GANNET53
EUROPEAN PROJECT

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

GANNET53: **Ganet**espib in metastatic, p**53**-muta**n**t, platinum-resistant ovarian cancer

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Confidentiality statement

The information contained in this protocol, especially unpublished data, is confidential. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Independent Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the coordinating investigator Nicole Concin and the Austrian AGO trial centre, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.

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1.1 Declaration of the sponsor and the coordinating investigator

The present study protocol was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the IMP as well as with the moral, ethical and scientific principles of good clinical practice, the latest version of the Declaration of Helsinki, the local laws and the regulations and the applicable regulatory requirements.

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The signatories above confirm that they have read this study protocol and agree that it contains all information required for study performance. They also agree to conduct the study as set out in this protocol. It has been understood that all documentation previously not published will be kept in strictest confidence.

Protocol authorisation – Investigator

Study title

GANNET53
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 peritoneal cancer.

Version: 1. 9
EudraCT Number: 2013-003868-31

Principal investigator (Name in capital letters) _____

I declare that the study mentioned above will be conducted according to AMG/ICH-GCP Guidelines (ICH-E6; CPMP/135/95) and the most recent version of the Declaration of Helsinki.
To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating in this study.

I consent to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor or national and/or foreign regulatory, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorised individuals.
I agree to inform the sponsor immediately in case a regulatory authority inspection is scheduled.

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2. TABLE OF CONTENTS

1. CONTACTS & SIGNATURES 3
1.1 Declaration of the sponsor and the coordinating investigator 4
2. TABLE OF CONTENTS 6
3. PROTOCOL SYNOPSIS 9
Part I: dose escalation/de-escalation phase I study 13
Part II: randomised, open-label, two-arm, phase II study 13
4. SCHEMATIC DIAGRAM OF THE STUDY DESIGN 14
5. ABBREVATIONS AND DEFINITIONS 15
6. BACKGROUND INFORMATION 18
6.1 Disease 18
6.2 Scientific background 19
6.3 The investigational medicinal product ganetespib 21
6.3.1 Preclinical experience 21
6.3.2 Clinical experience 22
6.3.3 Ganetespib synergises with paclitaxel in vitro and in vivo 24
6.3.3.1 Clinical evidence for combination of taxane + ganetespib 24
6.3.4 Other clinical data of interest 27
7. STUDY DESIGN 27
7.1 Description of study 27
7.2 Part I: phase I dose escalation/de-escalation study 27
7.2.1 3 + 3 design 28
7.2.2 Dose-limiting toxicity (DLT) at the ganetespib dose level of 75 mg/m^2 30
7.3 Part II randomised, open-label, two-arm phase II study 30
7.4 Subject population 31
7.4.1 Subject eligibility 32
7.4.1.1 Inclusion criteria 32
7.4.1.2 Exclusion criteria 33
7.5 Study duration 34
7.6 End of study 35
7.6.1 Premature termination of the study 35
7.6.1.1 Study site discontinuation 36
7.6.2 Withdrawal and replacement of subjects 36
7.6.2.1 Discontinuation from IMP or non-IMP 37
7.6.2.2 Replacement of patients during part I of the trial 37
7.6.2.3 Replacement of patients during part II of the trial 37
7.7 Study objectives 37
7.7.1 Part I: dose escalation/de-escalation phase I study 37
7.7.2 Part II: randomised, open-label, two-arm, phase II study 38
7.8 Randomisation and stratification 38
7.9 Statistical analysis 39
7.9.1 Analysis populations 39
7.9.2 Part I statistical analysis 39
7.9.3 Part II statistical analysis (including sample size calculation) 39

7.10 Risk-benefit considerations 42
8. STUDY PROCEDURES 43
8.1 Before treatment start/screening (days -28 to -1) 44
8.2 Treatment period 45
8.3 Part I & II end of treatment/Safety follow-up 49
8.4 Part I and II long-term follow-up 49
8.4.1 Long-term FU in patients who discontinues treatment prior to progression 50
9. STUDY ASSESSMENTS 50
9.1 Tumour response assessment 50
9.1.1 Radiologic tumour assessments 51
9.1.2 GCIG criteria 51
9.2 Patient-reported outcome (PRO) 52
9.2.1 PRO instruments 52
9.2.2 PRO assessment schedule 52
9.2.3 PRO assessment procedure 52
9.3 Concomitant medications/therapies 53
9.4 Physical examination 53
9.5 Electrocardiography and LVEF 53
9.6 Laboratory assessments 55
9.7 Biomarker analysis in part II 55
9.7.1 Determination of p53 status and other biomarkers in collected biomaterials in phase II 55
9.8 Pharmacokinetic (PK) analysis in Phase II, at selected centres 56
10. STUDY MEDICATION 58
10.1 Dosage and administration 58
10.1.1 Dose reduction levels for ganetespib 59
10.1.2 Dose reduction levels for paclitaxel 60
10.1.3 Dose modifications 61
10.1.3.1 Dose modification for hypertransaminasaemia (AST/ALT) 61
10.1.3.2 Dose modification for neutropenia 61
10.1.3.3 Dose modification for hyperbilirubinaemia 62
10.1.3.4 Dose modification for thrombocytopenia 62
10.1.3.5 Dose modification for peripheral neuropathy 63
10.1.3.6 Dose modification for ganetespib-related gastrointestinal toxicity 63
10.1.3.7 Dose modification for ganetespib-related QTc prolongation 63
10.1.4 Management guidelines of the most significant AE diarrhoea 64
10.1.5 Study drug interruption or discontinuation 64
10.1.6 Dose-limiting toxicity (DLT) in phase I 65
10.2 Summary of known and potential risks of the study drug ganetespib 69
10.2.1 Medications used with caution 70
10.2.1.1 Inhibitors of P-glycoprotein efflux Transporters 70
10.2.1.2 Medications associated with QTc interval prolongation 70
10.2.1.3 Substrates of CYP3A4 or CYP2C19 70
10.3 Summary of known and potential risks of paclitaxel 71
10.3.1 Study drug delivery & drug storage conditions 72
10.3.2 Study drug packaging and labelling 73

10.4 Concomitant medications 73
11. SAFETY DEFINITIONS AND REPORTING REQUIREMENTS 75
11.1 Adverse events 75
11.2 Serious adverse events (SAEs) 75
11.2.1 Hospitalisation – Prolongation of existing hospitalisation 76
11.2.2 Suspected unexpected serious adverse reactions (SUSARs) 76
11.2.3 Pregnancy 76
11.3 Severity of adverse events/Grading 77
11.4 Relationship to study drug 77
11.5 Procedures for recording of adverse events 78
11.5.1 Diagnosis versus signs and symptoms 78
11.5.2 Persistent or recurrent adverse events 78
11.5.3 Abnormal laboratory values or vital signs 78
11.5.4 Progression of underlying malignancy 79
11.6 Reporting procedures 79
11.6.1 Reporting procedures for SAEs and SUSARs 80
11.6.2 Adverse event reporting period 81
11.7 Handling of safety parameters 81
11.7.1 Treatment and follow-up of adverse events 81
11.7.2 Follow-up of abnormal laboratory test value 81
12. DOCUMENTATION AND DATA MANAGEMENT 82
12.1 Retention of documents/Investigator site file 82
12.1.1 Case report form (CRF) 82
12.2 Data and safety monitoring committee (DSMC) 82
12.3 Quality control and quality assurance 83
12.3.1 Periodic monitoring 83
12.3.2 Audit and inspections 83
12.4 Reporting and publications 83
12.4.1 Reports 83
12.4.2 Publication of study results 84
13. ETHICAL AND LEGAL ASPECTS 84
13.1 Informed consent of subjects 84
13.2 Acknowledgement/Approval of the study 84
13.2.1 Changes in the conduct of the study 85
13.3 Insurance 85
13.4 Ethics and Good Clinical Practice (GCP) 85
14. REFERENCES 86
15. APPENDICES 89

3. PROTOCOL SYNOPSIS

Title	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
Short title	**GANNET53**
EudraCT number	2013-003868-31
Protocol version/date	V 1.9 18 February 2016
Indication	Women with platinum-resistant, high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer
Phase/Design	**Part I:** Prospective, multicentre, international, phase I, dose escalation / de-escalation study. **Part II:** Prospective, multicentre, international, randomised, open-label, two-arm, phase II study.
Investigational product	**Ganetespib** Part I: initial dose: 100 mg/m^2, target dose: 150 mg/m^2 Part II: 150 mg/m^2
Non-investigational product	**Paclitaxel weekly**
Planned study duration	**Part I:** First patient in: June 2014 **Part II:** First patient in: April 2015 Estimated study duration: 66 months
Number of patients	**Part I:** 10 patients **Part II:** 222 patients
Sites / Countries	12 sites in 4 countries (Austria, Belgium, France, Germany)

Inclusion criteria Patients must meet the following criteria to be eligible for study entry:

- Ability to understand and willingness to sign and date a written informed consent document
- Female patients ≥18 years of age
- High-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer.
    - Patients in part II: High-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer confirmed by central histopathology through archival FFPE
- Platinum-resistant disease:
    - primary platinum-resistant disease: progression > 1 month and ≤ 6 months after completion of primary platinum-based therapy
    - secondary platinum-resistant disease (including secondary platinum-refractory disease): progression ≤ 6 months after (or during) reiterative platinum-based therapy
- Patients must have disease that is measurable according to RECIST 1.1 or assessable according to the GCIG CA-125 criteria, and require chemotherapy treatment ECOG performance status of 0-1
- Life expectancy of at least 3 months as assessed by the investigator
- Adequate function of the bone marrow:
    - Platelets ≥ 100 x 10^9/L
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Haemoglobin ≥ 8.5 g/dl. Patients may receive blood transfusion(s) to maintain haemoglobin values > 8.5 g/dl.
- Adequate organ functions:
    - Creatinine < 2 mg/dl (<177 µmol/L)
    - Total bilirubin ≤ 1.5 x upper limit of normal
    - SGOT/SGPT (AST/ALT) ≤ 3 x upper limit of normal
    - Urinanalysis or urine dipstick for proteinuria less than 2+. Patients with ≥ 2+ on dipstick should undergo 24-hour urine collection and must demonstrate < 1 g of protein/24 hours; except the proteinuria is clearly related to a catheter in the urinary system.
- Adequate coagulation parameters: aPTT ≤ 1.5 x ULN (patients on heparin treatment must have an aPTT between 1.5 – 2.5 x ULN), or INR ≤ 1.5. (In patients receiving anticoagulants (such as warfarin) INR must be between 2.0 and 3.0 in two consecutive measurements 1-4 days apart).
- Negative urine/serum pregnancy test in women of childbearing potential (WOCBP, see section 5). WOCBP who are sexually active, agree to use highly-effective means of contraception during the study and for at least 6 months post-study treatment. Allowed are accepted and effective non-hormonal methods of contraception and sexual abstinence or vasectomised partners (> 3 months

previously). Vasectomy has to be confirmed by two negative semen analyses.

Only in part II of the trial:

- *Availability of archival ovarian cancer tissue for central histopathological review and p53 mutational analysis*

Exclusion criteria Patients who meet any of the following criteria will be excluded from study entry:

CANCER-RELATED:

- Ovarian tumours with low malignant potential (i.e. borderline tumours)
- Carcinosarcoma of the ovary
- Primary platinum-refractory disease (progression during primary platinum-based chemotherapy)

PRIOR, CURRENT OR PLANNED TREATMENT:

- Previous treatment with > 2 chemotherapy regimens in the platinum-resistant setting (excluding targeted and endocrine therapies).
- Previous weekly paclitaxel in relapse treatment
- More than 4 previous lines of chemotherapy.
- Any prior radiotherapy to the pelvis or abdomen
- Surgery (including open biopsy and traumatic injury) within 4 weeks prior to first dose of ganetespib, or anticipation of the need for major surgery during study treatment
- Minor surgical procedures, within 24 hours prior to the first study treatment
- Current or recent (within 10 days prior to the first study drug dose) chronic daily treatment with aspirin (>325 mg/day).
- Chronic daily treatment with corticosteroids (dose >10 mg/day methylprednisolone equivalent), excluding inhaled steroids.

PRIOR OR CONCOMITANT CONDITIONS OR PROCEDURES:

- Patients with a history of prior malignancies, except:
    - disease-free time-frame of ≥ 3 years prior to randomisation.
- Patients with prior in-situ carcinomas, except:
    - complete removal of the tumour is given
- Known history of severe (grade 3 or 4) allergic or hypersensitivity reactions to excipients (e.g. polyethylene glycol [PEG] 300 and Polysorbate 80)
- History of intolerance or hypersensitivity to paclitaxel and/or adverse events related to paclitaxel that resulted in paclitaxel being permanently discontinued
- Peripheral neuropathy of grade > 2 per NCI CTCAE, version 4.03, within 4 weeks prior to randomisation

- Clinically significant gastro-intestinal (GI) tract abnormalities that may increase the risk for GI bleeding and/or perforation including but not limited to: active peptic ulcer disease, known intraluminal metastatic lesion/s with risk of bleeding, inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), history of bowel obstruction within 1 year prior to first study treatment (excluding postoperative, i.e. within 4 weeks post surgery), other GI condition with increased risk of perforation such as a recurrence deeply infiltrating into the muscularis or mucosa of the rectosigmoid or the mucosa of the bladder, or history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess
- Non-healing wound or non-healing bone fracture
- Patients with symptomatic brain metastases
- Left ventricular ejection fraction defined by ECHO below the institutional lower limit of normal
- Cerebrovascular accident (CVA) / stroke or transient ischemic attack (TIA) or sub-arachnoid haemorrhage within ≤6 months prior to first study treatment.
- Significant cardiac disease: New York Heart Association (NYHA) Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary artery bypass graft (CABG) within the past 6 months; or uncontrolled atrial or ventricular cardiac arrhythmias.
- History of prolonged QT syndrome, or family member with prolonged QT syndrome
- QTc interval > 470 msec when 3 consecutive ECG values are averaged
- Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug (e.g. quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g. sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted
- Second- or third-degree atrioventricular (AV) block, except:
    - treated with a permanent pacemaker
- Complete left bundle branch block (LBBB)
- History of evidence of haemorrhagic disorders, patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorders, coagulopathy or tumour involving major vessels.

Any other condition that, in the opinion of the investigator, may compromise the safety, compliance of the patient, or would preclude the patient from successful completion of the study.

- Participation in another clinical study with experimental therapy within 28 days before start of treatment.
- Women who are pregnant or are lactating

Endpoints

Part I: dose escalation/de-escalation phase I study

The primary aim of the phase I study is to determine the safety of ganetespib in combination with weekly paclitaxel and also to determine the ganetespib combination dose to be used in the randomised phase II study.

Primary endpoint:

- Safety: Adverse events (AEs) (measure according to NCI CTCAE, version 4.03), laboratory parameters, Eastern Cooperative Oncology Group (ECOG) performance status (PS), vital signs

Secondary endpoint:

- Objective response rate (ORR)
- Progression-free survival (PFS)

Part II: randomised, open-label, two-arm, phase II study

The primary aim of the phase II study is to determine efficacy of ganetespib in combination with weekly paclitaxel compared to weekly paclitaxel alone.

Primary endpoint:

- Progression-free survival (PFS) and PFS rates at 6 months

Secondary endpoints:

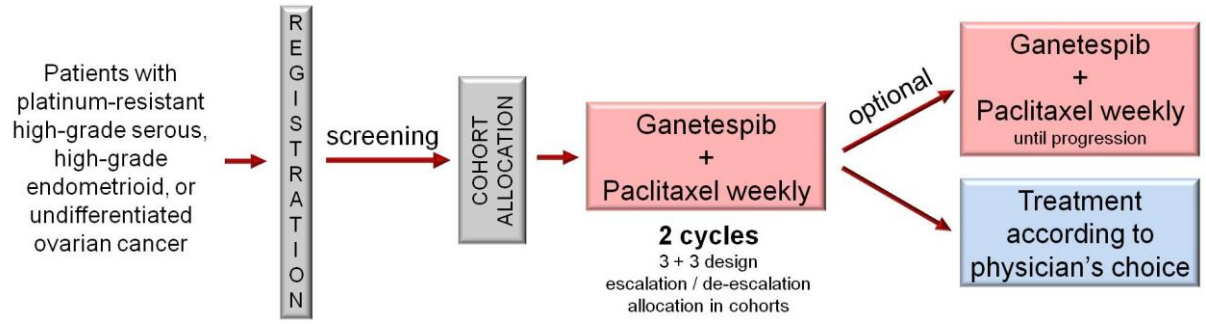
- Overall survival (OS),
- Objective response rate (ORR): best ORR, confirmed ORR
- Post-progression PFS (PFS II)
- Patient-reported outcome: EORTC C30, EORTC OV28, and additional items
- Safety: AEs (according to NCI CTCAE, version 4.03), laboratory parameters, ECOG PS, vital signs
- Pharmacokinetics (only in 30 patients in selected sites)
    - evaluate the possible effects of paclitaxel on ganetespib pharmacokinetics
    - evaluate the possible effects of ganetespib on paclitaxel pharmacokinetics
    - quantify ganetespib and ganetespib metabolite exposures in the presence of paclitaxel

Exploratory endpoints

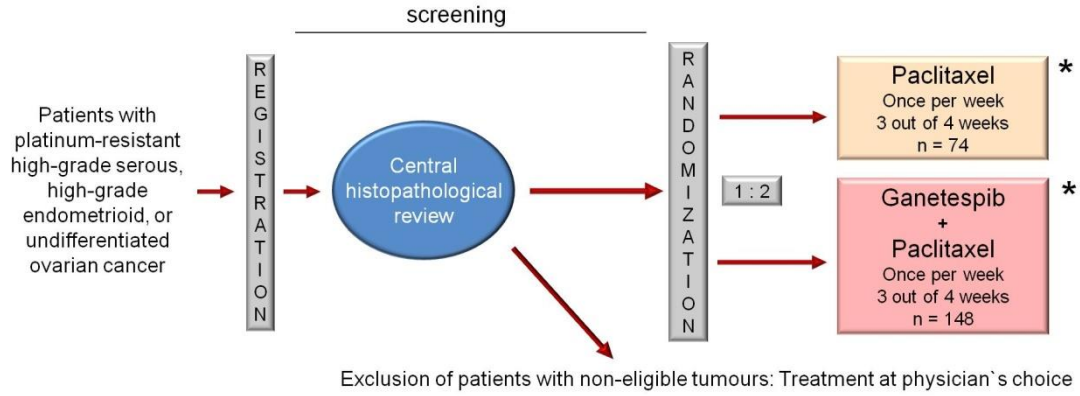
- Molecular efficacy analysis
- Biomarker analysis e.g. p53 status on DNA, RNA and protein level

4. SCHEMATIC DIAGRAM OF THE STUDY DESIGN

Part I



Part II



* until disease progression or EOT of any other causes.

5. ABBREVATIONS AND DEFINITIONS

17AAG	17-allylamino-17-demethoxygeldanamycin
AE	adverse events
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
Akt	protein kinase B
ALT (SGPT)	alanine-aminotransferase
ALK	anaplastic lymphoma kinase
AMG	Arzneimittelgesetz (Austrian Drug Law, German Drug Law)
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST (SGOT)	aspartate-aminotransferase
ATPase	adenosine triphosphatase
AUC	area under the curve
bcr-abl	fusion gene
BRAF	v-raf murine sarcoma viral oncogene homolog B
BSA	body surface area
B-Raf	proto-oncogene
CA	Competent Authority
CA-125	carbohydrate antigen 125
CABG	coronary artery bypass graft
CDK4	cyclin-dependent kinase 4
C_{max}	maximum drug concentration
c-MET	proto-oncogene
CRF	case report form
CRO	clinical research organisation
c-Src	proto-oncogene tyrosine-protein kinase Src
CT	computed tomography
CTC	circulating tumour cells
CTCAE	common terminology criteria for adverse events
CTNNB1	catenin (cadherin-associated protein), beta 1
CYP	cytochrome protein
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DSMC	data and safety monitoring committee
EC	Ethics Committee
ECG	electrocardiography
ECOG PS	Eastern Co-Operative Oncology Group performance status
EGFR	epidermal growth factor receptor
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EOS	end of study
EOT	end of treatment
EpCAM	epithelial cell adhesion molecule
ERBB2	v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2

FP6	6th framework programme
FPI	first patient in
GCIG	Gynaecologic Cancer Intergroup
GCP	Good Clinical Practice
GI	gastrointestinal
GOF	gain-of-function
GOG	Gynaecologic Oncology Group
HER2	human epidermal growth factor receptor 2
HGS	high-grade serous
HR	hazard ratio
Hsp90	heat shock protein 90
Hsp90i	Hsp90 inhibitor
ICH	International Conference of Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMP	investigational medical product
IRB	institutional review board
IST	investigator-sponsored clinical trial
ITT	intention-to-treat
iv	intravenous
KIT	signalling protein
KRAS	v-ki-ras2 kirsten rat sarcoma viral oncogene homolog
LCK	lymphocyte-specific protein tyrosine kinase
LDH	lactate dehydrogenase
LLT	lower level terms
M	month
MDM2	mouse double minute 2 homolog
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUC1	mucin 1
mutp53	mutant p53
NCI	National Cancer Institute
NSCLC	non small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
p53	tumour protein
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PICCS	peripherally-inserted central catheters
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PK	pharmacokinetics
PLA	proximity ligation assay
PLD	pegylated liposomal doxorubicin
PROC	platinum-resistant ovarian cancer

PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
Pt-R	platinum-resistant
QT	interval between Q wave and T wave in the hearts electrical cycle
R172H	hot-spot mutation in human tumours
RBC	red blood cells
RECIST	response evaluation criteria in solid tumours
SAE	serious adverse event
SAHA	suberoylanilide hydroxamic acid
SOP	standard operating procedures
SGOT	serum glutamate-oxaloacetate-transaminase
SGPT	serum glutamate-pyruvate-transaminase
SUSAR	suspected unexpected serious adverse reaction
TCGA	Cancer Genome Atlas Research Network
TdP	Torsades de Pointes
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
VAD	vascular access devices
VEGFR	vascular endothelial growth factor receptors
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential
wtp53	wild type p53

Definitions

Women of childbearing potential (WOCBP): is defined as premenopausal women or less than 12 months of amenorrhoea post-menopause, and women who have not undergone surgical sterilisation or hysterectomy or bilateral salpingo-oophorectomy.

6. BACKGROUND INFORMATION

6.1 Disease

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy. Recent data from the EUROCARE database showed an age-standardised 5-year overall survival rate of EOC patients of only 36.1% (95% CI 35.4–36.8; (1)). Across Europe 66,700 women are diagnosed with ovarian cancer and 41,900 die of the disease every year. This high mortality rate is due to the predominance of late-stage diagnoses, a high relapse rate after primary therapy and poor response of metastatic platinum-resistant tumours to current regimens. 70% of EOC patients present with metastasised disease at the time of primary diagnosis (peritoneal carcinosis). The current standard of primary therapy is cytoreductive surgery and adjuvant platinum-based chemotherapy. The addition of bevacizumab has recently been shown to improved progression-free survival in women with ovarian cancer (2;3). Initial response rates to primary therapy are high, but *inevitably* the vast majority of patients will relapse within a short period of time and ultimately die of the disease.

A major treatment obstacle is the 25-30% of patients who are resistant to first-line platinum-based chemotherapy. By definition, they experience progressive or persistent disease *during* initial platinum-based therapy (primary platinum-refractory), or relapse of disease after *less than 6 months* after completion of first-line platinum-based therapy (primary platinum-resistant). Eventually most patients will become resistant to platinum after repetitive therapy with platinum-based regimens (secondary platinum-resistant disease).

Treatment options are limited for platinum-resistant (Pt-R) patients. There is general consensus that surgery is only indicated in selected cases, where palliation of symptoms has priority (4). No “standardised” chemotherapy is currently available and systemic treatment is highly dependent on the physician’s choice. A number of cytotoxic agents including non-pegylated or pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine and alkylating agents such as treosulphan or cyclophosphamide have shown a relatively modest anti-tumour activity as single agent. This is reflected by low response rates < 20% for each agent and only short lasting remissions (5;6). However, paclitaxel given as single agent on a weekly basis at a dose of 80-90 mg/m^2/week, proved to be *one of the most effective* regimens in this situation, with response rates in the range of 20-60% (7) (Richard et al, Nature Reviews Clinical Oncology 7:575-82, 2010). This efficacy is even seen in cases that exhibit resistance to paclitaxel administered every 3 weeks. It is noteworthy that the weekly schedule is by far less toxic. However, the progression-free interval may be short.
The large subgroup of ovarian cancer patients with PROC disease face particularly dismal survival rates with a *median progression-free survival* of 4 months and a *median overall survival* of only 14 months that did not improve in over 10 years (8). In sum, there is a pressing need for truly innovative and more effective treatment strategies to improve the survival in ovarian cancer patients with metastatic Pt-R disease.

Data from clinicopathological and molecular studies performed to date led to a model in which EOC can be divided into two broad categories, designated **type I and type II** tumours (9;10). In this model, type I and type II refer to critical molecular tumorigenic pathways and not to specific histopathological patterns.

Type II tumours are highly aggressive. They evolve rapidly, have a high metastatic activity and therefore have almost always already spread beyond the ovaries at primary diagnosis. Thus, this tumour type is the most problematic from a clinical point of view. Moreover, type II tumours account for the overwhelming majority (>70%) of epithelial ovarian cancer (EOC). Histologically, type II tumours are mainly high-grade serous (HGS) carcinomas, and the remainder are high-grade endometrioid, undifferentiated carcinomas or a subset of clear cell carcinomas. HGS carcinoma accounts for ~ 85 % of all ovarian cancer deaths.
Importantly, type II tumours are characterised by the near ubiquitous presence of *p53* mutations - their preeminent molecular hallmark, which in contrast are very rare in type I tumours. This strongly suggests that mutp53 is a central oncogenic driver in the pathogenesis of these tumours. Ahmed et al (11) sequenced exons 2-11 and intron-exon boundaries in DNA from 145 patients with HGS tumours and identified p53 mutations in 96.7% of cases. Also, the Cancer Genome Atlas Research Network (TCGA) completed whole-exome sequencing on an unprecedented 316 cases of HGS tumours and established that *p53 mutations* are present in > 96 % (12).
In sharp contrast, type I tumours almost always lack *p53* mutations, but often harbour somatic mutations of protein kinase genes including *PIK3CA* and *ERRB2*, and other signalling molecules including *KRAS*, *BRAF, CTNNB1* and *PTEN* (13). Type I tumours are slow-growing, often confined to the ovary at diagnosis, and develop in a stepwise fashion from well-recognised precursors, in most cases borderline tumours. Type I tumours include low-grade serous carcinomas, low-grade endometrioid carcinomas, mucinous carcinoma and a subset of clear cell carcinomas.
Based on the fact that type II tumours are the most lethal and the most prevalent EOC type and that mutp53 is the central oncogenic driver in these tumours, we will apply our novel therapeutic approach in a stratified molecularly-defined patient population with high-grade serous, high-grade endometrioid and undifferentiated EOC. This offers the highest potential for achieving the most profound survival benefit.

6.2 Scientific background

Stabilised mutant p53 protein (mutp53) is a novel, rational and potent druggable target in cancer treatment.

Missense mutp53 proteins (which make up > 85% of all p53 mutations) not only lose their tumour suppressor function, but often acquire new oncogenic functions (gain-of-function, GOF) to actively drive higher proliferation, metastatic ability and chemoresistance.

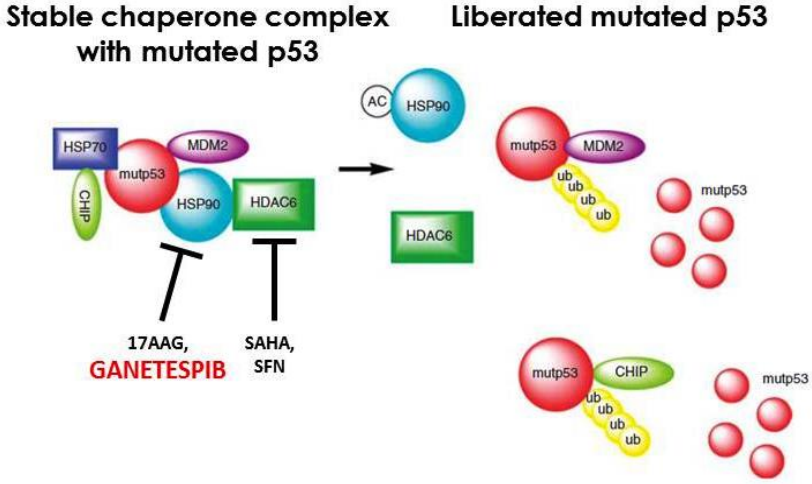
Compelling new evidence from mutp53 knock-in (KI) mice carrying human hotspot mutations provide definitive genetic proof for GOF in vivo (14-16): The knock-in mice show a broader tumour spectrum including adenocarcinomas, higher tumour bulk, grade and invasion, multiple tumour types per mouse, and newly gained metastatic ability compared to the traditionally used p53 null mice (knock-out) that mainly get T-lymphomas and never metastasise.

- Constitutive stabilisation is the hallmark of (full-length missense) mutp53 proteins in tumour cells and their aberrant accumulation is the prerequisite for exerting GOF. Most importantly, mutp53 cancers develop a strong dependency on high levels of mutp53 for survival (‘addiction’ to mutp53). This was recently proven with KI mice.

- As a consequence, acute withdrawal of mutp53 triggers strong spontaneous cytotoxicity, blocking invasion and metastasis and restoring chemotherapy-induced cell death in human cancer xenografts in vivo (17-20).

Due to their aberrant conformation mutp53 proteins depend on permanent folding support by the multi-component HspP90 chaperone machinery (which in turn is constitutively activated in tumour but not in normal cells), and it is this stable interaction between mutp53 and Hsp90 that is largely responsible for mutp53 accumulation specifically in tumour cells (Figure 1).
Pharmacological inhibition of the machine's core ATPase Hsp90 (such as by the highly potent second generation Hsp90 inhibitor ganetespib) destroys the complex between Hsp90 and mutp53, thereby liberating mutp53 and inducing its degradation by MDM2 and CHIP E3 ubiquitin ligases. As a consequence, Hsp90 blockade shows preferential and strong cytotoxicity for mutp53 cancer cells in culture and in xenografts. In contrast, wtp53 or nullp53 cells show only minimal responses. Moreover, Hsp90 blockade - by virtue of depleting mutp53 - dramatically sensitises mutp53 cancer cells to chemotherapeutics. Thus, Hsp90 inhibition mediates effective destabilisation and degradation of mutp53 in human tumour cells, acutely withdrawing an oncoprotein these cells depend on for survival. This is strongly cytotoxic in mutp53 harbouring tumour cells. Given the advanced development of Hsp90 inhibitors, this new paradigm holds immediate strong translational potential for significantly improving outcome in mutp53-driven cancers such as type II EOC.

Figure 1: Scientific principle of the GANNET53 trial (18)**.**



Destabilisation of mutant p53 protein by inhibition of the Hsp90 chaperone causes subsequent degradation by MDM2 or CHIP E3 ligases: Stable complex formation with Hsp90 causes aberrant stabilisation of mutp53 in cancer cells. MDM2 and CHIP, which in principle are capable of degrading mutp53, are unable to degrade mutp53 as long as it is protected by the complex ('caging'). Stabilised mutp53 exerts oncogenic gain-of-function (GOF). Acute depletion of mutp53 in tumour cells is strongly cytotoxic in all mutp53 solid cancer cell types tested (ovarian, breast, colon, and prostate). Small molecule inhibitors of the Hsp90 ATPase (such as the highly potent second generation Hsp90i ganetespib, or the weaker first generation 17AAG + SAHA [causes Hsp90 inhibition via HDAC6 inhibition, an obligate positive regulator of the Hsp90 ATPase]) acutely deplete mutp53, which is strongly cytotoxic in mutp53 harbouring tumour cells.

Hsp90 chaperone alterations in cancer: essential adaptive response to the malignant lifestyle and a second alteration that accounts for stabilisation of mutant p53 protein upon malignant transformation.
Molecular chaperones from the heat shock family (Hsp) - in particular the multi-component Hsp90 machine (which includes Hsp90 and Hsp70 ATPases, co-chaperones, CHIP) - are essential to guide proper (re)folding of stress-damaged and nascent polypeptide clients into

mature proteins. Intimately linked to this support function is that Hsp90 interactions also regulate protein levels of their clients (21). By a poorly understood mechanism the chaperone-associated E3 ubiquitin ligase CHIP can under certain conditions bind to Hsp90 and Hsp70 and promote degradation of a number of Hsp90-regulated clients, possibly if they cannot be rescued. Importantly, the normal Hsp90 function is subverted during oncogenesis to enable maintenance of malignant transformation ('co-oncogenesis'). This is due to massive up-regulation of Hsp90 that almost ubiquitously accompanies malignant transformation, and to differences in structure/affinity: Hsp90 purified from tumours has a 100-fold stronger binding affinity to its inhibitor 17AAG than Hsp90 purified from normal tissue, generating a cancer-specific therapeutic window (22). Cancer cells are in a constant state of proteotoxic stress, both from an adverse microenvironment (hypoxia, acidosis) and from within (conformationally aberrant or over-expressed oncoproteins such as ErbB2, bcr-abl, Akt and ALK fusions; high reactive oxygen species, spontaneous DNA damage, aneuploidy) - and require massive chaperone support to prevent oncoprotein aggregation and degradation and to promote cell survival. Hsp90 plays a key role in conformational stabilization of many mutant oncoprotein signalling clients and is a powerful anti-apoptotic system. Hence, in addition to their oncogene addiction, cancer cells are addicted to massive Hsp90 chaperone support (23).

6.3 The investigational medicinal product ganetespib

Ganetespib **(**Figure 2**)** exhibits its function by competitively inhibiting the ATPase activity of the Hsp90 core protein. The multicomponent Hsp90 (which includes Hsp90 and Hsp70 ATPases, co-chaperones, CHIP) is a molecular chaperone machine from the heat shock family and includes many important signalling proteins that cancers depend on, such as chimeric Alk, Akt, bcr-abl, B-Raf, CDK4, KIT, c-MET, c-Src, EGFR, LCK, HER2 and VEGFR. Of central importance is the fact that mutp53 was recently found to be a Hsp90 client (24;25). In vitro, ganetespib leads to degradation of oncogenic client proteins and is a potent inducer of cell death in many cancer cell lines that depend on high levels of the respective client.
In vivo, it inhibits the growth of human tumour cell lines in mouse xenograft models.

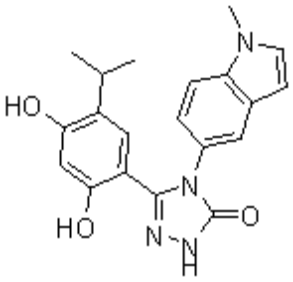


Figure 2: Chemical structure of ganetespib, chemical name: 5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-2,4 dihydro-4-(1-methyl-1H-indol-5-yl)-3H-1,2,4-triazole-3-one. Ganetespib is a novel triazolone heterocyclic compound. Its molecular formula is C20H20N4O3. Ganetespib is a white-to-off-white solid with a molecular weight of 364.40 g/mol.

6.3.1 Preclinical experience

ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION:
A series of nonclinical pharmacokinetic studies have been conducted in mice, rats, and monkeys. Ganetespib serum levels generally increased in a dose-proportional manner in all species after intravenous (iv) administration. No significant gender differences were observed. In mice, ganetespib's terminal half-life was about 4 hours after intravenous

administration. In rats, ganetespib's terminal half-life ranged from 2.8 to 12.6 hours. In monkeys, its terminal half-life was 6.3 to 12.3 hours. Ganetespib did not appear to accumulate after repeat dosing. There was minimal cytochrome P450 (CYP) involvement in the metabolism of ganetespib. The major metabolites were glucuronide conjugates.
Radioactively labelled ganetespib in rats was widely distributed throughout the body except in the brain. Ganetespib-associated radioactivity was mainly excreted via faeces in rats, and via faeces and urine in monkeys. Ganetespib was extensively bound to plasma proteins in rats, monkeys and humans. Ganetespib appears to be an inhibitor of CYP2C19 and CYP3A4 (midazolam-specific), but does not appear to be an inducer of CYP or uridine diphosphate-glucuronosyltransferase (UGT) enzymes.

TOXICOLOGY:
Several studies have been conducted in animals to assess the safety of ganetespib. Acute toxicity studies revealed that rats survived a single 30 mg/kg dose of ganetespib. Ganetespib at doses of 85 or 250 mg/kg elicited more pronounced effects, including morbidity and mortality. Histopathological findings were present in the spleen, thymus, adrenal glands, gastrointestinal (GI) tract, and the epiphyseal regions of the bones. High-dosed rats allowed to recover for 14 days generally returned to normal, although some effects persisted. In rats dosed with 30 mg/kg all findings reversed by 14 days. The maximum tolerated single-administration dose in cynomolgus monkeys was 11 mg/kg; clinical findings at that dose included emesis, watery faeces, and decreased activity. There was also a transient decrease in absolute lymphocyte counts. At 15 mg/kg, the clinical signs above were more pronounced and full recovery required 14 days.
Ganetespib administered once weekly at 4, 7 or 10 mg/kg for four weeks was generally well tolerated by cynomolgus monkeys. One female monkey given 10 mg/kg was euthanized after three doses due to ganetespib-related toxicity. Monkeys that were analysed to scheduled necropsy had clinical signs that were mild and included soft or liquid faeces. Target organs identified in the treated groups were stomach, gallbladder, testes and the sternal bone marrow; histopathologic changes included degeneration, apoptosis/single cell necrosis and decreased spermatogenesis/spermiogenesis. After four weeks of dosing-free recovery, all changes in the stomach and sternal bone marrow had resolved completely, while in the gallbladder and testes the changes had resolved partially. The mean exposure (AUC 0-24 h) in monkeys after four weekly doses of ganetespib at 7 mg/kg was 4729 ng/mL. The highest non-severely toxic dose administered once weekly was determined to be 7 mg/kg. In addition, a rising-dose cardiovascular assessment in cynomolgus monkeys showed acceptable cardiac effects, in particular no QT prolongation (Rising dose cardiovascular study, Study No: ECA00170, Charles River).

6.3.2 Clinical experience

Ganetespib has been studied in 10 completed Synta Pharmaceuticals-sponsored clinical trials (studies 9090-01, 9090-02, 9090-03, 9090-04, 9090-05, 9090-06, 9090-07, 9090-08, 9090-09 and 9090-11) and 3 completed Synta-sponsored studies in normal healthy volunteers (9090-12, 9090-13, and 9090-15). Ganetespib is currently being studied in 1 Synta-sponsored clinical trial (9090-14).Ganetespib has also been studied in 27 investigator-sponsored clinical trials (ISTs), 15 of which are currently enrolling patients and 12 ISTs that are closed to enrolment. The majority of ISTs are proof-of-concept studies across a variety of tumour types as well as hematologic malignancies. The ISTs currently enrolling include: four

phase I studies, six phase I/II studies, three phase II studies, one phase II/III study, and one phase III study. Please refer to Investigator's Brochure and http://clinicaltrials.gov for further information.
As of 21 September 2015, 1524 individuals (patients and normal, healthy volunteers) have received at least 1 dose of ganetespib in one of these 41 studies. A total of 402 patients have been treated with single-agent ganetespib (studies 9090-01 through study 9090-06, study 9090-09, and study 9090-11). A total of 412 patients have been enrolled in studies 9090-07 and 9090-08, of which 222 have been treated with ganetespib in combination with docetaxel. Six hundred forty seven (647) patients have been enrolled in study 9090-14, of which 327 patients received at least one dose of ganetespib. In Synta-sponsored studies of normal healthy volunteers, 102 subjects received ganetespib: 8 in the Human Mass Balance study (9090-12), 46 in the Thorough QT study (9090-13), and 48 in the DDI study (9090-15). The remaining patients (471) have been treated in investigator sponsored trials (ISTs).

PHARMACOKINETICS IN HUMANS:
The PK of ganetespib, administered at various doses on a weekly or twice weekly schedule, are under investigation in three phase I trials. Preliminary data and calculated parameters are available from these trials in patients with solid and hematologic tumours and normal healthy male subjects, and are summarised below.
Ganetespib PK shows distribution and elimination phases with concentrations declining by approximately 10-fold within the first hour and nearly 100 fold within 10 hours following infusion termination. Mean terminal half-lives have ranged from approximately 5 to 15 hours in most studies. In the human mass balance study, where PK sampling was most complete and longest (through 96 hours), the mean plasma terminal half-life was 17.9 h (n=8). Ganetespib plasma concentrations following the first and subsequent doses are comparable following either once or twice weekly dosing, indicating the lack of drug accumulation. Ganetespib plasma concentrations are also comparable in the solid and hematologic tumour patients. Cmax and AUC increase in approximate proportion to dose irrespective of dosing day with virtually identical dose exposure ratios for doses given on different days, indicating linear PK (r2 = 0.6680 and 0. 7234 for C_{max} and AUC versus dose, respectively). At doses of 150 mg/m² and 200 mg/m², AUC values of approximately 5600 ng•h/mL and 7600 ng•h/mL are generally expected, respectively. At these same doses, C_{max} values of approximately 3800 ng/mL and 5000 ng/mL, respectively, are generally expected. Ganetespib C_{max} correlates well with AUC (r2 = 0.9309). CL and Vd are approximately constant across therapeutic doses. Ganetespib median CL is approximately 27 L/h/m2.
Two ganetespib glucuronide metabolites (STA-12-0671 and STA-12-0672) were quantified in three studies; studies 9090-07 (ganetespib in combination with docetaxel), 9090-12 (human mass balance), and 9090-13 (thorough QT). Metabolite STA-12-0671 mean half-life values ranged from 11.9 to 27 hours. Metabolite STA-12-0672 mean half-life values ranged from 9.4 to 17.9 hours. For both metabolites, T_{max} was typically at the end of the ganetespib infusion and PK parameters were consistent across sampling days (days 1, 8, and 15).
In study 9090-12 following a single 1-hour IV infusion of 86 mg/m^2 [14C]-ganetespib, median T_{max} total radioactivity in plasma and whole blood occurred at the end of the IV infusion. Total plasma radioactivity half-life was 26.4 hours and 19.6 hours in whole blood.
Ganetespib was extensively metabolised to STA-12-0671, and moderately metabolised to STA-12-0672. Based on the comparison of AUC0-∞, exposure to ganetespib accounted for approximately 14% of the total radioactivity in plasma, with exposure to metabolites STA-12-0671 and STA-12-0672 accounting for approximately 50% and 6% of the total radioactivity,

respectively, resulting in the classification of STA-12-0671 as a "major" metabolite according to the Metabolites in Safety Testing (MIST) guidance.

6.3.3 Ganetespib synergises with paclitaxel in vitro and in vivo

The combination of ganetespib with the microtubule stabiliser paclitaxel was shown to result in synergistic anti-proliferative effects *in vitro* in the H1975 non-small-cell lung cancer (NSCLC) cell line, which expresses an activated and erlotinib-resistant form of the epidermal growth factor receptor ($EGFR_{L858R/T790M}$). This synergistic benefit translated to improved efficacy in H1975 xenografts *in vivo*, with nearly complete inhibition of tumour growth when ganetespib was combined with paclitaxel (Figure 3).

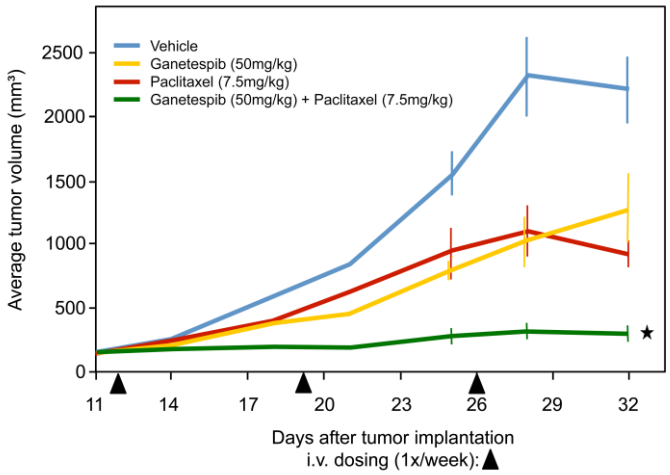


Figure 3: In vivo activity of ganetespib in combination with paclitaxel in H1975NSCLC xenografts (26)**.** SCID (severe combined immunodeficiency) mice bearing H1975 NSCLC tumours were iv dosed with ganetespib (50 mg/kg) and paclitaxel (7.5 mg/kg) alone or in combination on a 1x/week schedule for 3 weeks (arrowheads). Data represent the mean and standard error of the mean (SEM). Weekly administration of ganetespib (50 mg/kg) and paclitaxel (7.5 mg/kg) reduced tumour growth by 45% and 62%, respectively. Concurrent treatment with both drugs resulted in a significant enhancement of antitumor activity compared to either agent alone, blocking tumour growth by 93%.

6.3.3.1 ***Clinical evidence for combination of taxane + ganetespib***

Two Synta-sponsored trials, one phase I and one ongoing phase IIb/III trial, have evaluated/are evaluating the combination of **ganetespib + docetaxel**. As of 21 September 2015, 408 patients were treated with this combination. Important (preliminary) results are summarised below:

Phase I (study 9090-07; n=27 patients), pharmacokinetic (PK) study of ganetespib in combination with docetaxel in patients with advanced solid malignancies; design: open-label, dose-escalation; status: enrolment completed.

Results: Data from this study established that 150 mg/m^2 ganetespib on days 1 and 15 and 75 mg/m^2 docetaxel on day 1 in a 21-day cycle is the recommended combination dose in patients with solid tumours. This dose was selected for further study in the phase IIb/III trial. The study also demonstrated that the combination of ganetespib + docetaxel was well tolerated. The safety profile was similar to that observed in single-agent studies. Under the dosing regimen of this study (docetaxel infusion was initiated 1 hour after the end of ganetespib infusion), docetaxel PK estimates were similar to those of docetaxel alone (27-29), indicating absence of drug-drug-interaction (DDI) between ganetespib and docetaxel.

Phase IIb/III (GALAXY-1; study 9090-08; n=385 patients, 195 received ganetespib), randomised study of ganetespib in combination with docetaxel *versus* docetaxel alone in stage IIIb or IV non-small cell lung cancer (NSCLC); study design: randomised, multicentre, parallel group study; status: enrolment completed.
Results: The safety profile of patients treated with the combination of ganetespib and docetaxel was generally similar to that of docetaxel alone, consistent with previously reported results. The most common AEs, all grades, were neutropenia (46% vs. 43%), diarrhoea (46% vs. 15%) and fatigue (29% vs. 26%), for ganetespib and docetaxel (N=123) vs. docetaxel alone (N=126), respectively. Diarrhoea was effectively managed with supportive care; the incidence of grade 3 or 4 diarrhoea was 3% (ganetespib and docetaxel) vs. <1% (docetaxel). Fatigue was predominantly grade 1 and grade 2; grade 3 or 4 fatigue was 5% (ganetespib and docetaxel) vs. 4% (docetaxel).
The most common grade 3 or 4 AEs were neutropenia (42% vs. 40%), febrile neutropenia (9% vs. 5%), and anaemia (8% vs. 1%). The proportions of patients deaths while on treatment were 17.3% (1% of them were treatment-related) vs. 12.2% (<1.1% were treatment-related), and SAEs leading to treatment discontinuation were 7.2% vs. 4.3% for ganetespib and docetaxel vs. docetaxel, respectively. Consistent with prior findings with ganetespib, reports of visual impairment in this study were infrequent: 1 (1%) in the ganetespib and docetaxel arm and 0 (0%) in the docetaxel arm. The case of visual impairment was transient and was grade 1.

Summary of the latest safety data of the GALAXY-1 trial

Table 1: Safety Summary: Intention-to-treat population

Number of patients who experienced at least one of the following:	**Ganetespib + docetaxel** n=123 n (%)	**Docetaxel** n=126 n (%)
Any AE	190 (97.4)	171 (91.9)
Any AE grade ≥3	141 (72.3)	116 (62.4)
SAE	78 (40.0)	54 (29.0)
Treatment-related SAE	33 (16.9)	22 (11.8)
Treatment discontinuation due to AE	28 (14.4)	14 (7.5)
Treatment discontinued due to SAE	14 (7.2)	8 (4.3)
SAE leading to hospitalisation	61 (31.3)	36 (19.4)
Death on treatment	34 (17.3)	23 (12.2)
Death, treatment-related	2 (1.0)	2 (1.1)
Death due to cardiac events	1 (<1)	2 (1.1)

Table 2: Adverse events: intention-to-treat population

	Grade 1		**Grade 2**		**Grade 3 & 4**	
	G + D n=195 n (%)	**D** n=186 n (%)	**G + D** n=195 n (%)	**D** n=186 n (%)	**G + D** n=195 n (%)	**D** n=186 n (%)
Key AEs > 10%	n (%)					
Neutropenia	3 (2)	0	5 (3)	5 (3)	81 (42)	75 (40)
Diarrhoea	53 (27)	22 (12)	30 (15)	5 (3)	6 (3)	1 (<1)
Fatigue	20 (10)	23 (12)	26 (13)	18 (10)	10 (5)	7 (4)
Nausea	27 (14)	23 (12)	17 (9)	8 (4)	3 (2)	2 (1)
Anaemia	4 (2)	5 (3)	26 (13)	21 (11)	16 (8)	2 (1)
Alopecia	19 (10)	17 (9)	18 (9)	13 (7)	0	0
Decreased appetite	21 (11)	17 (9)	13 (7)	4 (2)	4 (2)	3 (2)
Dyspnoea	13 (7)	9 (5)	15 (8)	9 (5)	9 (5)	5 (3)
Asthenia	13 (7)	6 (3)	14 (7)	11 (6)	9 (5)	5 (3)
Neurotoxicity	18 (9)	18 (10)	9 (5)	6 (3)	4 (2)	1 (<1)
Cough	14 (7)	17 (9)	8 (4)	9 (5)	2 (1)	1 (<1)
Pain	19 (10)	9 (5)	8 (4)	6 (3)	5 (3)	1 (<1)
Tachycardia	19 (10)	19 (10)	3 (2)	2 (1)	1 (<1)	0
Leukopenia	0	4 (2)	4 (2)	5 (3)	16 (8)	9 (5)
Pyrexia	11 (6)	14 (8)	7 (4)	6 (3)	0	0
Vomiting	17 (9)	11 (6)	6 (3)	3 (2)	1 (<1)	0
Other AEs of Interest	n (%)					
Febrile Neutropenia	0	0	0	0	17 (9)	10 (5)
Mucositis	10 (5)	9 (5)	5 (3)	3 (2)	4 (2)	2 (1)
Haemoptysis	7 (4)	4 (2)	5 (3)	2 (1)	1 (<1)	0
Pulmonary Embolism	0	0	1 (<1)	0	4 (2)	6 (3)
Visual Impairment	1 (<1)	0	0	0	0	0

G = ganetespib, D = docetaxel

Preliminary results indicate an improvement in efficacy with the addition of ganetespib to docetaxel for second-line therapy of advanced adenocarcinoma of the lung [Wong et al, JCO 29:2011 (Suppl; Abstract 7500 ASCO 2011)]. Most promising, a significant improvement in survival was observed across key predefined subgroups (e.g. in patients >6 months since their diagnosis of advanced disease: combination arm (n=90) *versus* Docetaxel alone (n=88), Overall Survival HR 0.75; p = 0.065; Ramalingam et al, WLC Meeting 2013, Vienna, Austria; Abstract # 003.01).

The combination of ganetespib with the taxane docetaxel has shown:
1) to be well tolerated, 2) a lack of DDI in phase I trials, 3) a similar safety profile in phase IIb/III trials compared to single agent use, and has 4) promising synergistic effects in vitro and in xenografts, and 5) promising efficacy in patients with advanced adenocarcinoma of the lung.

6.3.4 Other clinical data of interest

The results from a thorough QT study conducted in healthy volunteers (Study 9090-13) reported a modest increase in QT interval 24 hours post ganetespib dose. The mean ΔΔQTcF reached 21.5 msec. ΔΔQTcF was back to baseline 7 days after ganetespib dose. One (2%) subject exhibited QTcF > 450 msec and none greater than 480 msec after ganetespib administration. Two (4%) subjects exhibited ΔQTcF > 30 msec and none greater than 60 msec after ganetespib administration. To date, clinical experience with ganetespib does not support an evidence of a clinical safety risk for QTc interval prolongation and Torsade de Pointes or other uncontrolled arrhythmias.

7. STUDY DESIGN

7.1 Description of study

This is a multicentre, international two part trial, with a safety run-in phase I study (part I), and a randomised, open-label, two-arm phase II study (part II).

Depending on the results of part I, the ganetespib dose to be used in part II of the trial will be chosen.

7.2 Part I: phase I dose escalation/de-escalation study

Note: as of Amendment 4, enrolment for the phase I dose escalation/de-escalation study has been completed. The description of planned assessments for these patients is retained in the protocol for completeness.

Phase I will be open at selected trial sites in four European countries (i.e. Austria, Germany, France, and Belgium).

Study type: interventional
Study design: single group assignment; open label
Estimated enrolment: 9-18 patients

An estimated number of 9-18 high-grade serous, high-grade endometrioid or undifferentiated PROC patients will take part in the dose escalation/de-escalation study with a traditional 3+3 design. There will be no intra-patient dose escalation. Each patient will receive 2 cycles of experimental therapy, followed by a safety follow-up 28 days (± 7 days) after the last administration of the IMP (Figure 4).

All patients may continue to receive ganetespib in combination with paclitaxel until progression if a benefit for the patient has been observed (same schema; for dose reductions and dose modifications after the first 2 cycles of experimental therapy please see sections 10.1, 10.1.2, 10.1.3). After six cycles of ganetespib combination therapy, the physician is allowed to discontinue paclitaxel (e.g. in case of peripheral neuropathy) and to continue maintenance therapy with ganetespib (i.e. ganetespib once a week for 3 out of 4 weeks; at the dose level previously used in the combination or re-escalated to the ganetespib dose level 0). Patients who did not appear to have had a benefit of the combination therapy after the two mandatory cycles, including also patients who have stopped experimental therapy due to the occurrence of dose-limiting toxicity in their dose group, will be treated according to physician's choice. Safety will continuously be evaluated until 28 days (±7 days) after the last IMP administration (safety follow-up visit) or EOT or until initiation of the new anti-cancer treatment, whichever occurs first.

A total of 6 patients will be treated at the dose level to be used in part II (phase II) of the trial.

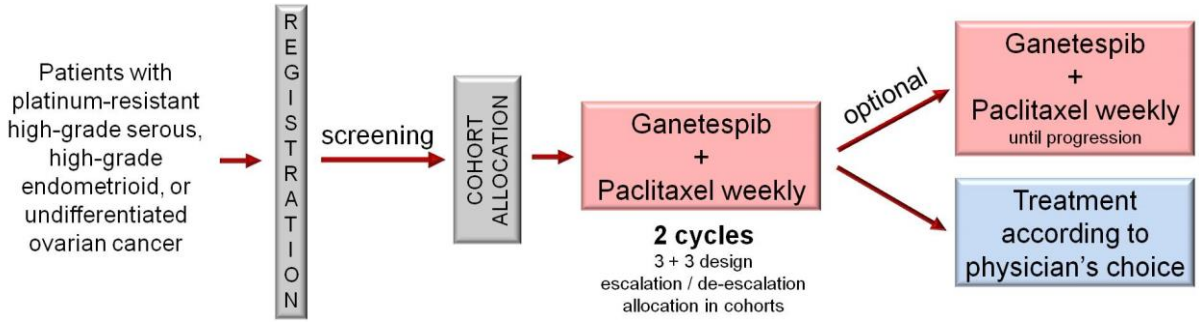


Figure 4: phase I trial design

Arm	Assigned intervention
Experimental	Paclitaxel 80 mg/m^2 and ganetespib will be given once weekly (on 3 weeks out of a 4-week cycle) for 2 cycles (days 1, 8, 15 of each 4-week cycle). Agents will be administered as a separate 1-hour infusion. The sequence of administration will be ganetespib followed by paclitaxel.

7.2.1 3 + 3 design

The first three patients will be treated with a starting dose of **100 mg/m^2 ganetespib** and a standard dose of paclitaxel weekly (80 mg/m^2, fixed dose). If this dose does not cause a dose-limiting toxicity (DLT) [as defined per protocol (see section 10.1.6 for grading of DLT) and measured according to NCI CTCAE, version 4.03, Appendix C] in the first cohort during cycle 1 (weeks 1-4, i.e. D1-D28), ganetespib will be escalated to **150 mg/m^2**, as a second cohort takes part in the study.

In general, should one of the first three patients at a given dose level experience DLT, three more patients will be treated at the same dose level.

Dose escalation from 100 mg/m^2 to 150 mg/m^2 ganetespib will be performed if only one of six patients among a cohort of six experience DLT (i.e. < 33% of patients with a DLT).

If the dose of 150 mg/m^2 does not cause dose-limiting adverse effects during cycle 1 of the first cohort, a second cohort at this ganetespib dose level will be included in the study. In case of DLT at 150 mg/m^2 in < 2 patients in a cohort of six, this ganetespib dose will be used in the phase II trial (Figure 5a: expected course).

In case of DLT at 150 mg/m^2 in ≥ 2 patients in a cohort of three to six (i.e. ≥ 33% of patients with DLT) a dose reduction of ganetespib to 125 mg/m^2 is permitted (Figure 5b: unexpected course).

In case of DLT at 125 mg/m^2 in ≥ 2 patients in a cohort of three to six, another cohort at the ganetespib starting dose level of 100 mg/m^2 will be included (Figure 5c: unexpected course).

In the highly improbable case of DLT in ≥ 2 patients among a cohort of three to six at the ganetespib starting dose level of 100 mg/m^2 a dose reduction of ganetespib to 75 mg/m^2 is permitted (Figure 5d: unexpected course).

After all phase I patients have completed two cycles of treatment the Data Safety and Monitoring Committee (DSMC) will meet and decide if the established dose is safe to be used in the GANNET53 phase II study.
The DSMC will be informed by the sponsor of any dose-limiting adverse events (as defined in section 10.1.6) immediately after knowledge of it. A teleconference of the DSMC will be held before the dose escalation step from 100 mg/m^2 to 150 mg/m^2.

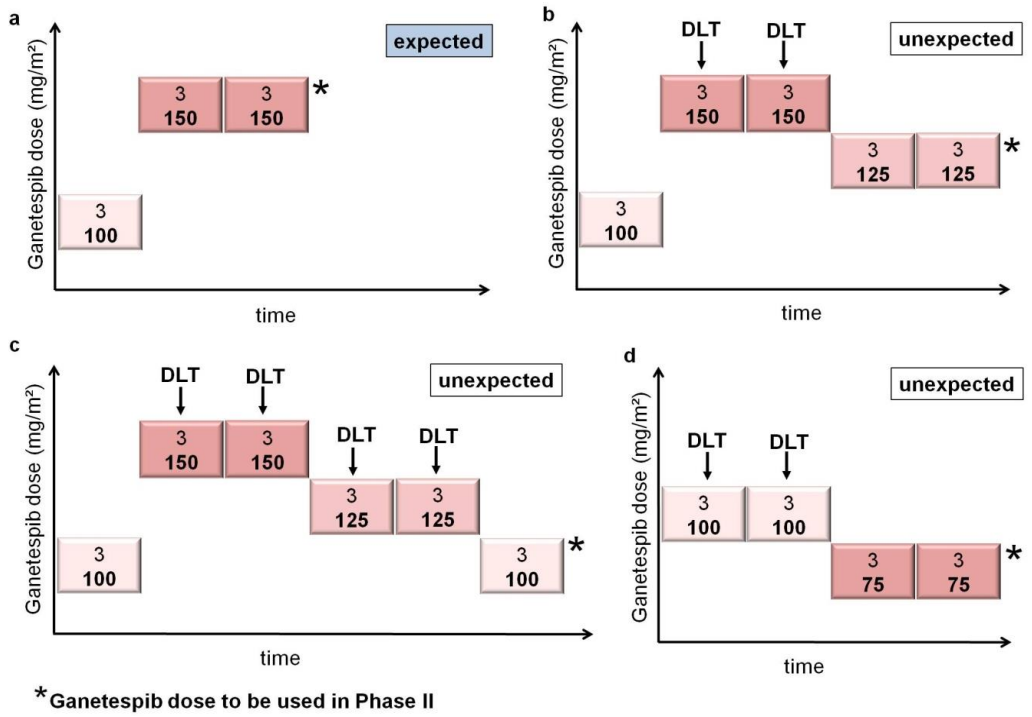


Figure 5: **Potential courses of the phase I study. a) expected course, b), c), and d) unexpected courses**

7.2.2 Dose-limiting toxicity (DLT) at the ganetespib dose level of 75 mg/m^2

Of note, the risk for DLT at the ganetespib dose level of 75 mg/m^2 is considered insignificantly low and seems highly improbable, taking the comprehensive previous findings of clinical ganetespib testing into account (see 6.3.3.1).
However, if ganetespib at a dose level of 75 mg/m^2 should cause DLT in ≥ 33% of patients (≥ 2 patients among a cohort of three to six) we will conclude that the combination of ganetespib with weekly paclitaxel is not feasible. The randomised phase II trial will then examine single agent ganetespib at a dose of 200 mg/m² weekly (i.e. the recommended weekly ganetespib single agent dose in solid tumours) versus paclitaxel weekly (Figure 6 highly improbable course).

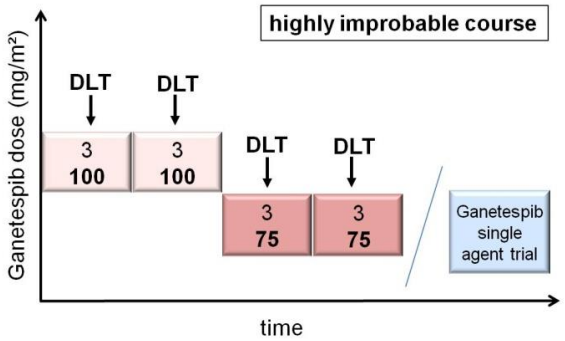


Figure 6: Highly improbable course

7.3 Part II randomised, open-label, two-arm phase II study

The randomised, open-label, two-arm phase II study will be conducted in 12 trial sites in four European countries (Austria, Germany, France and Belgium), the ganetespib dose to be used in phase II has been determined to be 150 mg/m² in the phase I study. The expected number of enrolled patients is 222.

Study type: interventional
Study design: randomised 1:2 ratio, parallel assignment, open-label
Estimated enrolment: 222 patients (74 + 148 patients)

Eligible patients will undergo central histopathological review of archival ovarian cancer tissue at primary diagnosis to ensure high-grade serous, high-grade endometrioid or undifferentiated histology. Two hundred and twenty-two patients with verified histology will be randomised in a 1:2 ratio (74 + 148) to receive either paclitaxel once a week for 3 out of 4 weeks alone or the combination of ganetespib and paclitaxel once a week for 3 out of 4 weeks. The ganetespib dose used was determined in phase I of this trial to be 150 mg/m². For paclitaxel weekly the standard dose of 80 mg/m^2 will be used (Figure 7).

Patient will receive the respective therapy until disease progression or End of Treatment due to any other cause. After at least six cycles of ganetespib combination therapy, the physician is allowed to discontinue paclitaxel (e.g. in case of peripheral neuropathy) and to continue maintenance therapy with ganetespib (i.e. ganetespib once a week for 3 out of 4 weeks; at

the dose level previously used in the combination or re-escalated to the ganetespib dose level 0).

All patients included will be analysed for p53 mutational status from archival ovarian cancer tissues.

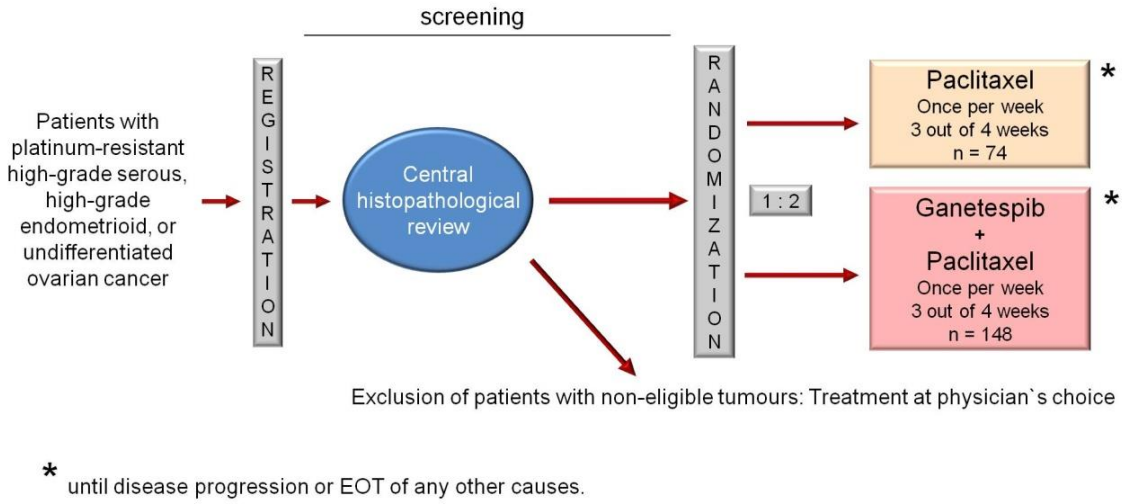


Figure 7: Phase II trial design

Arm	Assigned intervention
Experimental arm	*Drug*: ganetespib, 150 mg/m², given iv once weekly for 3 out of 4 weeks (days 1, 8, 15 of each 4-weeks/28-days cycle); *Drug: p*aclitaxel, 80 mg/m^2, given iv once weekly for 3 out of 4 weeks (days 1, 8, 15 of each 4-weeks/28-days cycle), until progression. The sequence of administration will be ganetespib followed by paclitaxel.
Active comparator	*Drug*: paclitaxel: 80 mg/m^2, given iv once weekly for 3 out of 4 weeks (days 1, 8, 15 of each 4-weeks/28-days cycle), until progression or EoT due to any other cause.

A schedule of assessments is provided in Appendix A.

7.4 Subject population

For both parts of the trial the target study population consists of female patients with high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer with previous platinum-resistant disease. By definition, patients will have experienced progressive disease > 1 month and ≤ 6 months after initial platinum-based therapy (primary platinum-resistant) or ≤ 6 months after (including during) reiterative therapy with platinum-based regimens in recurrent disease (secondary platinum-resistant disease; including secondary platinum-refractory disease).

7.4.1 Subject eligibility

Before any study-specific procedure, the appropriate written informed consent must be obtained.

7.4.1.1 ***Inclusion criteria***

Patients must meet the following criteria to be eligible for study entry:

- Ability to understand and willingness to sign and date a written informed consent document
- Female patients ≥18 years of age
- High-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer.
    - Patients in part II: *High-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal cancer confirmed by central histopathology through archival FFPE.*
- Platinum-resistant disease:
    - primary platinum-resistant disease: progression > 1 month and ≤ 6 months after completion of primary platinum-based therapy
    - secondary platinum-resistant disease (including secondary platinum-refractory disease): progression ≤ 6 months after (or during) reiterative platinum-based therapy
- Patients must have disease that is measurable according to RECIST 1.1 or assessable according to the GCIG CA-125 criteria, and require chemotherapy treatment
- ECOG performance status of 0-1
- Life expectancy of at least 3 months as assessed by the investigator
- Adequate function of the bone marrow:
    - Platelets ≥ 100 x 10^9/L
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Haemoglobin ≥ 8.5 g/dl. Patients may receive blood transfusion(s) to maintain haemoglobin values > 8.5 g/dl.
- Adequate organ functions:
    - Creatinine < 2 mg/dl (< 177 µmol/L)
    - Total bilirubin ≤ 1.5 x upper limit of normal
    - SGOT/SGPT (AST/ALT) ≤ 3 x upper limit of normal
    - Urinanalysis or urine dipstick for proteinuria less than 2+. Patients with ≥ 2+ on dipstick should undergo 24-hour urine collection and must demonstrate < 1 g of protein/24 hours, except the proteinuria is clearly related to a catheter in the urinary system.
- Adequate coagulation parameters: aPTT ≤ 1.5 x ULN (patients on heparin treatment must have an aPTT between 1.5 – 2.5 x ULN), or INR ≤ 1.5. (In patients receiving anticoagulants (such as warfarin) INR must be between 2.0 and 3.0 in two consecutive measurements 1 – 4 days apart).
- Negative urine/serum pregnancy test in women of childbearing potential (WOCBP, see section 5). WOCBP who are sexually active, agree to use highly-effective means of contraception during the study and for at least 6 months post-study treatment. Allowed are accepted and effective non-hormonal methods of contraception and sexual

abstinence or vasectomised partners (> 3 months previously). Vasectomy has to be confirmed by two negative semen analyses.

Only in part II of the trial:

- *Availability of archival ovarian cancer tissue for central histopathological review and p53 mutational analysis*

7.4.1.2 ***Exclusion criteria***

Patients who meet any of the following criteria will be excluded from study entry:

CANCER-RELATED:

- Ovarian tumours with low malignant potential (i.e. borderline tumours)
- Carcinosarcoma of the ovary
- Primary platinum-refractory disease (progression during primary platinum-based chemotherapy)

PRIOR, CURRENT OR PLANNED TREATMENT:

- Previous treatment with > 2 chemotherapy regimens in the platinum-resistant setting (excluding targeted and endocrine therapies).
- Previous weekly paclitaxel in relapse treatment
- More than 4 previous lines of chemotherapy.
- Any prior radiotherapy to the pelvis or abdomen.
- Surgery (including open biopsy and traumatic injury) within 4 weeks prior to first dose of ganetespib, or anticipation of the need for major surgery during study treatment
- Minor surgical procedures, within 24 hours prior to the first study treatment
- Current or recent (within 10 days prior to the first study drug dose) chronic daily treatment with aspirin (>325 mg/day)
- Chronic daily treatment with corticosteroids (dose >10 mg/day methylprednisolone equivalent), excluding inhaled steroids.

PRIOR OR CONCOMITANT CONDITIONS OR PROCEDURES:

- Patients with a history of prior malignancies, except:
    - disease-free time-frame of ≥ 3 years prior to randomisation.
- Patients with prior in-situ carcinomas, except:
    - complete removal of the tumour is given
- Known history of severe (grade 3 or 4) allergic or hypersensitivity reactions to excipients (e.g. polyethylene glycol [PEG] 300 and Polysorbate 80)
- History of intolerance or hypersensitivity to paclitaxel and/or adverse events related to paclitaxel that resulted in paclitaxel being permanently discontinued
- Peripheral neuropathy of grade > 2 per NCI CTCAE, version 4.03, within 4 weeks prior to randomisation
- Clinically significant gastro-intestinal (GI) tract abnormalities that may increase the risk for GI bleeding and/or perforation including but not limited to: active peptic ulcer disease, known intraluminal metastatic lesion/s with risk of bleeding, inflammatory bowel disease (e.g. ulcerative colitis, Crohn’s disease), history of bowel obstruction within 1 year prior to

first study treatment (excluding postoperative, i.e. within 4 weeks post-surgery), other GI condition with increased risk of perforation such as a recurrence deeply infiltrating into the muscularis or mucosa of the rectosigmoid or the mucosa of the bladder, or history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess
- Non-healing wound or non-healing bone fracture
- Patients with symptomatic brain metastases
- Left ventricular ejection fraction defined by ECHO below the institutional lower limit of normal
- Cerebrovascular accident (CVA) / stroke or transient ischemic attack (TIA) or sub-arachnoid haemorrhage within ≤6 months prior to first study treatment
- Significant cardiac disease: New York Heart Association (NYHA) Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary artery bypass graft (CABG) within the past 6 months; or uncontrolled atrial or ventricular cardiac arrhythmias.
- History of prolonged QT syndrome, or family member with prolonged QT syndrome
- QTc interval > 470 msec when 3 consecutive ECG values are averaged
- Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug (e.g. quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g. sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted
- Second- or third-degree atrioventricular (AV) block, except:
    - treated with a permanent pacemaker
- Complete left bundle branch block (LBBB)
- History of evidence of hemorrhagic disorders, patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorders, coagulopathy, or tumour involving major vessels
- Any other condition that, in the opinion of the investigator, may compromise the safety, compliance of the patient, or would preclude the patient from successful completion of the study.
- Participation in another clinical study with experimental therapy within 28 days before start of treatment.
- Women who are pregnant or are lactating

7.5 Study duration

Part I: dose escalation/de-escalation phase I

Active study participation for the individual study participant in phase I will consist of at least *two* 4-weeks cycles of ganetespib and paclitaxel (administered on days 1, 8 and 15) and a safety follow-up 28 days after the last IMP application. Consequently the duration of study participation for each patient in phase I is at least 10 weeks. Patients who continue receiving experimental therapy beyond the two cycles will actively participate in phase I until discontinuation of experimental therapy and a safety follow-up 28 days after the last IMP application.

Part II: randomised phase II

Once the DSMC has reviewed the applicable data from part I of the trial and determined the ganetespib dose to be used in part II, the phase II trial will start. Two hundred and twenty-two patients will be enrolled into the randomised phase II trial over a time-frame of active enrolment of approximately 2.5 years.
Analysis of the phase II endpoints (apart from PFS-rates at 6 months) will be performed approximately 1.5 years after enrolment of the last patient into phase II. This is estimated to be approximately 4 years after the randomisation of the first patient, unless all patients in part II have been lost to follow-up, withdrawn consent, or died, or the trial is prematurely terminated by the sponsor or the DSMC.

7.6 End of study

The GANNET53 clinical trial ends after approximately 5.5 years.

Part I (phase I):
The phase I study ends when a total of six patients have received at least *two* cycles of experimental therapy at the ganetespib dose level to be used in the phase II trial and after all participating patients have discontinued experimental therapy and had a safety follow-up 28 days after the last IMP application, unless the trial is prematurely terminated by the sponsor or the DSMC.

Part II (phase II):
Part II of the study ends approximately 18 months after the last patient was randomised, or when all subjects are lost to follow-up, have withdrawn consent, or died, or if the trial is prematurely terminated by the sponsor or the DSMC, whichever occurs first.

7.6.1 Premature termination of the study

The trial or single dose steps in part I (phase I) can be terminated prematurely by the sponsor or the DSMC in the following cases:

- If adverse events occur which are so serious that the risk-benefit ratio is not acceptable
- If the number of dropouts is so high that a proper completion of the trial cannot realistically be expected

In that case the Independent Ethics Committee (IEC) and the competent regulatory authority must be informed within 15 days of early termination.

Every effort should be made to follow-up phase II patients until progression in case they have dropped out before progression. Especially the safety follow-up should be completed in phase I and phase II patients who have dropped out of the trial.

7.6.1.1 Study site discontinuation

The Sponsor has the right to terminate this study or discontinue a site participating in this trial at any time. Reasons for terminating the study or discontinuing a site participation may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients (recommendation of the DSMC)
- Patient enrolment is unsatisfactory.
- Administrative reasons

The Sponsor will notify the investigator if the study is placed on hold, or if the sponsor decides to discontinue the study or the participation of a study site.

7.6.2 Withdrawal and replacement of subjects

Criteria for withdrawal

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.
Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the subject's study data, but no further information will be collected unless a separate consent has been given. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Withdrawal of partial consent means that the subject does not wish to take protocol-specified product(s) any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in the EOT or safety follow-up visit, provided samples can be evaluated and do not need to be destroyed and/or provide overall survival information).

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information and the primary reason for withdrawal should be reported on the applicable eCRFs.

Reasons for removal from investigational treatment or observation might include:

- progression of disease
- withdrawal of consent
- administrative decision by the investigator
- pregnancy
- significant protocol deviation
- subject noncompliance
- adverse event
- other safety concern of the investigator or sponsor
- death
- lost to follow-up.

For any patient who has received IMP and withdrew prematurely from the study every effort should be made for attendance of the safety follow-up visit 28 days after the last dose of IMP. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn, unless a separate consent has been given for further survival data collection.

*7.6.2.1 **Discontinuation from IMP or non-IMP***

The investigator has the right to discontinue a patient from IMP or non-IMP or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue IMP or non-IMP or withdraw from the study at any time for any reason. Reasons for discontinuation of IMP and non-IMP or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if she continues in the study.
- Investigator or sponsor determines it is in the best interest of the patient.

More detailed information on IMP and non-IMP modifications and discontinuation is found in section 10.1

Patients who discontinue IMP and non-IMP prematurely (i.e., before disease progression) will receive local standard of care according to physician's choice, should undergo the safety follow-up visit 28 days after the last dose of IMP and may undergo follow-up assessments.

The primary reason for premature IMP or non-IMP discontinuation should be documented on the appropriate eCRF.

*7.6.2.2 **Replacement of patients during part I of the trial***

If a patient discontinues study participation for reasons unrelated to an adverse event, an additional patient must be enrolled to replace that subject in the cohort.

*7.6.2.3 **Replacement of patients during part II of the trial***

There will be no replacement of subjects who withdraw after they have been randomised for part II of this trial.

7.7 Study objectives

7.7.1 Part I: dose escalation/de-escalation phase I study

The primary aim of the phase I study is to determine the safety of ganetespib in combination with weekly paclitaxel and also to determine the ganetespib combination dose to be used in the randomised phase II study.

Primary endpoint:

- Safety: Adverse events (AEs) (measure according to NCI CTCAE, version 4.03), laboratory parameters, Eastern Cooperative Oncology Group (ECOG) performance status (PS), vital signs

Secondary endpoint:
- Objective response rate (ORR)
- Progression-free survival (PFS)

7.7.2 Part II: randomised, open-label, two-arm, phase II study

The primary aim of the phase II study is to determine efficacy of ganetespib in combination with weekly paclitaxel compared to weekly paclitaxel alone.

Primary endpoint:
- Progression-free survival (PFS) and PFS rates at 6 months

Secondary endpoints:
- Overall survival (OS)
- Objective response rate (ORR): best ORR, confirmed ORR
- Post-progression PFS (PFS II)
- Patient-reported outcome: EORTC C30, EORTC OV28, and additional items
- Safety: AEs (according to NCI CTCAE, version 4.03), laboratory parameters, ECOG PS, vital signs
- Pharmacokinetics (only in 30 patients in selected sites)
    - evaluate the possible effects of paclitaxel on ganetespib pharmacokinetics
    - evaluate the possible effects of ganetespib on paclitaxel pharmacokinetics
    - quantify ganetespib and ganetespib metabolite exposures in the presence of paclitaxel

Exploratory endpoints
- Molecular efficacy analysis
- Biomarker analysis e.g. p53 status on DNA, RNA and protein level

7.8 Randomisation and stratification

In phase I no randomisation will take place. However, patients will be allocated into the respective cohort via the electronic CRF system after verification of inclusion and exclusion criteria and after all screening assessments have been performed.

Randomisation of the phase II study will be performed in a 1:2 ratio stratified by 1) sites and 2) duration of platinum-free interval (PFI): PFI < 3 months (including secondary platinum-refractory cases with no platinum-free interval) *versus* PFI ≥ 3 months.
Platinum free interval is defined as the interval between the date of the last platinum dose until the date the progression of disease is documented.
The randomisation code will be generated by the study statistician using permutated blocks and implemented into the electronic CRF system. Patients will be randomised automatically via the electronic CRF system after verification of inclusion and exclusion criteria as well as stratification status and after all screening assessments have been performed.

7.9 Statistical analysis

7.9.1 Analysis populations

The following populations will be used for statistical analysis

Safety population
The safety population will include all patients who received at least one dose of study drug. In the safety analyses, patients will be included in the treatment arm into which they have actually been randomised. This study population refers to phase I and phase II study parts.

Intention-to-treat population
The intention-to-treat (ITT) population will consist of all randomised patients. Analyses of this population will assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications. This study population refers to the randomised phase II study.

Per-protocol population
The per-protocol (PP) population will include all patients who received at least one dose of study treatment without major protocol deviations. Major protocol deviations will be determined and documented prior to database lock. This study population refers to phase I and phase II study part.

7.9.2 Part I statistical analysis

In phase I, a 3+3 dose escalation/de-escalation study will be performed.
The primary aim of the phase I study is to determine the safety of ganetespib in the new combination with paclitaxel weekly.
For the determination of the ganetespib combination dose in phase II, the endpoint of interest in phase I is whether or not a patient experiences a DLT. The observation period for DLT lasts from the first day (D1) of cycle 1 to the last day (D28) of cycle 2. The 3+3 design is rule-based with a statistical power of greater than 87% to detect at least one out of three patients with a DLT when the probability for a DLT is 50%.

Further analyses in the phase I study include a description of toxicities in regards to frequency, grade, cycle and dose. Efficacy measures (objective response rate and progression-free survival) will be reported in per-patient listings. All analyses will be in a descriptive way.
Analyses will be performed for the safety and PP population.

7.9.3 Part II statistical analysis (including sample size calculation)

In phase II, a randomised, open-label, two-arm study will be performed. Group allocation ratio will be 1:2. Twice as many patients will be on ganetespib combination treatment as are in the paclitaxel alone treatment group.
The primary aim of the phase II study is to determine the efficacy of the new agent regarding progression-free survival (PFS).

Efficacy analysis

Progression-free survival (PFS) serves as the primary endpoint of the phase II study. PFS is defined as the days between randomisation and the date of documented progression or death of any cause. For patients whose progression status cannot be determined, their PFS data will be censored at the last assessment date that the patient is confirmed to have no progression. Additionally post-progression PFS (PFS II) will be analysed as a secondary endpoint.

Hypothesis testing between the two treatment arms will be performed using a log-rank test. For each treatment arm the median time to progression will be estimated using the Kaplan-Meier method and the 95% confidence interval of the median will be reported. The restricted mean as a measure for PFS will be calculated using the area under the survival curve (AUC) at 6 months (24 weeks) after randomisation and at the end of the study (approximately 18 months after the last patient was randomised).

Overall survival (OS), objective response rate (ORR: best and confirmed ORR), post progression PFS (PFS II), and patient-reported outcome (PRO) serve as secondary endpoints with respect to efficacy.
OS is defined as the days between randomisation and the date of documented death from any cause. For patients whose survival status cannot be determined, their OS data will be censored at the last documented date that the patient is confirmed to be alive. Statistical analysis of OS will be carried out in the same way as described for PFS.

ORR will be 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 is considered confirmed when the result is repeated in the following efficacy assessment, no less than four weeks later. Hypothesis regarding ORR testing between the two treatment arms will be performed using a Mantel-Haenszel test. The odds ratio and 95% confidence interval of the odds ratio will be presented.

Post progression PFS (PFS II) is defined as the days between randomization to the date of progression or death following the first recorded progression (PFS).
Patients will be followed-up for secondary progression status regularly following the progression event used for the primary variable PFS (PFS). Patients alive and for whom a second disease progression has not been observed should be censored at the date of the last known tumour assessment.

PRO will be assessed using validated questionnaires and additional items. Statistical analysis of PRO will be based on linear mixed models. These models will include the PRO scales as dependent variables, study group and time point as fixed effects, a random intercept on patient level and an unstructured covariance matrix. In the case of non-ignorable drop-outs (e.g., patients with low PRO are more likely to die), a joint model of longitudinal and survival data will be estimated. This modelling approach allows to simultaneously analyse a continuous longitudinal PRO response with time to progression or overall survival. Sensitivity analyses will be done using different methods for data imputation, to investigate robustness of results.

Efficacy analyses will be performed on the ITT and PP populations. The analysis of the ITT population will be considered as the primary analysis. All statistical tests are two-sided with a significance level of 0.05.

Safety analysis

Safety evaluations will be based on the incidence, type, severity and consequences (e.g. study discontinuation) of an adverse event (AE) as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Statistical analysis includes tabulation per treatment group using descriptive measures which are absolute and relative frequencies for categorical data and means, standard deviations, medians and interquartile ranges for continuous data.

All safety analyses will be performed on the safety population.

Pharmacokinetics

PK analysis will be performed in a subgroup of phase II patients (n=15 per treatment group).
Plasma samples will be analysed for ganetespib concentrations using a validated liquid chromatography-mass spectrometry / mass spectrometry (LC-MS/MS) method. Plasma samples may be analysed for ganetespib metabolites. Ganetespib and metabolite concentrations (if available) will be summarized descriptively.
Plasma samples will also be analysed for paclitaxel concentrations using a validated liquid chromatography-mass spectrometry / mass spectrometry (LC-MS/MS) method.
For both ganetespib and paclitaxel, concentration-versus-time curves for plasma concentrations will be displayed. Noncompartmental parameters for ganetespib and paclitaxel will include: maximum concentrations achieved (C_{max}), elimination rate constant (ke), half-life ($t_{1/2}$), clearance (CL), volume of distribution (Vss), and area-under-the-concentration time curve (AUC). Other parameters may also be computed. Noncompartmental parameters will be computed using WinNonlin software version 6.3 or later (Pharsight Inc, Mountain View, CA). Pharmacokinetic parameters may also be computed for ganetespib metabolites, data permitting.

Paclitaxel parameters from the experimental arm (ganetespib + paclitaxel) will be compared to paclitaxel parameters from the active comparator arm (paclitaxel alone). Ganetespib parameters from this study will be compared to historical data. Other analyses methodologies may also be utilized such as modelling, possibly in conjunction with PK data of other studies.

Comparability of treatment arms

The two treatment arms will be assessed descriptively for comparability of demographic and baseline characteristics. Administered study treatment, medical history, disease duration, use of prior treatments and concomitant medications will be summarised by treatment arm using descriptive statistics.

Subgroup analysis

Efficacy analyses will also be done for a subgroup of patients with tumours harbouring proven p53 mutations and for the subgroup of patients with tumours harbouring missense

p53 mutations. Furthermore, efficacy analyses will be performed in subgroups of primary platinum-resistance, of secondary platinum-resistance (including and excluding secondary platinum-refractory cases) and of secondary platinum-refractory cases (if case numbers are sufficient).

Interim analysis

No interim analysis will be performed.

Sample size estimation

Sample size estimation was performed for the primary endpoint PFS and for the secondary endpoint OS. The study is sufficiently powered to show superiority for both of these endpoints.

Endpoint PFS: When the sample size in the treatment groups is 64 versus 128 patients (a total of n=192 patients), the study design provides 80% power to detect a PFS hazard ratio (HR) of 0.65 with 2-sided log-rank test and α=0.05 after 185 events, assuming a median PFS of 4 months with paclitaxel weekly alone and 6.2 months with paclitaxel weekly in combination with ganetespib.
Endpoint OS: When the sample size in the treatment groups is 63 versus 126 patients (a total of n=189 patients), the study design provides 80% power to detect a OS hazard ratio (HR) of 0.6 with 2-sided log-rank test and α=0.05 after 126 events, assuming a median OS of 14 months with paclitaxel weekly alone and 23.3 months with paclitaxel weekly in combination with ganetespib.

In order to ensure a power of 80% for the study subpopulation with proven p53 mutations (more than 95% of all included type II EOC patient are expected to have mutp53 tumours) and to account for drop-out-rate of approximately 15%, the aspired patient number is expanded to a final sample size of **74 versus 148 patients (a total of n=222)** in the two treatment arms, respectively.

7.10 Risk-benefit considerations

Ovarian cancer patients with mutp53 platinum-resistant tumours face a dismal prognosis. The aim of the GANNET53 trial is to improve the wellbeing and survival in this subgroup of ovarian cancer patients by destabilising mutp53 using the most advanced Hsp90 inhibitor ganetespib. This aim links the awareness of human dignity, quality of patient's life and the patient's best interest, as pronounced in the Declaration of Helsinki (§3 - §5) and the Charter of Fundamental Rights of the European Union (2000/C 364/01; Article 1-3).

The risk to harm patients in the phase II trial is minimised by the preceding phase I trial. Our guiding principle for the design of phase I dose escalation/de-escalation trial is to avoid exposing too many patients to subtherapeutic doses while preserving safety. The first three patients will receive 2/3 of the recommended combination ganetespib dose in solid tumours (the recommended combination dose is 150 mg/m^2). Only after a waiting period and assurance that no significant serious adverse effect has occurred, a further cohort of three patients will be treated at an increased ganetespib dose level, namely at the recommended

ganetespib combination dose in solid tumours of 150 mg/m^2. The observation time-frame for dose limiting toxicity has been set relatively long (compared to general practice in phase I trials), namely at a total of *two* cycles of treatment covering two months in the present phase I trial. This also decreases the risk of exposing subsequent patients to harmful effects in phase II by choosing the safest dosage observed.
There is a risk in the GANNET53 trial by treating patients with ganetespib who may not benefit from this treatment but may experience adverse effects due to the experimental therapy. This risk is opposed by a potential benefit for these patients in terms of a possible survival advantage and a possibly higher life quality through better symptom control derived from this new therapeutic approach. Furthermore, the particular dismal prognosis of this specific subgroup of ovarian cancer patients and the lack of an efficient “golden standard therapy” has to be integrated into the risk-benefit considerations. Finally, the shown well tolerability of the combination-therapy of ganetespib with the taxane docetaxel (and the hypothesised better tolerability of the ganetespib combination with the taxane paclitaxel) together with the demonstrated efficacy of the ganetespib-docetaxel combination in NSCLC (in the GALAXY-1 trial, please see 6.3.3.1) clearly shifts the risk-benefit ratio in favour of a potential benefit dominance. A Data and Safety Monitoring Committee (DSMC) consistent of 4 independent experts in the field of gynaecologic oncology and statistics will closely and continuously monitor patient safety and trial development. The DSMC can, if required, amend the protocol and in case the risk to the patients outweighs the potential benefit end the study prematurely.

8. STUDY PROCEDURES

See Appendix A for treatment schedules for part I and for part II.

General rules for trial procedures

- All study measures like blood sampling and measurements (vital parameters, ECG, etc.) have to be documented at least with date (dd:mm:yyyy) and where appropriate with time.
- In case several study procedures are scheduled at the same time point, there is no specific sequence that should be followed, although e.g. blood drawing etc. should be done after ECGs.
- The dates of all procedures should be according to the protocol. The time frames mentioned in the study flow chart are admissible. If for any reason a study procedure is not performed within scheduled time frame a protocol deviation must be noted, and the procedure must be performed as soon as possible or as adequate.
- If it is necessary for organisational reasons, it is permissible to perform procedures which are scheduled for a single visit at two different time points. However, allowed time frames should not be exceeded.
- After patients have received the last study drug due to any reason, any cancer-related treatment is according to physician’s choice but should be recorded in the eCRF.
- Only the most recent available values should be documented for screening.

8.1 Before treatment start/screening (days -28 to -1)

All subjects must provide written informed consent before any study-specific assessments or procedures are performed.
The screening examinations must be performed between 1 and 28 days before being assigned into a cohort in part I and prior to randomisation in part II. Only subjects who fulfil all the inclusion and none of the exclusion criteria will be accepted into the study.

An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. In addition a screen failure log must be maintained by the investigator.

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 inclusion and exclusion criteria
- Medical history including ovarian cancer history, significant diseases and medical procedures (at Investigator's discretion) and concurrent illnesses
- Urine/serum pregnancy test in WOCBP (for definition see section 5)
- Demographic data (date of birth, ethnicity)
- Physical examination including
    - Height
    - Weight
    - Performance status (ECOG, see Appendix B)
- Vital signs
    - Heart rate
    - Blood pressure
    - Temperature
- Laboratory
    - Haematology
        - Haemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)†, platelets
          † Neutrophils, eosinophils, basophils, lymphocytes, monocytes
    - Biochemistry panel
        - Sodium, potassium, calcium
        - Serum albumin, serum urea
        - ALT, AST, LDH, alkaline phosphatase (AP), total bilirubin
        - Creatinine
    - Urinanalysis or urine dipstick for proteinuria should be < 2+. Patients with ≥ 2+ on dipstick should undergo 24-hour urine collection and must demonstrate < 1 g of protein/24 hours, except the proteinuria is clearly related to a catheter in the urinary system.
- Tumour marker:

Part I: CA-125 will be measured twice during the screening period; collections should be at least 1 day apart. One sample needs to be drawn within 1 week of treatment start.
Part II: CA-125 will be measured at least once during the screening period. One of these samples must be taken within 2 weeks before treatment start.

- Concomitant medications
- Electrocardiogram (ECG; average of triplicate ECG recording)
- Left ventricular ejection fraction (LVEF) by ECHO
- Tumour assessment which is not older than 28 days at the time of randomisation: chest, abdomen and pelvis CT scan or MRI and chest CT/MRI or X-ray. Pre-operative chest X-ray is allowed. PET scans are allowed; the same technique is to be used for all assessments.

For part II additionally:

- Additional demographic data (marital status, highest level of education, current employment status)
- Archival tissue samples sent to central histopathological review (for confirmation of high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal carcinoma) and for biomarker analysis such as p53 mutational status.
- Whenever technically feasible CT- or sonographically-guided biopsy samples of the actual relapse are to be performed after informed consent has been obtained but prior to the first study drug administration. Biopsy tissue of the actual relapse will be collected in all patients.
- The collection of ascites is highly recommended
- Completion of PRO [EORTC QLQ-C30, EORTC QLQ-OV28, and additional items (Appendix D)].

8.2 Treatment period

Note: as of Amendment 4, enrolment for the phase I dose escalation/de-escalation study has been completed. The description of planned assessments for these patients is retained in the protocol for completeness.

Laboratory tests from screening can be used for treatment day 1 of cycle 1, if drawn within the 3 days range.

Part I

In part I of the trial the treatment will start after the patient has been allocated to a treatment cohort after screening. Treatment will last for 2 treatment cycles. If the patient has had a benefit from the treatment, continued administration of ganetespib and paclitaxel at the prior received dosage is allowed at the physician's discretion. After six cycles of ganetespib combination therapy, the physician is allowed to discontinue paclitaxel (e.g. in case of peripheral neuropathy) and to continue maintenance therapy with ganetespib (i.e. ganetespib once a week for 3 out of 4 weeks; at the dose level previously used in the combination or re-escalated to the ganetespib dose level 0.

One treatment cycle will consist of 28 days with the following schedule:

- Strongly recommended: Loperamide 2 mg 1-2 hours prior to ganetespib administration. And every 4 hours for the first 12 hours.
- Ganetespib infusion given intravenously over 1 hour on days 1, 8, 15 per (28-day) cycle.
- Premedication according to hospital standards (e.g. Dexamethasone 20 mg 30 min prior to each paclitaxel-infusion), see section 10.3
- Paclitaxel on days 1, 8, 15 as a 1 hour infusion, per 28 day cycle. The sequence of administration will be ganetespib followed by paclitaxel

The following parameters have to be gathered within 3 days prior to IMP administration:

- Physical examination including
  - Weight
  - Heart rate
  - Blood pressure
  - Temperature
- Laboratory
  - Haematology
    - Haemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)†, platelets

      † Neutrophils, eosinophils, basophils, lymphocytes, monocytes
  - Biochemistry panel (on day 1 of every cycle)
    - Sodium, potassium, calcium
    - Serum albumin, serum urea
    - ALT, AST, LDH, AP, total bilirubin
    - Creatinine
- Concomitant medications
- Adverse event evaluation using the NCI-CTCAE criteria, version 4.03 (Appendix C)
- Performance status according to ECOG Performance Status (Appendix B)

Additional assessments:

- The tumour marker (CA-125) will be evaluated monthly (on day 1 of each cycle; +/- 7 days).
- Pre-ganetespib dose ECG will be performed, in patients who receive ganetespib. In addition, a 24-hours post-ganetespib-dose ECG (+/- 4 hours) will be performed on day 1 of cycle 1. Furthermore, a 24-hours post-ganetespib dose ECG (+/- 4 hours) is strongly recommended on day 1 of each subsequent cycle.
- A urine/serum pregnancy test will be performed monthly (on day 1 of each cycle; +/- 7 days) in WOCBP.
- Tumour assessments for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. This assessment should be performed every 8 weeks, +/- 1 week, starting from date of cohort assignment or if recurrence is suspected.

Part II

In part II of the trial treatment will start after central histopathological review has confirmed high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian or fallopian tube or primary peritoneal cancer and the patient has been randomised into one of the two treatment arms.

Treatment should begin within 7 days of randomisation.

Treatment will be administered until progression or drop out of the trial. A minimum of six cycles of ganetespib and paclitaxel combination therapy will be administered. Thereafter, paclitaxel may be discontinued and ganetespib may be administered as a mono therapy at the same dosage level as used in the combination therapy or re-escalated to the ganetespib dose level 0.

For treatment schedule please refer to Appendix A.

One treatment cycle will consist of 28 days with the following schedule:

- Strongly recommended for patients receiving ganetespib: Loperamide 2 mg 1-2 hours prior to ganetespib administration. And every 4 hours for the first 12 hours.
- Ganetespib infusion given intravenously over 1 hour on days 1, 8, 15 per 28-day cycle.
- Paclitaxel premedication will be given according to hospital standards (with the exception of day 1 cycle 1 in **patients participating in PK analysis**; for standardised paclitaxel premedication scheme in PK patients, please see section 9.8).
  Of note, in patients receiving ganetespib, paclitaxel premedication schemes must exclude any QTc interval prolonging medications *with known* risk for Torsade de Pointes (see APPENDIX F; for example but not exclusively: do not use granisetron in the paclitaxel premedication scheme).
- Paclitaxel on days 1, 8, 15 as a 1 hour infusion, per 28-day cycle. The sequence of administration will be ganetespib followed by paclitaxel.

The following parameters have to be gathered within 3 days prior to IMP administration:

- Physical examination including
  - Weight
  - Heart rate
  - Blood pressure
  - Temperature
- Laboratory
  - Haematology
    - Haemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†], platelets

      [†] Neutrophils, eosinophils, basophils, lymphocytes, monocytes
  - Biochemistry panel (only on day 1 of each cycle)
    - Sodium, potassium, calcium
    - Serum albumin, serum urea

    - ALT, AST, LDH, AP, total bilirubin
    - Creatinine
- Concomitant medications
- Adverse event evaluation using the NCI-CTCAE criteria 4.03 (see Appendix C)
- Performance status according to ECOG Performance Status (Appendix B)

Additional assessments:

- Pharmacokinetics (30 patients, 15 in each study arm, at selected sites), see section 9.8
- Blood sampling for biomarker analysis (e.g. for circulating tumour cells [CTCs]) in all part II patients:
    - Blood collection will be performed before and 24 hours after (+/- 3 hours) the administration of study drug on day 1 of cycle 1 (the sample time is relative to the start of the study drug infusion). On day 1 of cycles 2 and 3 blood collection will be performed exclusively *before* the study drug administration. After cycle 3, blood collection will take place on day 1 of every *other* cycle (i.e. cycles 5, 7, 9 etc.) *prior* to administration of study drug.
- Completion of PRO [EORTC QLQ-C30, EORTC QLQ-OV28, and additional items (Appendix D)] will be performed on day 1 and day 15 of each cycle prior to IMP administration.
- The tumour marker (CA-125) will be evaluated monthly (on day 1 of each cycle; +/- 7 days).
- On day 1 of cycle 1 a pre-ganetespib dose ECG (day 1 cycle 1, or one day prior to day 1 cycle 1), a 24-hours post-ganetespib dose ECG (+/- 4 hours) and on day 1 of each subsequent cycle a pre-dose ECG is performed in patients who receive ganetespib.
    - A risk-based ECG monitoring will be followed after evaluation of the day 1 cycle 1 ECG findings according to section 9.5.
- A urine/serum pregnancy test will be performed monthly (on day 1 of each cycle; +/- 7 days) in WOCBP (for definition see section 5).
- Tumour assessments for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. This assessment should be performed every 8 weeks, +/- 1 week, starting from date of randomisation until progression, regardless of any study interruptions, or if recurrence is suspected.
- The collection of ascites (for tumour cell isolation of the actual relapse and biomarker analysis) is highly recommended and will be collected at the time of occurrence.

8.3 Part I & II end of treatment/Safety follow-up

End of treatment will be after last dose of study drug.
All patients receiving ganetespib will receive a safety follow-up 28 days (+/- 7 days) after the last dose of the IMP ganetespib or prior to initiation of a new anti-cancer treatment, whichever occurs earlier.

Safety follow-up includes the following:

- Physical examination including
  - Weight
  - Heart rate
  - Blood pressure
- Laboratory
  - Haematology
    - Haemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)†, platelets
      † Neutrophils, eosinophils, basophils, lymphocytes, monocytes
  - Biochemistry panel
    - Sodium, potassium, calcium
    - Serum albumin, serum urea
    - ALT, AST, LDH, AP, total bilirubin
    - Creatinine
- Tumour marker CA-125
- Electrocardiography (ECG)
- LVEF
- Concomitant medications
- Adverse event evaluation using the NCI-CTCAE criteria, version 4.03 (see Appendix C)
- Performance status according to ECOG Performance Status (see Appendix B)
- A urine/serum pregnancy test will be performed monthly (on day 1 of each cycle; +/- 7 days) in WOCBP (for definition see section 5)

For part II additionally:

- Patient-reported outcome questionnaire: EORTC QLQ-C30, EORTC QLQ-OV28, and additional items (Appendix D)

8.4 Part I and II long-term follow-up

In all patients a long-term follow-up period will be performed after the EOT and the safety follow-up visit.
In patients who had end of treatment due to progression of disease, the following assessments should be recorded in three-monthly intervals (+/- 14 days) until death of the patient or the end of study, whichever occurs first.

Part I

- Survival status
- Additional cancer therapy

Part II

- Survival status
- Additional cancer therapy
- Date of next progression following the subsequent cancer therapy
- Patient-reported outcome questionnaire: EORTC QLQ-C30, EORTC QLQ-OV28, and additional items (Appendix D)

8.4.1 Long-term FU in patients who discontinues treatment prior to progression

Patients who discontinue study treatment **without having developed progressive disease** will first continue to be followed as listed below until progression and will then continue with long-term follow-up as described above after progression.

- Tumour assessments through CT scans of the pelvis and abdomen and (by X-ray or preferably by CT scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. This assessment should be performed every 8 weeks, +/- 1 week or if recurrence is suspected, until progression.
- Tumour marker: CA-125 every 4 weeks (+/- 1 week)
- Additional cancer therapy
- Date of progression

And for patients in part II additionally:

- Patient-reported outcome questionnaire: EORTC QLQ-C30, EORTC QLQ-OV28, and additional items (Appendix D) every 2 weeks

9. STUDY ASSESSMENTS

Details of the timing of assessments are presented in the Schedule of Assessments (Appendix A).

9.1 Tumour response assessment

Patients will be assessed for disease response or progressive disease throughout the clinical trial.
Response or progression will be evaluated in this study according to RECIST 1.1 (see Appendix E), CA-125 (GCIG criteria (30)) and by the investigator on the basis of physical and/or gynaecological examinations.

Evidence of progressive disease is considered clear radiological, clinical, or symptomatic evidence. CA-125 elevation alone is not defined as disease progression. An objective response should be confirmed by repeated assessment not earlier than 4 weeks after initial documentation (e.g. CA-125 measurement) or at the next scheduled tumour assessment if it is to occur more than 4 weeks after the initial response.

9.1.1 Radiologic tumour assessments

Tumour assessments require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. The same method of tumour assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Positron emission technology scans are not acceptable for monitoring target lesions. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Baseline tumour assessment of the chest (by X-ray of preferably by CT scan), abdomen and pelvis by CT scan (or MRI scan in case of allergic reactions to radiographic contrast agents) must be performed within a maximum of 28 days before first dose of study drug treatment. Already existing CT scan can be used as screening CTs, if not older than 28 days at the time of randomisation.
Post baseline assessments are to be performed every 8 weeks (+/- 1 week) from date of randomisation and/or cohort assignment, (e.g. on day 1 of cycle 3, 5, 7, 9, 11 etc.) independent of any treatment interruptions using the same imaging technique as used during screening until disease progression.
If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

9.1.2 GCIG criteria

CA-125 elevation alone is not defined as disease progression unless accompanied by clear radiological, clinical or symptomatic progression. Patients on treatment who are well but have rising CA-125 levels should continue protocol treatment until RECIST 1.1 defined radiological, clinical or symptomatic progression of disease.
Patients can be evaluated according to CA-125 (30) only if they have a pre-treatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pre-treatment sample.
The date when the CA-125 level is first reduced by at least 50% is the date of the CA-125 response. However, the response must be confirmed and maintained for at least 28 days. The (28-day) confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample for to be a confirmed response.

Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days.

Timing of CA-125 measurements

- Part I: two CA-125 blood samples prior to treatment,
- Part II: one CA-125 blood sample prior to treatment. One of these samples must be taken at least 2 weeks prior to treatment start
- Once every 1 month during treatment in part I and part II

For each patient the same assay method must be used. The assay must be tested in a quality control scheme.

9.2 Patient-reported outcome (PRO)

9.2.1 PRO instruments

The following PRO questionnaires will be used in both study arms in part II / phase II of this study: EORTC QLQ-C30, EORTC QLQ-OV28, and additional items (Appendix D).

The EORTC QLQ-C30, an internationally validated and widely used cancer-specific QOL-instrument, assesses various facets of functioning and symptoms common in cancer patients. It comprises five functioning scales (physical, social, role, emotional, cognitive), a scale for global QOL, and nine symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, sleeping disturbances, appetite-loss, constipation, diarrhoea, and financial impact).

The QLQ-OV28 module is a supplement of the QLQ-C30 for assessing issues relevant to ovarian cancer patients. The module covers abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning.

Additional items for the assessment of distress associated with diarrhoea and constipation are added in line with the EORTC item format.

All scales are scored according to EORTC guidelines resulting in a score range from 0 to 100 points.

9.2.2 PRO assessment schedule

The PRO questionnaires should be given to the patient to complete during their visit (i.e. patients should not be sent home with the questionnaires to complete and return at their next visit), but prior to administration of investigational product. These will be assessed during screening, on day 1 and day 15 of each cycle. After end of therapy and safety visit PRO assessments will be continued in both study arms in three-monthly intervals (+/- 14 days) until death of the patient or the end of study, whichever occurs first.
Patients who had EOT prior to progression will have PRO assessments every 2 weeks (+/- 1 week) until progression and thereafter in three-monthly intervals (+/- 14 days) until death of the patient or the end of study, whichever occurs first.

9.2.3 PRO assessment procedure

The patient will be approached by a study nurse or an investigator and will be asked to complete the PRO questionnaires on her own. The PRO assessments will take place prior to patient-clinician consultation to avoid the immediate impact of issues discussed in the clinical encounter. A quiet place providing sufficient privacy will be provided to the patient for questionnaire completion. The study nurse or investigator will be available for any questions

arising during questionnaire completion. In case of problems with reading (e.g. due to limited literacy or impaired eyesight) the questionnaire will be conducted as a structured interview.

9.3 Concomitant medications/therapies

All medication (other than study drug) and significant non-drug therapies (including, but not limited to, herbal/natural medications and blood transfusions) will be recorded at Screening and on an ongoing basis thereafter. Any surgical and medical procedures (i.e. paracentesis) will also be recorded.

9.4 Physical examination

Physical examinations will be performed by trained medical personnel at the time points specified in Appendix A.
Vital signs (blood pressure, heart rate and temperature, as appropriate) and body weight will be measured per institutional standards as part of the physical examination. Height will be measured only at Screening. All physical examinations occurring on dosing days must be performed prior to study drug administration. Any treatment-emergent abnormal findings will be recorded as AEs.
Heart rate and blood pressure will be measured after patient has been in a seating position for 10 minutes.

9.5 Electrocardiography and LVEF

ECG:
A standard 12-lead ECG assessment will be performed at screening and at EOT/safety follow-up in both parts of the trial.

For part I of the trial further ECG assessments will be performed on day 1 of each cycle (on the day of medication dosing, or one day prior) in patients who receive ganetespib. In addition, a 24-hours post-ganetespib-dose ECG (+/- 4 hours) will be performed on day 1 of cycle 1. A 24-hours post-ganetespib-dose ECG (+/- 4 hours) is strongly recommended to be performed on day 1 of each subsequent cycle.

In part II of the trial a pre-ganetespib dose ECG will be performed on day 1 of each cycle (on the day of medication dosing, or one day prior), in patients who receive ganetespib. In addition, a 24-hours post-ganetespib-dose ECG (+/- 4 hours) will be performed on day 1 of cycle 1. Furthermore on day 1 of each subsequent cycle a pre-dose ECG is performed in patients who receive ganetespib.

- In case of normal findings on the day 1 cycle 1 pre- *and* 24-hours post-ganetespib dose ECGs (option 1 in Figure 8), further **standard ECG monitoring** will be performed consisting of **pre-ganetespib dose** ECGs **on days 1 of all following cycles**.
- In case of QT prolongation in the initial 24-hours post-ganetespib dose ECG only (option 2 in graph, Figure 8), another pre- and 24-hours post-ganetespib

dose ECG will be performed at the following dosing of ganetespib (day 8 of cycle 1).

- In case of QT prolongation in the initial pre-ganetespib dose ECG only (option 3 in Figure 8), another pre-ganetespib dose ECG will be performed before the following dosing of ganetespib (day 8 of cycle 1).
- In case of QT prolongation in both (option 4 in Figure 8), the initial pre-ganetespib dose and the 24-hours post-ganetespib dose ECG, another pre- and 24-hours post-ganetespib dose ECG will be performed at the following dosing of ganetespib (day 8 of cycle 1).

For options 2, 3 and 4 thereafter, the principal investigator of each clinical centre will decide on a possible necessity for further intensified ECGs based on previous ECG findings and after thorough review of the patients' medical history including concomitant medication. At least the standard ECG monitoring needs to be performed (pre-dose ECGs on days 1 of all following cycles).
Thus, an individual risk-adjusted ECG monitoring will be performed (see Figure 8).

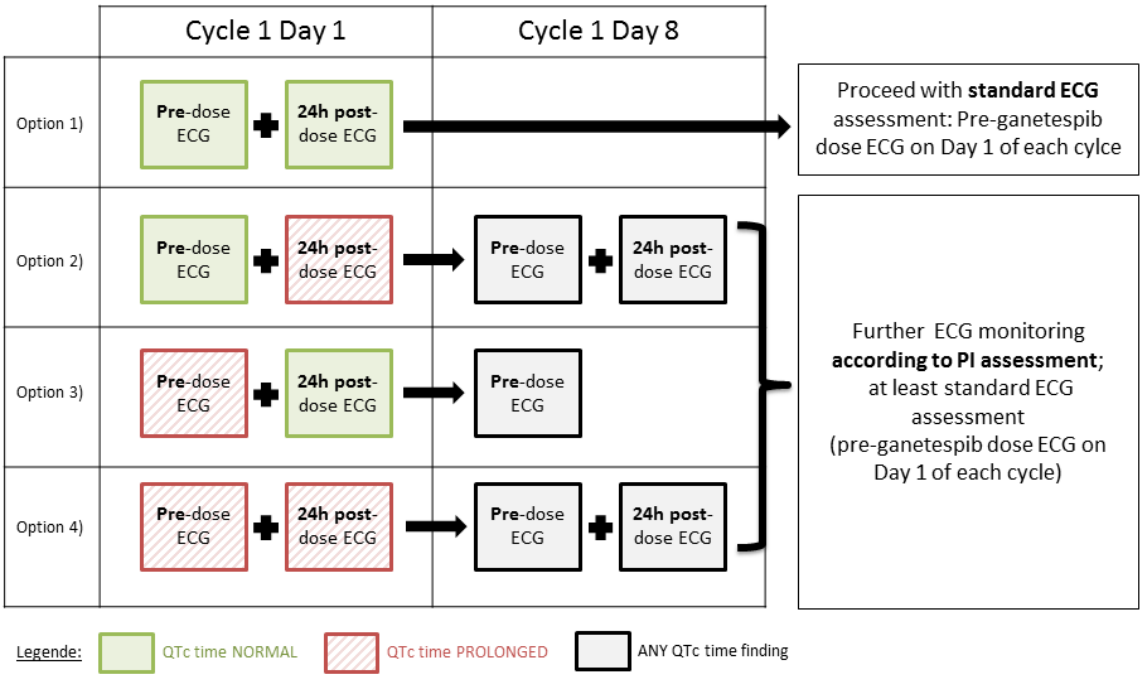


Figure 8**: risk-adjusted ECG schedule**

ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary.

To minimise variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG

recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws.
For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site as part of the patient's file.

LVEF:
Cardiac ejection fraction will be assessed by transthoracic echocardiography (ECHO) at the time points specified in Appendix A (Schedule of assessments).

9.6 Laboratory assessments

Samples for laboratory tests will be analysed at the local laboratory of each participating site.

Blood analysis will be done as part of regular safety assessments at screening/baseline, every treatment cycle (prior to study drug administration), and at the post-treatment safety follow-up. Assessments must be performed at each cycle within 3 days (with results available) prior to the administration of study medication.
Blood samples for the analysis of biomarkers (including CTCs analysis) will be taken before and during experimental therapy with ganetespib in all phase II patients (both arms; one arm for control) as outlined in section 8.2.

9.7 Biomarker analysis in part II

The following samples will be collected to determine the p53 status and other potential biomarkers (such as other HSP90 clients) and to confirm high-grade serous, high-grade endometrioid or undifferentiated EOC in patients of part II of the trial:

- Mandatory archival tumour tissue (formalin-fixed paraffin-embedded tissue)
- Mandatory blood collection before and during experimental therapy as previously specified (topic 8.2).
- It is strongly recommended to prospectively collect ascites
- Whenever technically feasible it is mandatory to collect biopsy tissue of the actual platinum-resistant relapse in all phase II patients. Biopsy tissues will be collected using CT-guided or sonography-guided biopsy collection after informed consent has been obtained but prior to the first study drug application.

Samples remaining after completion of biomarker studies and prospectively collected biomaterials will be stored in a biobank. Tumour samples from screen-failed patients will also be included in a biobank.
Details of tissue requirements, processing, and handling instructions are given separately in the Sample Handling Manual and Logistics Manual.

9.7.1 Determination of p53 status and other biomarkers in collected biomaterials in phase II

The availability of archival tissues (FFPE) is mandatory for inclusion of patients into phase II. In addition, tissues and/or tumour cells of the actual platinum-resistant relapse (biopsy tissue

and/or ascites) will be collected. DNA, RNA and/or protein will be extracted from the respectively collected biomaterials. The p53 status (e.g. genomic mutations, isoforms, splice variants, protein) and other biomarkers analyses (e.g. analysis of the p53-homologues p73 and p63, or other HSP90 clients) will be performed.
Ascites fluid from phase II patients will be collected and isolated for epithelial cells to be cultured in the presence or absence of ganetespib to investigate the interaction of p53 with Hsp90 in vitro. Alternatively to ascites, biopsy tissue of the actual platinum-resistant relapse site tissue can be used. To this end, fresh tumour biopsies will be disaggregated into single-cell suspensions, incubated in the presence or absence of ganetespib and subsequently analysed (molecular efficacy analysis).
Blood samples for biomarker analysis including e.g. circulating tumour cells (CTCs) will be taken before and during experimental therapy with ganetespib in all phase II patients (both arms; one arm for control).

9.8 Pharmacokinetic (PK) analysis in Phase II, at selected centres

PK samples will be collected from 30 patients (15 paclitaxel, 15 ganetespib + paclitaxel) at selected sites in phase II.

- Ganetespib + paclitaxel patients: on day 1 to day 3 of cycle 1, blood samples will be drawn at 0 (pre-dose), 1, 1.5, 2.5, 3.5, 4.5, 6.5, 8, 24, and 55 hours following the start of the ganetespib infusion. The 0 (pre-dose) sample is to be taken immediately prior the start of the ganetespib infusion. The 1-hour and 2.5 hour nominal time samples are to be taken prior to stopping the ganetespib and paclitaxel infusion, respectively and may be drawn as early as 55 ± 5 minutes. The day 2 and day 3 samples (24 and 55 hour time points) may be drawn ± 2 hours from the nominal times.
  All samples are to be drawn contralateral to the infusion. All sample times are relative to the start of the ganetespib infusion (i.e.: ganetespib infusion start is defined as time zero) and presume the paclitaxel infusion starts 30 minutes after termination of the 1-hour ganetespib infusion In the 30 min between ganetespib and paclitaxel infusion a standardised paclitaxel pre-medication will be administered, please see below.

- Paclitaxel-only patients: on day 1 to day 3 of cycle 1, blood samples will be drawn at 0 (pre-dose), 1, 2, 3, 5, 6.5, 22.5, and 53,5 hours following the start of the paclitaxel infusion. The 0 (pre-dose) sample is to be taken after the application of the standardised paclitaxel premedication scheme immediately before the start of the paclitaxel infusion. The 1-hour nominal time samples are to be taken prior to stopping the paclitaxel infusion and may be drawn as early as 55 ± 5 minutes. The Day 2 and Day 3 samples (22.5 and 53.5 hour time points) may be drawn ± 2 hours from the nominal times. All samples are to be drawn contralateral to the infusion. All sample times are relative to the start of the paclitaxel infusion (i.e.: paclitaxel infusion start is defined as time zero; immediately prior to the start of the paclitaxel infusion is pre-dose).

Of note, all patients participating in PK analysis (both arms: ganetespib plus paclitaxel and paclitaxel only) will receive a **standardised (regarding drug,**

dosage, application form, timing of application) premedication for paclitaxel on day 1 of cycle 1.
For all further dosings of study treatment in PK patients, paclitaxel premedication can be given according to hospital standards. However, in patients receiving ganetespib the premedication must be excluding any QTc interval prolonging medications *with known risk* for Torsade de Pointes (see APPENDIX F).

The standardised paclitaxel premedication scheme in PK patients consists of:

1) Dexamethason 20 mg i.v. (in 100 ml NaCl), 30 min prior to the start of the paclitaxel-infusion (given as i.v. infusion over 10 min)
2) Diphenhydraminhydrochlorid 50 mg tablets orally; 30 min prior to start of the paclitaxel infusion.
3) Ranitidine 50 mg i.v. (in 20 ml NaCl), 20 min prior to the start of the paclitaxel-infusion (given as iv bolus-injection over a minimum of 2 and a maximum of 10 min)

10. STUDY MEDICATION

The test drug used in the GANNET53 trial, ganetespib, is a 2nd generation Hsp90 inhibitor (synthetic small molecule).

10.1 Dosage and administration

The route of administration of ganetespib and paclitaxel is intravenously. The agents will be administered as two separate 1-hour infusions. The sequence of administration will be ganetespib followed by paclitaxel.
Paclitaxel premedication can be given according to local standards with the exception of day 1 cycle 1 in patients participating in PK analysis (in this situation a standardised paclitaxel premedication is necessary, see section 9.8). Drugs which prolong QTc interval and have a known risk to cause Torsade de Pointes (TdP, see APPENDIX F), are to be avoided and drugs which prolong QTc interval and have a possible risk to cause TdP (see APPENDIX G) are to be used with caution in patients receiving ganetespib.

Prophylactic medication with loperamideLoperamide 2 mg is strongly recommended in all patients who receive ganetespib and should be given 1-2 hours before ganetespib administration, to be repeated every 4 hours for the first 12 hours. Sufficient hydration should be provided in all patients.

Part I: The first 3 patients will be treated with a starting dose of ganetespib of 100 mg/m^2 in combination with paclitaxel (80 mg/m^2, fixed dose). If this dose does not cause significant side effects (DLT) in the first cohort during cycle 1 (weeks 1-4), ganetespib will be escalated to 150 mg/m^2, as a second cohort takes part in the study. If the dose of 150 mg/m^2 does not cause significant side effects (DLT), it will be used in the GANNET53 phase II trial.

In case of significant side effects (DLT) in the cohorts in phase I dose reductions of ganetespib are planned and described in section 7.2.

Each patient will receive at least two cycles of experimental therapy and may continue treatment according to physician's choice. If a patient did benefit from the experimental therapy it is recommended to continue treatment at dosage received until progression.

Part II: An expected number of 222 patients will be treated with either the combination of ganetespib weekly (150 mg/m²) in combination with paclitaxel (80 mg/m^2) or with paclitaxel (80 mg/m^2) alone. Patients will receive the respective therapy until disease progression.

After at least six cycles of ganetespib combination therapy, the physician is allowed to discontinue paclitaxel (e.g. in case of peripheral neuropathy) and to continue maintenance therapy with ganetespib (i.e. ganetespib once a week for 3 out of 4 weeks, at the same dose as used in the combination or re-escalated to the ganetespib dose level 0).

The IMP ganetespib must be diluted prior to administration. The drug product is a clear, colourless-to-pale-yellow solution. The appropriate drug administration instructions per the preparation guidelines must be carefully followed prior to use.

The use of vascular access devices (VADs) such as ports and peripherally-inserted central catheters (PICCS) containing silicone for ganetespib/paclitaxel administration is permitted. Use of VADs made of any other material is not permitted. Following ganetespib administration through a VAD, care should be taken to flush the line after each dose of study drug.

Ganetespib dose is calculated based on the patient's body surface area (BSA). No dose capping will be performed in case of greater BSA.

Please refer to the Pharmacy Manual for detailed ganetespib preparation guidelines.

10.1.1 Dose reduction levels for ganetespib

DLT for phase I is defined in section 10.1.6.

Ganetespib dose reductions in the first 2 cycles of **phase I** are detailed in section 7.2.1.
If a patient stays on experimental treatment for more than 2 cycles in the phase I study, please follow the dose reduction and dose modification guidelines for ganetespib and paclitaxel described below (as in phase II).
Patients in **phase II** of the trial, requiring a ganetespib dose reduction will be de-escalated one dose level with a maximum of three dose reductions allowed.
A further indication for dose reduction will result in the patient being taken off study, see below.

No dose re-escalation will be allowed with the exception of those who permanently discontinued paclitaxel, in which circumstance ganetespib may be re-escalated to dose level 0 at the discretion of the investigator.

Dose delay and dose modification guidelines for specific ganetespib-related toxicity are described below.

Table 3: Dose reduction levels for ganetespib

DOSE LEVEL	GANETESPIB DOSE
0	baseline dose (depending on cohort in phase I and established dose for phase II)
Dose -1	minus 25 mg/m^2*
Dose -2	minus 25 mg/m^2 further*
Dose -3	minus 25 mg/m^2 further*
Indication for further dose reduction	off study

* if dosage to be reduced should be 75 mg/m², then no further reduction is possible.

In addition to the specific toxicities presented in the tables in section 10.1.3, if a patient develops any other significant and clinically relevant grade 3 or 4 toxicity thought to be related specifically to ganetespib, ganetespib will be held until the symptoms resolve to grade $\leq$ 1 or to the baseline grade. When treatment is resumed, ganetespib dose is reduced by 1 dose level or discontinued if the patient is already receiving 75 mg/m^2.

If grade ≥ 3 toxicity persists for more than 2 weeks from the last planned study drug administration or recurs after the maximum dose reduction, the patient will discontinue ganetespib treatment and receive a safety follow-up and will continue to be followed for unresolved adverse events and SAEs. The patient will receive long-term follow-up according to Appendix A.

For Ganetespib no dose reduction is necessary due to a body surface area (BSA) above 2.0.

10.1.2 Dose reduction levels for paclitaxel

Dose delay and dose modification guidelines for specific paclitaxel-related toxicity are described in the tables below.
No re-escalation of paclitaxel dose will be allowed.
Patients who permanently discontinue paclitaxel may continue ganetespib. Only these patients may be allowed to escalate ganetespib to dose level 0, per the clinical judgment of the investigator.

Table 4: Dose reduction levels for paclitaxel

DOSE LEVEL	PACLITAXEL DOSE
0	80 mg/m^2
Dose -1	60 mg/m^2
Dose -2	40 mg/m^2
Indication for further dose reduction	off paclitaxel

In addition to the specific toxicities presented in the tables in section 10.1.3, if a patient experiences any other significant and clinically relevant grade 3 or 4 toxicity thought to be related to paclitaxel, paclitaxel will be held until symptoms resolve to grade ≤ 1 or to the baseline grade. When treatment is resumed, the paclitaxel dose will be reduced by 1 dose level permanently, or Paclitaxel will be discontinued if the patient is already receiving 40 mg/m^2.

If grade ≥ 3 toxicity persists for more than 2 weeks from the last planned study drug administration or recurs after the maximum dose reduction, the patient will discontinue paclitaxel treatment.

10.1.3 Dose modifications

10.1.3.1 ***Dose modification for hypertransaminasaemia (AST/ALT)***

	Grade 2 (AST/ALT)	**Grade 3** (AST/ALT)	**Grade 4** (AST/ALT)
Ganetespib	treat at same dose level	**1st occurrence** hold dose; reduce one dose level when recovered to ≤ grade 2	hold dose; reduce one dose level when recovered to ≤ grade 2
		2nd occurrence hold dose; reduce one dose level when recovered to ≤ grade 2	
Paclitaxel	hold dose; treat at same dose level when recovered to ≤ grade 1	hold dose; reduce one dose level when recovered to ≤ grade 1	Discontinue

Patients who experience a grade ≥ 3 hepatic adverse event should have their liver enzymes and/or bilirubin checked twice per week until they are stable or recovered to ≤ grade 2.

10.1.3.2 ***Dose modification for neutropenia***

	Grade 2 neutropenia	**Grade 3** neutropenia	**Grade 4** neutropenia
Ganetespib	treat at same dose level	**1st or 2nd occurrence** hold dose; treat at same dose level when recovered to ≥ 1,000 cells/mm^3	**1st occurrence** hold dose; treat at the same dose level when recovered to ≥ 1,000 cells/mm^3
		3rd occurrence hold dose; reduce one dose level when recovered to ≥ 1,000 cells/mm^3	**2nd occurrence** hold dose; treat at same dose of ganetespib when recovered to ≥ 1,000 cells/mm^3
Paclitaxel	treat at same dose level	**1st occurrence** Hold dose, treat at the same dose level when recovered to ≥ 1,000 cells/mm^3	**1st occurrence** Hold dose, if recovery to ≥ 1,000 cells/mm^3 occurs, by the next scheduled dose (or within 7 days) reduce one dose level. If prolonged (14 days) neutropenia of < 1,000 cells/mm³ occurs, discontinue paclitaxel
		2nd occurrence Discontinue	**2nd occurrence** Discontinue

In case of severe neutropenia paclitaxel will be reduced one dose level first, before reducing ganetespib.

10.1.3.3 ***Dose modification for hyperbilirubinaemia***

	Grade 1 hyperbilirubinaemia	**Grade 2** hyperbilirubinaemia	**Grade 3** hyperbilirubinaemia	**Grade 4** hyperbilirubinaemia
Ganetespib	treat at same dose level	hold dose; treat at same dose level when recovered to ≤ grade 1	hold dose; reduce one dose level when recovered to ≤ grade 1 or baseline	hold dose; reduce one dose level when recovered to ≤ grade 1 or baseline
Paclitaxel	treat at same dose level	hold dose; treat at same dose level when recovered to ≤ grade 1	hold dose; reduce one dose level when recovered to ≤ grade 1 or baseline	Discontinue

Patients who experience a grade ≥ 3 hepatic adverse event should have their liver enzymes and/or bilirubin checked twice per week until they are stable or recovered to ≤ grade 2.

10.1.3.4 ***Dose modification for thrombocytopenia***

	Grade 2 thrombocytopenia	**Grade 3** thrombocytopenia	**Grade 4** thrombocytopenia
Ganetespib	treat at same dose level	**1st or 2nd occurrence** hold dose; treat at same dose level when recovered to ≤ grade 2	**1st occurrence** hold dose; treat at the same dose level when recovered to ≤ grade 2
		3rd occurrence hold dose; reduce one dose level when recovered to ≤ grade 2	**2nd occurrence, currently on concurrent paclitaxel** hold dose; treat at same dose of ganetespib when recovered to ≤ grade 2 (paclitaxel discontinued as described below)
			2nd cumulative occurrence, currently on single agent ganetespib hold dose; reduce one dose level when recovered to ≤ grade 2
Paclitaxel	treat at same dose level when recovered to ≥ 100,000 cells/mm³	**1st occurrence** Hold dose, treat at the same dose level when recovered to ≥ 100,000 cells/mm³	**1st occurrence** Hold dose, reduce one dose level when recovered to ≥ 100,000 cells/mm³.
		2nd occurrence Hold dose; reduce one dose level when recovered to ≥ 100,000 cells/mm³	**2nd occurrence** Discontinue

In case of severe thrombocytopenia paclitaxel will be reduced one dose level first, before reducing ganetespib.

10.1.3.5 ***Dose modification for peripheral neuropathy***

	Grade 2 peripheral neuropathy	**Grade 3 or 4** peripheral neuropathy
Ganetespib	treat at same dose level	hold dose; treat at same dose level when recovered to ≤ grade 2
Paclitaxel	treat, hold or discontinue at investigators discretion, if recurrent can also consider dose reduction	Discontinue

10.1.3.6 ***Dose modification for ganetespib-related gastrointestinal toxicity***

	Grade 2 gastrointestinal toxicity	**Grade 3 or 4** gastrointestinal toxicity
Ganetespib	treat at same dose level	hold dose; treat at same dose level when recovered to ≤ grade 2
		2nd occurrence: consider one dose level reduction

Ensure that optimal prophylactic and therapeutic measures are taken (e.g. loperamideLoperamide).

10.1.3.7 ***Dose modification for ganetespib-related QTc prolongation***

	Grade 2 QTc prolongation	**Grade 3** (> 500 ms on average of triplicate ECGs) **or repeated grade 3** **or grade 4** QTc prolongation
Ganetespib	treat at same dose level	Discontinue

Patients with reported QTc >500 ms (QTc prolongation Grade 3 severity) or with reported Grade 4 QTc prolongation (QTc >500 ms or >60 ms change from baseline and Torsades de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) at any of the specified ECG time points (average of triplicate recordings) must discontinue treatment with ganetespib.
Close cardiac monitoring should be ensured in case of a grade 3 QTc prolongation occurrence by:

- patient hospitalisation
- cardiac monitoring
- discharge of the patient after specialist review

Drugs which prolong QTc interval and have a known risk to cause Torsade de Pointes (TdP, see APPENDIX F), are to be avoided and drugs which prolong QTc interval and have a possible risk to cause TdP (see APPENDIX G) are to be used with caution in patients receiving ganetespib.

10.1.4 Management guidelines of the most significant AE diarrhoea

For diarrhoea the postulated mechanism of action is inhibition of EGFR in enterocytes that line the GI tract, leading to a transient secretory diarrhoea, limited to 24-48 hours following ganetespib infusion.
This AE is **readily manageable** by antidiarrheal medication (loperamideLoperamide). Prophylactic use of loperamideLoperamide can reduce the occurrence of diarrhoea to approximately 40%.

In the GANNET53 trial prophylactic medication with loperamideLoperamide is highly recommended. Loperamide 2 mg should be given prophylactically to patients receiving ganetespib before the onset of diarrhoea, starting approximately 1-2 hours before ganetespib administration, to be repeated every 4 hours for the first 12 hours.

In the event of diarrhoea it is highly recommended to apply **therapeutic medication with loperamideLoperamide.**
Patients should take loperamideLoperamide at an initial 4 mg dose (irrespective of the timing of the last prophylactic dose), followed by 2 mg doses every 4 hours. In the presence of uncomplicated grade 1 or 2 diarrhoea, **loperamideLoperamide should be continued until the patient is free from diarrhoea for 12 hours**. Total daily dose should not exceed 16 mg (eight capsules).

For grade 3 or 4 diarrhoea or complicated grade 1 or 2 (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, grade 3 or 4 neutropenia, frank bleeding, dehydration), iv fluids should be used as appropriate, as well as prophylactic antibiotics.

In addition, due to the potential for dehydration, patients will be advised to maintain appropriate hydration. Blood chemistries, including electrolytes, will be regularly monitored and corrected as appropriate.

10.1.5 Study drug interruption or discontinuation

The investigator must temporarily interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.
The interruption or premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., laboratory abnormalities; see chapter 11.5.3), or for administrative reasons, in particular withdrawal of the patient's consent.
The reason for study drug interruption or premature permanent discontinuation must be documented in the CRF.

The patient has to be taken off study drug permanently if interruption (time between two study drug applications) is longer than 4 weeks. It is permitted to omit 1 cycle during ganetespib maintenance therapy (after termination of paclitaxel after 6 cycles in phase I or phase II) in case of patients wish (e.g. because of vacation). An interruption of more than 1 cycle during ganetespib maintenance must be discussed with the sponsor.

Study drug premature permanent discontinuation

In case of premature permanent discontinuation of study treatment for any reason, the patient should have an EOT/safety follow-up visit with all the assessments performed 28 days (+/- 7 days) after last administration of IMP or, if the decision was reached after this time frame, on day of decision for discontinuation.

10.1.6 Dose-limiting toxicity (DLT) in phase I

For the phase I trial DLT will be defined as any of the following:

NON-HAEMATOLOGIC adverse events:
Any significant, clinically relevant **grade > 3** adverse event, *excluding*:

- alopecia
- grade > 3 nausea
- vomiting and diarrhoea. These will only be considered a DLT if they occurred despite of optimal prophylactic measures (e.g. loperamideLoperamide)

Fatigue must be grade 4 to be considered a DLT.

Any **grade ≥ 3** adverse event not improving to baseline or grade ≤ 1 within 21 days of last treatment dose and despite adequate supportive care/toxicity management.
The following adverse events are always considered a DLT:

- Any grade ≥ 3 elevation of serum bilirubin
- > 10x ULN elevation of hepatic transaminases (AST or ALT), or > 10x ULN elevation of alkaline phosphatase (ALP)
- Any > 5-10 x ULN elevation of hepatic transaminases (ALT or AST) or ALP not improving to ≤ 5 x ULN (grade ≤ 2) by day 7

HAEMATOLOGIC adverse events:

- Grade 4 thrombocytopenia
- Any grade 3 thrombocytopenia that has not recovered to grade $\leq$ 2 by day 7 of AE onset
- Grade 4 neutropenia lasting $\geq$ 7 days
- Febrile neutropenia

OTHER adverse events:

- Any treatment-related toxicity prompting a dose reduction of ganetespib during the DLT observation period (D1 of cycle 1 to D28 of cycle 2)
- Grade ≥ 3 laboratory toxicity that are thought by the principal investigator (of the respective trial site) to be clinically insignificant or related to an underlying condition will not be considered as a DLT but will be forwarded to the DSMC.
- Adverse events that have an outcome of death and are considered possibly related to the study drug will be considered as DLTs. The possible relation to the study drug will be determined by the principal investigator.
- Adverse events related to disease progression or clearly are not study drug-related will not be considered as DLTs.

Note: A dose hold of ganetespib during the DLT observation period does not constitute a DLT.

Delayed toxicities will be carefully monitored and documented and will be included in the assessment of the recommended phase II dose of the combination.

Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 5: Criteria for DLTs

	Adverse Event	Grade	Comment	DLT (yes/no)
NON-HAEMATOLOGIC	any (with exceptions)	4	significant, clinically relevant	Yes with the exceptions of 1. alopecia 2. nausea and 3. vomiting without optimal prophylactic measures
	alopecia	4		no
	nausea	4		no
	vomiting	4	occurred despite optimal prophylactic measures (e.g. antiemesis, loperamideLoperamide)	yes
		4	no optimal prophylactic measures applied	no
	diarrhoea	4	occurred despite optimal prophylactic measures (e.g. loperamideLoperamide)	yes
		4	no optimal prophylactic measures applied	no
	fatigue	4		yes
		1, 2, 3		no
	any	3, 4	Not improving to baseline or grade ≤ 1 within 21 days of last treatment dose and despite adequate supportive care/toxicity management	yes
	elevation of serum bilirubin	4		yes
	elevation of AST, ALT, or ALP		> 10 x ULN	yes
			> 5-10 x ULN and not improving to ≤ 5 x ULN (grade ≤ 2) by day 7	yes
			> 5-10 x ULN which improved to ≤ 5 x ULN (grade ≤ 2) by day 7	no
	any AEs		Related to disease progression or considered to be clearly not study drug-related	no

HAEMATOLOGIC	thrombocytopenia	4		yes
	thrombocytopenia	3	if not recovered to ≤ 2 by day 7 of AE onset	yes
		3	if recovered to ≤ 2 by day 7 of AE onset	no
	neutropenia	4	If lasting ≥ 7 days	yes
		4	If lasting less than 7 days	no
	febrile neutropenia	any grade		yes
OTHER	any toxicities		Which are treatment-related and prompt a dose reduction of ganetespib during DLT observation time*	yes
	Laboratory toxicity	3, 4	Considered as clinically insignificant by the PI or related to an underlying condition	no
	any death		Which is considered possibly related to the study drug (determined by the PI)	yes
			Which is considered not related to the study drug (determined by the PI)	no
	any AEs		Related to disease progression or considered to be clearly not study drug-related	no
	any dose hold during DLT observation time*			no

*** DLT observation time: D1 of cycle 1 to D28 of cycle 2**

10.2 Summary of known and potential risks of the study drug ganetespib

For the most up-to-date information on the safety profile of ganetespib, the list of expected AEs and those considered listed for regulatory purposes, please refer to the current version of the Investigator's Brochure. The safety information in the Investigator's Brochure is continually updated as the toxicity profile of ganetespib is refined.
Ganetespib is **well tolerated** with most reported adverse events (AEs) being mild or moderate and readily manageable. In addition, there has been no observed pattern of specific target organ severe toxicity.

The *most frequently* reported AEs (taking as reference the **largest pooled data set of single agent studies, n=402 patients**) were related to *gastrointestinal (GI) toxicity* and included **diarrhoea (80.1%)**, nausea (44.5%), decreased appetite (31.6%), vomiting (27.4%), constipation (21.9%), and abdominal pain (20.9%).
Non-GI-related events that occurred frequently included fatigue (53.5%), anaemia (21.1%), headache (20.4%), insomnia (21.1%), dyspnoea (17.4%), back pain (15.7%), blood alkaline phosphatase (AP) increase (15.9%), aspartate aminotransferase (AST) increase (16.2%), alanine aminotransferase (ALT) increase (15.4%), hypokalaemia (13.7%), and hyponatraemia (13.7%).

AEs of g*rade 3 or higher* [National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE)], were seen in 275 patients (68%), and 126 patients (31%) had an AE deemed *related* to treatment (defined as possibly, probably, or definitely related to treatment). The most common treatment-related ≥ grade 3 AEs were diarrhoea (10%), fatigue (6%), increased lipase and hyponatraemia (3%), and hypophosphatemia, nausea, increased ALT and increased AST (2% each).

160 patients (40%) experienced a treatment-emergent AE that was assessed as *serious* (SAE). 33 (8%) patients had an SAE deemed *related* to treatment. The most common treatment-related SAE was diarrhoea, which occurred in 7 (2%) patients. All other treatment-related SAEs occurred in <1% of study patients.

Note new safety information GIP (gastrointestinal perforation):
GIP is a hole that for example develops through the wall of the oesophagus, stomach, small intestine, large bowel, rectum, or gallbladder. According to the Ganetespib Safety Update letter (dated 28-Sep-2015) 11 cases out of 1.509 patients (0.7%) exposed to ganetespib were identified with GIP overall. In the GANNET53 trial, which is including patients with platinum-resistant ovarian cancer, GIP has been observed in 2 of 65 patients (3.1%; cut-off date 15-Jan-2016).
GIP was therefore identified as a new safety finding and as such has been added to the reference safety information of the Investigators Brochure (edition 11, dated 13-Nov-2015).

10.2.1 Medications used with caution

10.2.1.1 ***Inhibitors of P-glycoprotein efflux Transporters***

Concomitant medications that are strong inhibitors of P-glycoprotein efflux transporters should be used with caution during the study; examples of these medications include ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, and elacridar.

10.2.1.2 ***Medications associated with QTc interval prolongation***

Drugs which prolong QTc interval and have a *known* risk to cause Torsade de Pointes (TdP, see APPENDIX F), are to be avoided in patients receiving ganetespib.
Medications that have the potential of prolonging the QTc interval but that are not linked to the occurrence of Torsades de Pointes (i.e. drugs with *possible* Torsades de Pointes risk) should also be avoided or used with caution (see APPENDIX G) in patients receiving ganetespib. The decision whether or not such a medication with possible Torsades de Pointes risk may be used will be made by the investigator, taking into consideration the patient's medical history and current QTc values.

10.2.1.3 ***Substrates of CYP3A4 or CYP2C19***

Preliminary results of a clinical drug-drug interaction study, examining the effect of ganetespib on the pharmacokinetics of the CYP2C19-sensitive probe omeprazole, show a modest (20%) increase in omeprazole exposure when co-administered with ganetespib. In vitro data implies expectation of greater interaction with CYP2C19 substrates than with CYP3A4 substrates. Caution is advised when sensitive narrow therapeutic range CYP3A4 or CYP2C19 substrates are concomitantly administered.

Examples of compounds frequently used in oncology and metabolised predominantly by CYP3A4 or CYP2C19 are provided in Table 7.

Table 6: List of medications frequently used in oncology treatment that are substrates of CYP3A4 or CYP2C19

Drug Class	Drug	Washout
CYP3A4 substrate examples		
antibiotics (macrolide)	clarithromycin	17 hours
	erythromycin	8 hours
antifungals	ketoconazole	16 hours
	itraconazole	4 days
antiretrovirals	amprenavir	2 days
	indinavir	16 hours
	lopinavir	1 day
	nevirapine	9 days
	ritonavir	1 day
	saquinavir	2 ½ days
	nelfinavir	1 day
Benzodiazepines	midazolam	10 hours
	alprazolam	2 ½ days
	triazolam	15 hours
calcium channel blockers	diltiazem	1 day
	felodipine	3 days
	nifedipine	9 hours
	verapamil	1 day
Gastrointestinal (GI) Agents	aprepitant	1 week
CYP2C19 substrate examples		
anticonvulsants	phenytoin	5 days
antifungals	voriconazole	1 day
antiretrovirals	nelfinavir	1 day

10.3 Summary of known and potential risks of paclitaxel

Current information on the safety profile of paclitaxel is provided in detail in the Summary of Product Characteristics (SmPC). Investigators should refer to the SmPC for warnings and precautions particular to paclitaxel therapy.

Premedication
Due to the known potential for allergic reaction to paclitaxel and/or the cremophor vehicle, premedications should be administered in accordance with **local standard of care** in order to prevent severe hypersensitivity reactions.

Of note, drugs which prolong QTc interval and have a *known* risk to cause Torsade de Pointes (TdP, see APPENDIX F) are to be avoided and drugs which prolong QTc interval and have a *possible* risk to cause TdP (see APPENDIX G) are to be used with caution in patients receiving ganetespib.

Therefore, for patients receiving ganetespib *an example* of a possible paclitaxel premedication containing no QT interval prolonging medications with *known* Torsade de Pointes risk is as follows:

Dexamethasone	20 mg i.v.	30 minutes prior to paclitaxel
Diphenhydraminhydrochlorid	30 mg i.v.	20 minutes prior to paclitaxel
Ranitidine	50 mg i.v.	20 minutes prior to paclitaxel

And **patients participating in PK analysis in phase II** will receive a standardised pre-medication scheme see section 9.8.

Investigators may use their discretion in determining the regimen to be used according to institutional guidelines or practice.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.
Significant hypersensitivity reactions as characterised by dyspnoea and hypotension requiring treatment, angiooedema, and generalised urticaria have occurred in <1% of patients receiving paclitaxel after adequate premedication.
These reactions are probably histamine-mediated.

In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with paclitaxel.

34% of patients receiving paclitaxel (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be treated with paclitaxel in case neutrophil count is < 1,000 cells/mm^3 and platelet count is < 100,000 cells/mm^3.

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

10.3.1 Study drug delivery & drug storage conditions

The IMP ganetespib will be provided by Synta Pharmaceuticals Corp. (Lexington, MA, USA) at no charge. Paclitaxel is considered an NIMP and will be supplied and covered by the local hospital/health insurer.
The IMP ganetespib is a concentrate for solution for infusion provided in a single-use vial.

The IMP is supplied as ganetespib drug product, 25 mg/mL, 300 mg/vial (identified with a dark blue colour cap and applicable product label): Each vial contains 12 mL of deliverable volume (12.84 mL total including an overage per USP requirements) equivalent to 300 mg of ganetespib at a concentration of 25 mg/mL in a PEG 300, polysorbate 80, and dehydrated alcohol non-aqueous solvent system. The drug product, as noted, is a clear, colourless-to-pale-yellow solution essentially free of visible particles.
The 300 mg/vial drug products are shipped at ambient temperatures. No temperature monitoring devices are utilized during the shipping of this drug product.
Storage of the 300 mg/vial drug product should be at 20-25°C (68°F to 77°F) with excursions allowed between 15°C and 30°C (59°F and 86°F). Alternatively, ganetespib drug product may be stored in a cool place between 8°C (46°F) and 20°C (68°F). DO NOT FREEZE. Infusion solutions must be stored at room temperature and exposure to direct light should be avoided.
Please refer to the Pharmacy Manual for detailed information.

10.3.2 Study drug packaging and labelling

Drug labelling, storage and distribution to the patient-recruiting sites will be done in accordance with all local legal requirements and conducted according to Good Manufacturing Practice.

10.4 Concomitant medications

Throughout the study, investigators are permitted to use their clinical judgement when prescribing concomitant medications and treatments for trial patients. Local prescribing information and institutional guidelines should be followed as applicable. In all cases, concomitant medications and treatments should only be used with the intention of either maintaining existing medical conditions, or controlling cancer-related symptoms or treatment-related complications. Caution should be exercised when using treatments that could potentially interfere with any of the study medications or the interpretation of the study results. For specific information, please refer to the ganetespib Investigators' Brochure and the local prescribing information for whichever chemotherapy is being used.

- The use of erythropoietin or other specific red blood cell growth factors and red blood cell transfusions will be permitted as clinically indicated during the study after documentation of anaemia secondary to the study treatment. These agents cannot be used prior to this occurrence.
- The use of bone marrow colony-stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated after documentation of neutropenia secondary to the study treatment. These agents cannot be used prior to this occurrence.
- However, during the DLT observation time in Phase I (day 1 of cycle 1 through day 28 of cycle 2) these bone marrow colony-stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) should not be used in order not to bias the lasting of e.g. neutropenia.
- Other concomitant medications may be given as clinically indicated
- A standard 3-5 day course of dexamethasone following the institutions standard of care for the prevention of chemotherapy-induced nausea and vomiting is allowed; steroids (inhaled, topical, or for physiologic replacement, or for short-term treatment of conditions

such as allergic reactions and asthma flares, or for appetite stimulation) and glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed.
- Also see section “Medications Used with Caution” (section 10.2.1).

Not allowed are:

- Use of medications associated with a high incidence of QTc prolongation and *known* risk of TdP in subjects receiving ganetespib should be avoided and drugs with QTc prolongation and *possible* risk of TdP should also be avoided or used with caution. See Appendix F and Appendix G, respectively.
- Treatment with other systemic anticancer agents (e.g., chemotherapy, hormonal therapy, and immunotherapy) or other treatments not part of protocol-specified anticancer therapy.
- Any oral, injected or implanted hormonal methods of contraception. The use of non-hormonal contraceptives is required for WOCBP, as per the inclusion criteria in Section 7.4.1.1.
- Concurrent investigational agents of any type.
- Use of herbal remedies for cancer treatment.

The following treatments should be avoided because of the risk of immunosuppression:

- Chronic or high-dose oral corticosteroid therapy.
- Tumour necrosis factor-α inhibitors.
- Anti-T cell antibodies.

11. SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and recording AEs, including SAEs; measurement of protocol-specified vital signs deemed critical to the safety evaluation of the study.

11.1 Adverse events

It is the responsibility of the investigator(s) to report all adverse events in the eCRF.

An AE is any untoward adverse change from the subject's baseline condition, i.e. any unfavourable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the study drug.

Adverse events include:

- Worsening or increase in frequency or intensity of a pre-existing disease or medical condition.
- Abnormal laboratory tests (see section 11.5.3).

Adverse events do not include:

- Pre-planned interventions/hospitalisations (see also section 11.2.1)
- Medical or surgical procedures, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

11.2 Serious adverse events (SAEs)

A serious adverse event (SAE) is defined by the International Conference on Harmonisation (ICH) guidelines and WHO GCP guidelines as any AE fulfilling at least one of the following criteria:

- Results in death.
- Life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring subject's hospitalisation or prolongation of existing hospitalisation – inpatient hospitalisation refers to any inpatient admission, regardless of length of stay.
- Resulting in persistent or significant disability or incapacity (i.e. a substantial disruption of a person’s ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Is medically significant or requires intervention to prevent at least one of the outcomes listed above.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalisation may be considered as SAEs when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

11.2.1 Hospitalisation – Prolongation of existing hospitalisation

Hospitalisation is defined as an overnight stay in a hospital unit and/or emergency room.
An additional overnight stay defines a prolongation of existing hospitalisation.

The following is not considered a SAE and should be reported as an AE only:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalisation.

The following reasons for hospitalisation are not considered AEs or SAEs:

- Hospitalisation for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g. hospitalisation for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g. hospitalisation for chemotherapy for cancer, elective hip replacement for arthritis.
- Placement of a central venous catheter (e.g. port-a-cath) as a routine intervention

11.2.2 Suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse reactions with a suspected causal relationship to the study drug that is unexpected (not previously described in the SmPC - Summary of Product Characteristics or Investigator's Brochure) and serious.

11.2.3 Pregnancy

Any pregnancy that occurs during study participation must be reported to the investigator/sponsor immediately. If a pregnancy is confirmed during the study, the continued use of the study drug must be immediately evaluated. If a pregnancy should be confirmed after informed consent has been obtained, but prior to the initiation of the study drug, the patient must be excluded from the trial.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications (including spontaneous abortions) and elective terminations must be reported as an AE or SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the principal investigator/sponsor.

11.3 Severity of adverse events/Grading

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version v4.03 on a five-point scale (grade 1 to 5) and reported in detail on the eCRF.

Adverse events not listed in the CTCAE v4.03 should be graded as follows:

CTC grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall wellbeing or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

11.4 Relationship to study drug

Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication.

Is there a reasonable possibility that the study drug caused the event?
Answer **YES** (possibly, probably or definitely related) if one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.
  The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).

Otherwise answer **NO** (unlikely, probably not related or definitely not related).

11.5 Procedures for recording of adverse events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid lay terminology and abbreviations.
Only one AE term should be recorded in the event field on the Adverse Event eCRF. See section 11.1 for the definition of an AE.

11.5.1 Diagnosis versus signs and symptoms

Infusion-associated reactions
Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other adverse events
For AEs other than infusion-associated reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

11.5.2 Persistent or recurrent adverse events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (mild, moderate, severe, life-threatening/disabling) of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.
A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

11.5.3 Abnormal laboratory values or vital signs

Not every laboratory abnormality qualifies as an AE. A laboratory test result/vital sign should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g. potassium supplementation for hypokalaemia) or a change in concomitant therapy.
- Clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all laboratory findings/vital signs. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality or vital sign should be classified as an AE.
If a clinically significant laboratory abnormality or vital sign is a sign of a disease or syndrome (e.g. alkaline phosphatase and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e. cholecystitis) should be recorded on the Adverse Event eCRF. The supporting laboratory abnormalities should be included in the event description if the event qualifies as a SAE.

11.5.4 Progression of underlying malignancy

Progression of underlying malignancy and clinical symptoms of progression (e.g. ileus, sub-ileus, vomiting) are not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST 1.1 criteria or GCIG criteria for CA-125. Clinical symptoms of disease progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under trial. Hospitalisation due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.
If there is any uncertainty about an adverse event being due only to the disease under the clinical trial it should be reported as an AE or SAE.

11.6 Reporting procedures

A special section is designated to adverse events in the case report form where the following details must be entered:

- Type of adverse event (diagnosis or syndrome; if not known signs or symptoms)
- Start (date)
- End (date)
- Severity (mild, moderate, severe, life-threatening/disabling, death)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, ongoing, ongoing – improved, ongoing – worsening)
- Action taken (none, study medication dose reduced, study medication interrupted, study medication discontinued, medication therapy, surgical procedure, hospitalisation, other)
- Relation to study drug (possibly, probably or definitely related or unlikely, probably not related or definitely not related)

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events.
- Pregnancies.

The investigator must report new significant follow-up information for these events to the sponsor immediately (i.e. no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

11.6.1 Reporting procedures for SAEs and SUSARs

In the event of a serious adverse event, the investigator has to use all supportive measures for best patient treatment. And the SAE form must be completed by the investigator and reported no more than 24 hours after awareness of the event.

The following details should be available with the initial report:

- Patient number
- Patient: date of birth, ethnic origin
- Name of investigator and investigating site
- Period of administration
- The suspected investigational medicinal product (IMP)
- The adverse event assessed as serious
- Concomitant disease and medication
- Relevant medical history
- Short description of the event and outcome
    - Description
    - Onset and if applicable, end
    - Therapeutic intervention
    - Causal relationship to each of the study drugs
    - Hospitalisation or prolongation of hospitalisation
    - Death, life-threatening, persistent or significant disability or incapacity

If applicable, the initial report should be followed by the follow-up report, indicating the outcome of the SAE.

For SAEs, SUSARs and pregnancies, the sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g. from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. A follow-up SAE form must also be completed and reported appropriately.

SUSARs will be reported to the required regulatory authorities, investigators/institutions, and ethical committees in compliance with all reporting requirements according to local regulations and good clinical practice by the sponsor and/or its designees.

For detailed reporting procedures please refer to the SAE reporting manual.

11.6.2 Adverse event reporting period

Investigators will seek information on AEs at each patient contact throughout the trial. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of the study drug**, only SAEs considered to be related to a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as biopsies).

After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent.
After the safety follow-up, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with the study drug.

Any Serious Adverse Event (SAE) that is ongoing at the time of safety follow-up should be followed-up until resolved. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

11.7 Handling of safety parameters

11.7.1 Treatment and follow-up of adverse events

Adverse events, especially those for which a relationship to study drug is suspected, should be followed up until they have stabilised or returned to baseline status. If a clear explanation is established it should be recorded on the eCRF.

11.7.2 Follow-up of abnormal laboratory test value

In the event of unexplained and clinically significant laboratory test values, the tests should be repeated immediately if possible and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

12. DOCUMENTATION AND DATA MANAGEMENT

12.1 Retention of documents/Investigator site file

The sponsor must keep all essential documents of the clinical study after completion or discontinuation of the study for a minimum of 15 years. The sponsor must archive all study-relevant documents in accordance with the legal regulation.

The clinical trial centre is provided with an Investigator Site File (ISF). This contains all documents which are required for the clinical study. It is the responsibility of the investigator to file all documents in the ISF. During monitoring visits the ISF will be reviewed to verify accuracy and completeness in accordance with the regulations. After completion or discontinuation of the study this ISF has to be stored in a safe place for 15 years.

The investigators must keep all records and documents, which are related to the study or the allocation of investigational medicinal products (e.g. data entry form, consent form, list of the allocations of investigational medicinal products and further relevant documents), for a minimum of 15 years.
Medical records and other original data have to be kept for the longest possible duration, which the hospital, the institution or the private practice permits.

12.1.1 Case report form (CRF)

For each patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorised delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-enrolment screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.
The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

12.2 Data and safety monitoring committee (DSMC)

The DSMC will be responsible for independently evaluating the safety of the patients participating in the trial. All captured adverse events and safety reports will be reported to the DSMC for assessment. All SAEs will be forwarded to the DSMC immediately after knowledge of it. The DSMC can, if required, amend the protocol and in case the risk to the patients outweighs the potential benefit end the study prematurely.
The DSMC will meet (e.g. via teleconference) on a regular basis over the course of the study and may also meet on an unscheduled basis if any unexpected safety concerns arise.

12.3 Quality control and quality assurance

Monitorings and audits are performed for the quality assurance within the clinical study and the A-AGO trial centre and the project management team will continuously monitor the recruitment process.

12.3.1 Periodic monitoring

It is understood that the responsible sponsor-assigned monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs, source notes, and other pertinent data), provided that patient confidentiality is maintained in accord with local requirements.
Monitoring and auditing procedures developed or endorsed by the sponsor will be adhered to, in order to comply with ICH-GCP guidelines and local legal requirements to ensure acceptability of the study data.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them, evaluation of the SAEs reports according to the regulations, evaluation of compliance. The monitor should have access to laboratory test reports and other patient records needed to verify the entries in the eCRF. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.3.2 Audit and inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to competent authority inspectors. The main purposes of an audit or inspection are to confirm that the rights and wellbeing of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

12.4 Reporting and publications

12.4.1 Reports

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs within 24 hours after knowledge of which to the sponsor. Investigators may receive written safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such

reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

12.4.2 Publication of study results

The data from the whole trial will be reported together. Positive and inconclusive as well as negative results will be published or otherwise made publicly available.
The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor and the coordinating investigator (A-AGO, Nicole Concin) prior to submission.
The rights of the investigator and of the A-AGO with regard to publication and dissemination of the results of this trial are described in the Consortium Agreement.

13. ETHICAL AND LEGAL ASPECTS

13.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical trial, the patient must give written consent to participation in the study.
During the instruction the trial participants are to be made aware of the fact that they can withdraw their consent – without giving any reasons – at any time without their further medical care being influenced in any way.
In addition to the comprehensive instructions given to the trial participants by the investigator, the trial participants also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.
The patients must agree to the possibility of study-related data being passed on to relevant authorities.
The patients must be informed in detail of their obligations in relation to the trial participants insurance in order not to jeopardise insurance cover. The informed consent form has to be signed and dated by the patient and the investigator and stored in the Investigator Site File. One copy of the informed consent form has to be handed over to the patient.
No study specific procedures are allowed to be carried out prior to signing of the informed consent form.

13.2 Acknowledgement/Approval of the study

The study groups will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to the responsible Independent Competent Authority (ICA) and Independent Ethics Committee (IEC) or Institutional Review Board (IRB) in their respective country according to legal requirements. Approval from the committee must be obtained before starting the study.
The clinical trial shall be performed in full compliance with the legal regulations according to applicable local laws and regulatory requirements.

13.2.1 Changes in the conduct of the study

Protocol amendments

Proposed amendments must be submitted to the appropriate competent authorities (CAs) and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Study termination

If the sponsor or the investigator decides to terminate the study before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator/trial group or sponsor will notify the relevant CA and EC. Documentation will be filed in the Trial Master and Investigator Site Files.

Clinical study report (CSR)

Within one year after the final completion of the study, a full CSR will be prepared by the sponsor and submitted to the EC and the competent authority.
The investigator will be asked to review and sign the final study report.

13.3 Insurance

During their participation in the clinical trial the patients will be insured as defined by legal requirements. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/trial centre against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries will comply with the applicable regulations.

13.4 Ethics and Good Clinical Practice (GCP)

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 56th WMA General Assembly, Tokyo, Japan, 2008) and with the laws and regulations of the country in which the clinical research is conducted.
The investigator of the clinical trial shall guarantee that only appropriately trained personnel will be involved in the study. All studies must follow the ICH-GCP Guidelines (June 1996).

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15. APPENDICES

Appendix A - VISIT AND ASSESSMENT SCHEDULE

Part I

Phase I trial	**SCREENING**	**TREATMENT and OBSERVATION**												**Safety FU**[1]	**FOLLOW-UP**[2]
		Cycle 1				***Cycle 2***				***OPTIONAL*** ***Cycle 3***					
week number		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	9	10	11	12		
Cycle day	***- 28 days***	***1***	***8***	***15***	*21*	***1***	***8***	***15***	*21*	***1***	***8***	***15***	*21*		
Informed consent	X				No treatment				No treatment				No treatment		
Inclusion / Exclusion criteria	X														
Medical history	X														
Demographic data	X														
CT[a]	X									X[5]					(X)
Physical examination incl. vital signs[b] **(BP, HR, T)**	X	X	X	X		X	X	X		X	X	X		X	
Body weight	X	X	X	X		X	X	X		X	X	X		X	
Height	X														
ECOG performance status	X	X	X	X		X	X	X		X	X	X		X	
ECG[c]	X	X[6]				X				X				X	
LVEF	X													X	
Laboratory tests[d]	X	X	X[3]	X[3]		X	X[3]	X[3]		X	X[3]	X[3]		X	
CA-125[e]	X	X				X				X				X	(X)
Concomitant medication	X	X	X	X		X	X	X		X	X	X		X	
Pregnancy test[f]	X	X				X				X				X	
Administration of ganetespib and paclitaxel		X	X	X		X	X	X		X	X	X			
Adverse events[g]		X	X	X		X	X	X		X	X	X			
Survival status, additional cancer therapy															X

OPTIONAL

Follow schedule of cycle 1 through 3 for subsequent cycles until progression[4]***;***

after six cycles of combination treatment with ganetespib and paclitaxel, ganetespib mono therapy is allowed[7]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CA = cancer antigen; CT = computerised tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; FACT = Functional Assessment of Cancer Therapy; FU = follow-up; GOG = Gynecologic Oncology Group; HR = heart rate; LVEF = left ventricular ejection fraction; m² = meter squared; MRI = magnetic resonance imaging; RBC = red blood cell(s); T = temperature; WBC = white blood cell(s)

[a] Tumour assessments for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning.

[b] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes.

[c] ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary.

[d] Laboratory tests include assessment of

- o *Haematology*
  - § *Haemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†], platelets*
    - [†] *Neutrophils, eosinophils, basophils, lymphocytes, monocytes*
- o *Biochemistry panel*
  - § *Sodium, potassium, calcium*
  - § *Serum albumin, serum urea*
  - § *ALT, AST, LDH, AP, total bilirubin*
  - § *Creatinine*

Laboratory assessments from screening can be used for day 1 of cycle one if not older than 3 days.

[e] Measured twice during the screening period; collections should be at least 1 day apart, one sample needs to be within 1 week of treatment start.

[f] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[g] Between consent and first study drug dose only SAEs that are protocol-related will be recorded. Thereafter all AEs until Safety FU and all SAEs through Safety FU until resolved.

[1] 28 days (+/- 7 days) after last IMP administration, due to any reason

[2] Patients who had EOT of any reason prior to progression will have monthly (+/- 7 days) follow-up after EOT, incl. CA-125 and recording of additional cancer treatment, and a CT every eight weeks (± 7 days) until progression.
All patients after progression will have only survival status and information to additional cancer therapy collected every 3 months (+/- 14 days) until death of patient or end of study, whichever occurs first.

[3] Haematology only
[4] Patients who show a benefit from the treatment can continue to receive ganetespib and/or paclitaxel according to physician's choice. Treatment needs to be recorded in eCRF.
[5] CT should be done every 8 weeks (+/- 7 days) from date of cohort assignment regardless of any treatment delays or interruptions until progression
[6] additionally to the pre-dose ECG a 24-hours (+/- 4 hours) post-ganetespib-dose ECG will be performed on day 1 cycle 1; 24-hours post-ganetespib dose ECG is also strongly recommended to be performed at day 1 of each subsequent cycle.
[7]After six cycles of ganetespib combination therapy, the physician is allowed to discontinue paclitaxel (e.g. in case of peripheral neuropathy) and to continue maintenance therapy with ganetespib (i.e. ganetespib once a week for 3 out of 4 weeks; at the dose level previously used in the combination or re-escalated to the ganetespib dose level 0)

Part II

Phase II trial	**SCREENING**	**TREATMENT and OBSERVATION (-1/+2 days)**												**Safety FU[1]**	**FOLLOW -UP[2]**
		Cycle 1				***Cycle 2***				***Cycle 3***					
week number		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*		
Cycle day	***- 28 days***	**1**	**8**	**15**	21	**1**	**8**	**15**	21	**1**	**8**	**15**	21		
Informed consent	X				No treatment				No treatment				No treatment		
Inclusion / Exclusion criteria	X														
Medical history	X														
Demographic data	X														
Height	X														
Physical examination incl. vital signs[a] (BP, HR, T)	X	X	X	X		X	X	X		X	X	X		X	
Body weight	X	X	X	X		X	X	X		X	X	X		X	
ECOG Performance status	X	X	X	X		X	X	X		X	X	X		X	
CT/MRI[b]	X									X					(X)
ECG[c]	X	X[3]				X[3]				X[3]				X	
LVEF	X													X	
Laboratory tests[d]	X	X	X[4]	X[4]		X	X[4]	X[4]		X	X[4]	X[4]		X	
CA-125[e]	X	X				X				X				X	(X)
Pregnancy test[f]	X	X				X				X				X	
PRO questionnaire[g]	X	X		X		X		X		X		X		X	X
Adverse events[h]		X	X	X		X	X	X		X	X	X		X	
Concomitant medication	X	X	X	X		X	X	X		X	X	X		X	
Administration of ganetespib/paclitaxel or paclitaxel		X	X	X		X	X	X		X	X	X			
Survival status, additional cancer therapy, date of subsequent progression															X
Archival tissue samples[i]	X														
Biopsy of the actual relapse[j]	X														
Collection of ascites[k]	X								X						
Blood sample collection for biomarker analysis[l]		X				X				X					
Blood sample collection for PK analysis (selected sites only; in a subgroup of 30 patients)[m]		X													

Follow schedule of cycle 1 through 3 for subsequent cycles until progression

Combination of paclitaxel+ganetespib should be administered for a minimum of 6 cycles, thereafter ganetespib mono therapy is allowed in experimental arm.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CA = cancer antigen; CT = computerised tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; FACT = Functional Assessment of Cancer Therapy; FU = follow-up; GOG = Gynecologic Oncology Group; HR = heart rate; LVEF = left ventricular ejection fraction; m² = meter squared; MRI = magnetic resonance imaging; PRO = person reported outcome; RBC = red blood cell(s); T = temperature; WBC = white blood cell(s)

[a] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes.

[b] Tumour assessments for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning.
CTs will be performed every 8 weeks (+/- 7 days) starting from date of randomisation and/or cohort assignment regardless of any study drug interruptions until progression.

[c] ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary.

[d] Laboratory tests include assessment of

- o *Haematology*
  - § *Haemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†], platelets*
    - [†] *Neutrophils, eosinophils, basophils, lymphocytes, monocytes*
- o *Biochemistry panel*
  - § *Sodium, potassium, calcium*
  - § *Serum albumin, serum urea*
  - § *ALT, AST, LDH, AP, total bilirubin*
  - § *Creatinine*

[e] Measured at least once during the screening period. One of these samples needs to be within 2 weeks of treatment start.

[f] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[g] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28, and additional items

[h] Between consent and first study drug dose only SAEs that are protocol-related will be recorded. Thereafter all AEs until Safety FU and all SAEs through Safety FU until resolved.

[i] Archival tissue samples are mandatory for central histopathological review (for confirmation of high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal carcinoma) at screening and for the determination of p53 mutational status.

[j] CT- or sonographically-guided biopsy samples of the actual relapse (after informed consent has been obtained, but prior to the first study drug administration)

is mandatory whenever technically feasible. Biopsy tissue of the actual relapse will be collected in all patients.

[k] The collection of ascites is highly recommended at screening and during the course of treatment

[l] Blood collection for biomarker analysis will be performed before and 24 hours after (+/- 3 h) the administration of study drug on day 1 of cycle 1 (the sample time is relative to the start of the study drug infusion). On day 1 of cycles 2 and 3 blood collection will be performed exclusively *before* the study drug administration. After cycle 3, blood collection will take place on day 1 of every *other* cycle (i.e. cycles 5, 7, 9 etc.) prior to administration of study drug.

[m] **Ganetespib+paclitaxel patients:** on day 1 to day 3, blood samples will be drawn at 0 (pre-dose), 1, 1.5, 2.5, 3.5, 4.5, 6.5, 8, 24, and 55 hours following the start of the ganetespib infusion. The 1-hour and 2.5 hour nominal time samples are to be taken prior to stopping the ganetespib and paclitaxel infusions, respectively and may be drawn as early as 55 ± 5 minutes. The Day 2 and Day 3 samples (24 and 55 hour time points) may be drawn ± 2 hours from the nominal times. All samples are to be drawn contralateral to the infusion. All sample times are relative to the start of the ganetespib infusion and presume the paclitaxel infusion starts 30 min after termination of the 1-hour ganetespib infusion (i.e.: ganetespib infusion start is defined as time zero). In the 30 min between ganetespib and paclitaxel infusion a standardised paclitaxel pre-medication will be administered.

Paclitaxel-only patients: on day 1 to day 3, blood samples will be drawn at 0 (pre-dose), 1, 2, 3, 5, 6.5, 22.5, and 53.5 hours following the start of the paclitaxel infusion. Sample 0 (pre-dose) is to be taken immediately prior to the start of the paclitaxel infusion, i.e. after the application of the standardised paclitaxel premedication. The 1-hour nominal time samples are to be taken prior to stopping the paclitaxel infusion and may be drawn as early as 55 ± 5 minutes. The Day 2 and Day 3 samples (22.5 and 53.5 hour time points) may be drawn ± 2 hours from the nominal times. All samples are to be drawn contralateral to the infusion. All sample times are relative to the start of the paclitaxel infusion (i.e.: paclitaxel infusion start is defined as time zero).

[1] Safety follow-up to be performed 28 days (+/- 7 days) after last IMP (ganetespib) administration or drop out of the trial of any other cause

[2] Patients who had EOT of any reason prior to progression will have monthly (+/- 7 days) follow-up, incl. CA-125 and recording of additional cancer treatment until progression. PRO will be assessed every 2 weeks (+/- 7 days).
All patients after progression will have only survival status, date of second progression, information to additional cancer therapy and PRO collected every 3 months (+/- 14 days) until death of patient or end of study, whichever occurs first.

[3] ECGs during treatment period needs to be done only in patients who receive ganetespib. A pre-ganetespib dose ECG will be performed on day 1 of each cycle (on the day of medication dosing, or one day prior). In addition, a 24-hours post-ganetespib-dose ECG (+/- 4 hours) will be performed on day 1 of cycle 1. In case of QTc prolongation on day 1 cycle 1 (pre- or post-dose), further intensified ECG monitoring will be performed at the next dosing of ganetespib (day 8 cycle 1 according to Figure 8 options 2-4). In case of normal QTc findings on day 1 cycle 1 (pre- and post-dose), standard ECG monitoring will be performed consisting of pre-dose ECGs on days 1 of all following cycles (also see Figure 8, option 1)

[4] Haematology only

Appendix B – ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
Also see: http://www.ecog.org/general/perf_stat.html (last accessed: 05.09.2013)

Appendix C – CTCAE (version 4.03)

The NCI Common Terminology Criteria for Adverse Events version 4.03, instituted 14 June, 2010, is available at:
http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
(last accessed: 30. April 2014)

Appendix D – Patient-reported outcome questionnaire, additional items

These are the questionnaires in German. Questionnaires will be provided for each national language.

GERMAN

EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine „richtigen" oder „falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein:
Ihr Geburtstag (Tag, Monat, Jahr):
Das heutige Datum (Tag, Monat, Jahr): 31

	Überhaupt nicht	Wenig	Mäßig	Sehr
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen)?	1	2	3	4
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8. Waren Sie kurzatmig?	1	2	3	4
9. Hatten Sie Schmerzen?	1	2	3	4
10. Mussten Sie sich ausruhen?	1	2	3	4
11. Hatten Sie Schlafstörungen?	1	2	3	4
12. Fühlten Sie sich schwach?	1	2	3	4
13. Hatten Sie Appetitmangel?	1	2	3	4
14. War Ihnen übel?	1	2	3	4
15. Haben Sie erbrochen?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1 2 3 4 5 6 7
sehr schlecht ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1 2 3 4 5 6 7
sehr schlecht ausgezeichnet

GERMAN

EORTC QLQ – OV28

Patientinnen berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie, wie stark Sie diese Symptome oder Probleme während der letzten Woche empfunden haben.

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
31. Hatten Sie Bauchschmerzen?	1	2	3	4
32. Hatten Sie ein aufgeblähtes Gefühl in Ihrem Bauch/Magen?	1	2	3	4
33. Hatten Sie das Problem, dass Sie sich durch Ihre Kleidung beengt fühlten?	1	2	3	4
34. Haben Sie als Folge Ihrer Erkrankung oder Behandlung Veränderungen Ihrer Stuhlgewohnheiten erlebt?	1	2	3	4
35. Wurden Sie durch abgehende Winde belastet?	1	2	3	4
36. Hatten Sie schnell ein Völlegefühl, unmittelbar nachdem Sie zu essen begonnen hatten?	1	2	3	4
37. Hatten Sie Verdauungsstörungen oder Sodbrennen?	1	2	3	4
38. Hatten Sie Haarausfall?	1	2	3	4
39. Nur bei Haarausfall ausfüllen:Hat Sie der Haarausfall belastet?	1	2	3	4
40. War Ihr Geschmacksempfinden beim Essen oder Trinken verändert?	1	2	3	4
41. Hatten Sie kribbelnde Hände oder Füsse?	1	2	3	4
42. Hatten Sie ein Taubheitsgefühl in Ihren Fingern und Zehen?	1	2	3	4
43. Fühlten Sie sich in Ihren Armen und Beinen schwach?	1	2	3	4
44. Hatten Sie Muskel- und Gelenkschmerzen?	1	2	3	4
45. Hatten Sie Hörprobleme?	1	2	3	4
46. Mussten Sie häufig urinieren?	1	2	3	4
47. Hatten Sie Hautprobleme (z.B.: Jucken, Trockenheit)?	1	2	3	4
48. Hatten Sie Hitzewallungen?	1	2	3	4
49. Hatten Sie nächtliche Schweissausbrüche?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
50. Fühlten Sie sich als Folge Ihrer Krankheit oder Behandlung körperlich weniger anziehend?	1	2	3	4
51. Waren Sie mit Ihrem Körper unzufrieden?	1	2	3	4
52. Wie sehr hat Sie Ihre Krankheit belastet?	1	2	3	4
53. Wie sehr hat Sie Ihre Behandlung belastet?	1	2	3	4
54. Waren Sie wegen Ihres künftigen Gesundheitszustandes besorgt?	1	2	3	4

Während der letzten vier Wochen:	Überhaupt nicht	Wenig	Mäßig	Sehr
55. Wie sehr waren Sie an Sex interessiert?	1	2	3	4
56. Wie sehr waren Sie sexuell aktiv?	1	2	3	4
Nur ausfüllen, wenn Sie sexuell aktiv waren:				
57. Wie weit hatten Sie Freude am Sex?	1	2	3	4
58. Hatten Sie eine trockene Scheide während Sie sexuell aktiv waren?	1	2	3	4

Two additional items have been added to the mentioned questionnaires:

Did you have gastrointestinal problems during the past week?

- Not at all
- a little
- quite a bit
- very much

If yes, have you been upset by your gastrointestinal problems during the past week?

- Not at all
- A little
- Quite a bit
- Very much

Appendix E – Tumour assessment (RECIST) 1.1 (Eisenhauer et al. 2009)

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum of:

1. 10 mm by CT scan (CT scan slice thickness no >5 mm).
2. 10 mm calliper measurement by clinical exam (lesions which cannot accurately be measured with callipers should be recorded as non-measurable).
3. 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no >5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam and is not measurable by reproducible imaging techniques.

Method of Assessment
The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease-specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or SD in order to differentiate between response (or SD) and PD.

Tumour response evaluation

Assessment of overall tumour burden and measurable disease: To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.
Measurable disease is defined by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·to 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline.
Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria
Evaluation of target lesions:

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable disease (SD): Neither sufficient reduction to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of best overall response

The best overall response is the best response recorded from randomisation into the trial until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-~D	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Reference

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Appendix F – List of drugs with known Torsades de Pointes risk

This list was obtained from the Arizona Center for Education and Research on Therapeutics (AZCERT) website, accessed 18 February 2016.
https://www.crediblemeds.org

Substantial evidence supports the conclusion that these drugs, when used as directed in labelling, can prolong the QT interval and can have a risk of Torsades de pointes (TdP) in some patients.

Therefore Drugs that prolong QTc interval and have a known risk to cause TdP should be avoided.

Generic Name	Brand Names	Drug Class	Therapeutic Use	Route
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Trisenox®	Anti-cancer	Leukemia	injection
Astemizole *	Hismanal®	Antihistamine	Allergic rhinitis	oral
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection	oral, injection
Bepridil *	Vascor®	Anti-anginal	Angina Pectoris (heart pain)	oral
Chloroquine	Aralen®	Anti-malarial	Malaria infection	oral
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Anti-psychotic / Anti-emetic	Schizophrenia/ nausea	oral, injection, suppository
Cilostazol	Pletal®	Phospodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection	oral, injection
Cisapride *	Propulsid®	GI stimulant	Heartburn	oral
Citalopram	Celexa®, Cipramil®	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection	oral
Cocaine	Cocaine	Local anesthetic	Topical anesthetic	topical
Disopyramide	Norpace®	Anti-arrhythmic	Abnormal heart rhythm	oral
Dofetilide	Tikosyn®	Anti-arrhythmic	Abnormal heart rhythm	oral
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Anti-nausea	Nausea	oral, injection, suppository

Dronedarone	Multaq®	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea	injection
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection; increase GI motility	oral, injection
Escitalopram	Cipralex®, Lexapro®, Nexito®, Seroplex®, Elicea®, Lexamil®, Lexam®	Anti-depressant, SSRI	Major depression/ Anxiety disorders	oral
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection	oral, injection
Gatifloxacin *	Tequin®	Antibiotic	Bacterial infection	oral, injection
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection	oral
Halofantrine	Halfan®	Anti-malarial	Malaria infection	oral
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Anti-psychotic	Schizophrenia, agitation	oral, injection
Ibutilide	Corvert®	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial Infection	oral, injection
Levomethadyl	Orlaam®	Opiate	Pain control, narcotic dependence	oral
Mesoridazine	Serentil®	Anti-psychotic	Schizophrenia	oral
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opiate	Pain control, narcotic dependence	oral, injection
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection	oral, injection

Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Anti-emetic	Nausea, vomiting	oral, injection
Oxaliplatin	Eloxatin®	Antineoplastic Agent	Cancer	injection
Papaverine HCl	none	Vasodilator, Coronary	Diagnostic adjunct	injection
Pentamidine	Pentam®	Antibiotic	Pneumocystis pneumonia	injection
Pimozide	Orap®	Anti-psychotic	Tourette's tics	oral
Probucol *	Lorelco®	Antilipemic	Hypercholesterolemia	oral
Procainamide	Pronestyl®, Procan®	Anti-arrhythmic	Abnormal heart rhythm	injection
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia	injection
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia	inhaled
Sotalol	Betapace®, Sotalex®, Sotacor®	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin *	Zagam®	Antibiotic	Bacterial infection	oral
Sulpiride	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Anti-psychotic, atypical	Schizophrenia	oral
Terfenadine *	Seldane®	Antihistamine	Allergic rhinitis	oral
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Anti-psychotic	Schizophrenia	oral
Vandetanib	Caprelsa®	Anti-cancer	Thyroid cancer	oral

***** removed from market

Appendix G – List of drugs with possible Torsades de Pointes risk

This list was obtained from the Arizona Center for Education and Research on Therapeutics (AZCERT) website, accessed 18 February 2016.
https://www.crediblemeds.org

Substantial evidence supports the conclusion that these drugs, when used as directed in labelling, can prolong the QT interval and can possibly have a risk of Torsades de pointes (TdP) in some patients.

Therefore Drugs that prolong QTc interval and have a possible risk to cause TdP should be used with caution.

Generic Name	Brand Names	Drug Class	Therapeutic Use	Route
Alfuzosin	Uroxatral®	Alpha1-blocker	Benign prostatic hyperplasia	oral
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Dopamine agonist	Parkinson's disease	injection
Aripiprazole	Abilify®, Aripiprex®	Anti-psychotic, atypical	Psychosis, Adjunct for Depression	oral, injection
Artenimol + piperaquine	Eurartesim®	Animalarial	Malaria	oral
Asenapine	Saphris®, Syscrest®	Antipsychotics	Schizophrenia	oral
Atazanavir	Reyataz®	Anti-viral	HIV/AIDS	oral
Atomoxetine	Strattera®	Norepinephrine reuptake inhibitor	ADHD	oral
Bedaquiline	Sirturo®	Antibiotic	Tuberculosis, drug resistant	oral
Bortezomib	Velcade®, Bortecad®	Proteasome inhibitor	Multiple Myeloma,lymphoma	injection
Bosutinib	Bosulif®	Tyrosine kinase inhibitor	Leukemia	oral
Ceritinib	Zykadia®	Kinase Inhibitor	Cancer (Lung)	oral
Clomipramine	Anafranil®	Antidepressant, Tricyclic	Depression	oral
Clozapine	Clozaril®, Fazaclo®, Versacloz®	Anti-psychotic, atypical	Schizophrenia	oral
Crizotinib	Xalkori®	Kinase inhibitor	Anti-cancer	oral
Dabrafenib	Tafinlar®	Anti-cancer	Melanoma	oral
Dasatinib	Sprycel®	Tyrosine kinase inhibitor	Leukemia	oral
Delamanid	Deltyba®	Antibiotic	Tuberculosis, drug resistant	oral
Desipramine	Pertofrane®, Norpramine®	Antidepressant, Tricyclic	Depression	oral
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Sedative	Sedation	injection

Dolasetron	Anzemet®	Anti-nausea	Nausea, vomiting	oral, injection
Eribulin mesylate	Halaven®	Anti-cancer	Metastatic breast neoplasias	injection
Famotidine	Pepcid®, Fluxid®, Quamatel®	H2-receptor antagonist	Peptic ulcer/ GERD	oral, injection
Felbamate	Felbatol®	Anti-convulsant	Seizure	oral
Fingolimod	Gilenya®	Sphingosine phospate receptor modulator	Multiple Sclerosis	oral
Foscarnet	Foscavir®	Anti-viral	HIV/AIDS	injection
Gemifloxacin	Factive®	Antibiotic	Bacterial infection	oral
Granisetron	Kytril®, Sancuso®, Granisol®	Anti-nausea	Nausea, vomiting	oral, injection, topical
Hydrocodone - ER	Hysingla^{TM} ER, Zohydro ER	Analgesic	Pain, severe	oral
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Anti-psychotic, atypical	Schizophrenia	oral, injection
Imipramine (melipramine)	Tofranil®	Antidepressant, Tricyclic	Depression	oral
Isradipine	Dynacirc®	Anti-hypertensive	High blood pressure	oral
Lapatinib	Tykerb®, Tyverb®	Anti-cancer	Breast cancer, metastatic	oral
Lithium	Eskalith®, Lithobid®	Anti-mania	Bipolar disorder	oral, injection
Mifepristone	Korlym®, Mifeprex®	Progesterone antagonist	Pregnancy Termination	oral
Mirabegron	Myrbetriq®	Beta3 adrenergic antagonist	Overactive bladder	oral
Mirtazapine	Remeron	Anti-depressant, Tetracyclic	Depression	oral
Moexipril/HCTZ	Uniretic®, Univasc®	Anti-hypertensive	High blood pressure	oral
Nicardipine	Cardene®	Anti-hypertensive	High blood pressure	oral, injection
Nilotinib	Tasigna®	Anti-cancer	Leukemia	oral
Norfloxacin	Noroxin®, Ambigram®	Antibiotic	Bacterial infection	oral
Nortiptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Antidepressant, Tricyclic	Depression	oral
Ofloxacin	Floxin®	Antibiotic	Bacterial infection	oral, injection
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Anti-psychotic, atypical	Schizophrenia, bipolar	oral, injection
Oxytocin	Pitocin®, Syntocinon®	Oxytocic	Labor stimulation	injection

Paliperidone	Invega®, Xepilon®	Anti-psychotic, atypical	Schizophrenia	oral, injection
Panobinostat	Farydak®	Antineoplastic agent	Multiple myeloma	oral
Pasireotide	Signifor®	Somatostatin analog	Cushings Disease	injection, topical
Pazopanib	Votrient®	Tyrosine kinase inhibitor	Anti-cancer	oral
Perflutren lipid microspheres	Definity®	Imaging contrast agent	Echocardiography	injection
Pipamperone	Dipiperon (E.U)	Antipsychotic	Schizophrenia	oral
Promethazine	Phenergan®	Anti-psychotic / Anti-emetic	Nausea	oral, injection, suppository
Ranolazine	Ranexa®, Ranozex®	Anti-anginal	Chronic angina	oral
Rilpivirine	Edurant®, Complera®, Eviplera®	Anti-viral	HIV/AIDS	oral
Risperidone	Risperdal®	Anti-psychotic, atypical	Schizophrenia	oral, injection
Roxithromycin	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic	Bacterial infection	oral
Saquinavir	Invirase®(combo)	Anti-viral	HIV/AIDS	oral
Sertindole	Serdolect®, Serlect®	Anti-psychotic, atypical	Anxiety, Schizophrenia	oral
Sorafenib	Nexavar®	Tyrosine kinase inhibitor	Anti-cancer	oral
Sunitinib	Sutent®	Anti-cancer	Renal cell cancer, GIST	oral
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Immunosuppressant	Immune suppression	oral, injection
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	Anti-cancer	Breast cancer	oral
Telavancin	Vibativ®	Antibiotic	Bacterial infection	injection
Telithromycin	Ketek®	Antibiotic	Bacterial infection	oral
Tetrabenazine	Nitoman®, Xenazine®	Monoamine Transporter Inhibitor	Chorea (Huntington's disease)	oral
Tizanidine	Zanaflex®, Sirdalud®	Muscle relaxant	Spasticity	oral
Tolterodine	Detrol®, Detrusitol®	Muscle relaxant	Bladder spasm	oral
Toremifene	Fareston®	Estrogen agonist/antagonist	Anti-cancer	oral

Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Antidepressant, Tricyclic	Depression	oral
Tropisetron	Navoban®, Setrovel®	Antiemetic	Nausea, vomiting	oral, injection
Vardenafil	Levitra®	Phosphodiesterase inhibitor	Vasodilator	oral
Vemurafenib	Zelboraf®	Kinase inhibitor	Anti-cancer	oral
Venlafaxine	Effexor®, Efexor®	Anti-depressant, SNRI	Depression	oral
Vorinostat	Zolinza®	Anti-cancer	Lymphoma	oral