Adverse Events (AEs) were measured according to NCI CTCAE version 4.03; laboratory parameters, ECOG PS and vital signs.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Arm P+G
Reporting group description: -	
Reporting group title	Arm P

Reporting group description: -

Serious adverse events	Arm P+G	Arm P	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 86 (72.09%)	18 / 43 (41.86%)	
number of deaths (all causes)	64	29	
number of deaths resulting from adverse events	4	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemobilia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Fever			
subjects affected / exposed	1 / 86 (1.16%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 86 (2.33%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death NOS			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			

subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rupture of renal pelvis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Icterus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	1 / 86 (1.16%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 86 (3.49%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occlusive syndrome			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	2 / 86 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Subileus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subobstruction colon			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Erysipelas			
subjects affected / exposed	0 / 86 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystitis noninfective			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal insufficiency			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc prolapse			
subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter related infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection NOS	Additional description: Reported Term: Infection back		
subjects affected / exposed	0 / 86 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 86 (5.81%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Urinary tract infection			
subjects affected / exposed	3 / 86 (3.49%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm P+G	Arm P	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 86 (100.00%)	41 / 43 (95.35%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

Hot flashes			
subjects affected / exposed	0 / 86 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Hypotension			
subjects affected / exposed	5 / 86 (5.81%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Lymphoedema			
subjects affected / exposed	5 / 86 (5.81%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 86 (25.58%)	11 / 43 (25.58%)	
occurrences (all)	34	14	
Oedema limbs			
subjects affected / exposed	7 / 86 (8.14%)	4 / 43 (9.30%)	
occurrences (all)	7	4	
Oedema peripheral			
subjects affected / exposed	6 / 86 (6.98%)	7 / 43 (16.28%)	
occurrences (all)	6	7	
Fatigue			
subjects affected / exposed	26 / 86 (30.23%)	8 / 43 (18.60%)	
occurrences (all)	32	9	
Fever			
subjects affected / exposed	10 / 86 (11.63%)	0 / 43 (0.00%)	
occurrences (all)	10	0	
Malaise			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Mucosal inflammation			
subjects affected / exposed	5 / 86 (5.81%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	5 / 86 (5.81%)	3 / 43 (6.98%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			

Common cold			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	5	
Cough			
subjects affected / exposed	5 / 86 (5.81%)	3 / 43 (6.98%)	
occurrences (all)	5	3	
Dyspnoea			
subjects affected / exposed	13 / 86 (15.12%)	9 / 43 (20.93%)	
occurrences (all)	16	12	
Epistaxis			
subjects affected / exposed	5 / 86 (5.81%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 86 (18.60%)	4 / 43 (9.30%)	
occurrences (all)	16	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	13 / 86 (15.12%)	0 / 43 (0.00%)	
occurrences (all)	29	0	
Lymphocyte count decreased			
subjects affected / exposed	9 / 86 (10.47%)	4 / 43 (9.30%)	
occurrences (all)	13	9	
Neutrophil count decreased			
subjects affected / exposed	26 / 86 (30.23%)	10 / 43 (23.26%)	
occurrences (all)	45	21	
Weight loss			
subjects affected / exposed	9 / 86 (10.47%)	0 / 43 (0.00%)	
occurrences (all)	10	0	
White blood cell count decreased			

subjects affected / exposed	13 / 86 (15.12%)	6 / 43 (13.95%)	
occurrences (all)	20	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 86 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	5 / 86 (5.81%)	5 / 43 (11.63%)	
occurrences (all)	5	5	
Headache			
subjects affected / exposed	10 / 86 (11.63%)	2 / 43 (4.65%)	
occurrences (all)	10	2	
Neuropathy peripheral			
subjects affected / exposed	35 / 86 (40.70%)	21 / 43 (48.84%)	
occurrences (all)	42	26	
Paresthesia			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	56 / 86 (65.12%)	27 / 43 (62.79%)	
occurrences (all)	89	52	
Thrombocytopenia			
subjects affected / exposed	7 / 86 (8.14%)	0 / 43 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 86 (9.30%)	2 / 43 (4.65%)	
occurrences (all)	11	2	
Abdominal pain			
subjects affected / exposed	31 / 86 (36.05%)	12 / 43 (27.91%)	
occurrences (all)	41	13	
Constipation			
subjects affected / exposed	21 / 86 (24.42%)	9 / 43 (20.93%)	
occurrences (all)	32	12	
Diarrhoea			

subjects affected / exposed	73 / 86 (84.88%)	15 / 43 (34.88%)	
occurrences (all)	405	28	
Dry mouth			
subjects affected / exposed	6 / 86 (6.98%)	2 / 43 (4.65%)	
occurrences (all)	6	2	
Dyspepsia			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 86 (6.98%)	2 / 43 (4.65%)	
occurrences (all)	6	2	
Mucositis oral			
subjects affected / exposed	5 / 86 (5.81%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Nausea			
subjects affected / exposed	41 / 86 (47.67%)	21 / 43 (48.84%)	
occurrences (all)	97	51	
Vomiting			
subjects affected / exposed	29 / 86 (33.72%)	9 / 43 (20.93%)	
occurrences (all)	56	12	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	35 / 86 (40.70%)	14 / 43 (32.56%)	
occurrences (all)	36	14	
Dry skin			
subjects affected / exposed	8 / 86 (9.30%)	0 / 43 (0.00%)	
occurrences (all)	8	0	
Erythema			
subjects affected / exposed	0 / 86 (0.00%)	5 / 43 (11.63%)	
occurrences (all)	0	7	
Nail infection NOS			
subjects affected / exposed	0 / 86 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	7 / 86 (8.14%)	2 / 43 (4.65%)	
occurrences (all)	8	2	

Rash			
subjects affected / exposed	5 / 86 (5.81%)	4 / 43 (9.30%)	
occurrences (all)	5	5	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	9 / 86 (10.47%)	4 / 43 (9.30%)	
occurrences (all)	11	5	
Muscle spasms			
subjects affected / exposed	11 / 86 (12.79%)	2 / 43 (4.65%)	
occurrences (all)	13	2	
Myalgia			
subjects affected / exposed	0 / 86 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	9 / 86 (10.47%)	3 / 43 (6.98%)	
occurrences (all)	10	3	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	5 / 86 (5.81%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Urinary tract infection			
subjects affected / exposed	8 / 86 (9.30%)	6 / 43 (13.95%)	
occurrences (all)	11	6	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	18 / 86 (20.93%)	6 / 43 (13.95%)	
occurrences (all)	29	6	
Hypokalaemia			

subjects affected / exposed occurrences (all)	7 / 86 (8.14%) 7	3 / 43 (6.98%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2014	The protocol was amended to address the recommendations of the competent and ethical committees of the participating countries and the change in IMP labelling site from Landesapotheke Salzburg, Austria to Fisher Scientific Horsham, UK. (Protocol V1.5)
10 June 2014	The protocol was being amended to address the recommendations of the competent authority of France ANSM and a recommendation of the DSMC. The DSMC requests not to use bone marrow colony-stimulating factors during the DLT observation period in order not to bias the lasting of the neutropenia. The French competent authority ANSM requested restrictions in the cardiac monitoring procedure. (Protocol V1.6)
06 February 2015	The protocol was amended after the review of the Phase I DLT period data, to determine the safe dose of ganetespib to be used and to address the recommendations of the DSMC and agreements of the trial consortia. The entire document was changed to reflect the dosage of 150 mg/m² ganetespib to be used in Phase II of the GANNET53 protocol. Several chapters were changed according new information provided by the updated version of the Investigator's Brochure Edition 10 from 26 November 2014 and updated safety information from the GALAXY-1 trial. An adjustment to the PK sampling time points was made to incorporate the administration of the premedication for paclitaxel in the sampling time scheme. (Protocol V1.7)
11 January 2016	The protocol was amended after a change in the safety evaluation of the IMP ganetespib, review of the Phase II safety data, and to address the recommendations of the DSMC. The in- and exclusion criteria were extended to reduce the risk/increase the safety for GIP in our patient cohort. An adjustment to the updated IB Version 11 was made to keep safety information up to date. Time points of PRO assessment during Long-term FU were adapted to meet the decision of the PRO Committee. (Protocol V1.8)
18 February 2016	The protocol was amended to address the requests from the BfArM to reflect the gastro-intestinal perforation in the summary of known and potential risks of ganetespib. (Protocol V1.9)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

21 September 2016	The decision of the GANNET53 Steering Committee based on the recommendations of the DSMC and was taken primarily due to the decision of the company providing ganetespib to stop the production of ganetespib. As there were no proven significant unfavourable efficacy and safety concerns, the Steering Committee allowed screened and registered patients to be randomised. Patients who were on trial at the time of recruitment stop had to be informed by the investigator about the recruitment stop and the reasons for it and were allowed to continue the current treatment until progression, if the patient and their treating physician wished to do so.	-

Notes:

Limitations and caveats

None reported