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Deutsches Krebsforschungszentrum
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Thoraxklinik-Heidelberg
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Clinical Trial Protocol

CDK4/6 inhibition in locally advanced/metastatic chordoma
NCT-PMO-1601

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Summary

Chordoma is a rare bone tumor with slow growth. The standard treatment is en bloc excision, but the site of origin of the disease often prevents complete resection. For these patients, debulking surgery followed by radiation therapy (RT) or high-dose RT alone can be an alternative. However, local relapses or more rarely metastatic disease frequently occur, and there is no efficient standard systemic therapy available. Only very limited responses are seen with chemotherapy or targeted agents, such as imatinib and lapatinib. In chordoma cell lines and patient biopsies, the p16 (cyclin-dependent kinase Inhibitor 2a, CDKN2A) tumor suppressor is consistently deleted. Thus, chordomas are an example of a tumor with universal activation of the cyclin-dependent kinases 4 and 6 (CDK4/6) pathway, and experiments with patient-derived chordoma cell lines demonstrate aberrant CDK4/6 activity downstream of p16 loss can be efficiently inhibited by the CDK4/6 inhibitor palbociclib, resulting in reduced proliferation and growth of neoplastic cells. We aim to conduct a phase II clinical trial to evaluate the efficacy of the small-molecule CDK4/6 inhibitor palbociclib in patients with locally advanced/metastatic chordoma who are not candidates for standard therapy. The primary objective is disease control in patients with chordoma treated with palbociclib as single agent. The study design of this phase-II study is based on a Simon two-stage design. Correlative laboratory investigations includes extensive molecular screening at study entry, systematic biobanking, and correlative studies in primary samples and cell lines. Together, this trial establishes whether the overreliance of chordomas on the activation of the CDK4/6-Retinoblastoma 1 (RB1) pathway can be exploited for therapeutic benefit. Based on previous experience with 125 mg palbociclib once daily for 21 days followed by 7 days of rest in patients with breast cancer, liposarcoma, non-small cell lung cancer, hepatocellular carcinoma, ovarian cancer, mantle-cell lymphoma, and glioblastoma, this regimen is chosen. Based on a Simon optimal two-stage design, the disease control rate (DCR) is the primary endpoint, whereby response is defined as complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 criteria after six cycles. For sample size calculation, we estimate a poor response with 10% and a good response with 25% (power, 80%; alpha, 5%) leading to a first stage of 18 patients and, if three or more patients responded, to a second stage with additional 25 patients (total n=43).

Zusammenfassung

Chordome werden zu den Knochentumoren gezählt, obwohl sie nicht aus Knochengewebe stammen. Sie leiten sich aus Resten der Chorda dorsalis her und treten deshalb präferentiell an Schädelbasis und Steißbein an den Enden der Wirbelsäule auf. Die Standardtherapie ist eine chirurgische en bloc Resektion; wenn diese aufgrund der Lokalisation nicht möglich ist, dann ist ein chirurgisches Debulking gefolgt von Strahlentherapie eine alternative Therapieoption. Allerdings treten häufig lokale Rezidive und gelegentlich eine Metastasierung der Erkrankung auf. In diesem Stadium der Erkrankung steht aktuell keine Standardtherapie zur Verfügung. Therapeutische Ansätze mit zytostatischer Chemotherapie oder zielgerichteten Ansätzen mit Imatinib oder Lapatinib führen zu insgesamt niedrigen Ansprechraten. In Chordomzelllinien und primärem Tumormaterial ist der Tumorsuppressor p16 (Cyclin-dependent kinase Inhibitor 2a, CDKN2A) regelhaft deletiert. Somit sind Chordome eine beispielhafte Tumorentität mit einer universellen CDK4/6-Aktivierung. Experimente mit aus Patienten gewonnenen Chordom-Zelllinien zeigen, dass die aberrante CDK4/6-Aktivität „downstream“ von p16 mit dem spezifischen CDK4/6-Inhibitor Palbociclib gehemmt werden kann, mit einer deutlich reduzierten Proliferationsrate. Unser Ziel ist eine Phase-II Studie mit dem CDK4/6 Inhibitor Palbociclib bei Patienten mit lokal fortgeschrittenen bzw. metastasierten Chordomen, die nicht mit einer Standardtherapie behandelt werden können, durchzuführen. Das Studiendesign dieser Phase-II Studie fußt auf dem Simon two-stage design mit dem primären Endpunkt Ansprechen, welcher die Grade komplette Remission (CR), partielle Remission (PR), sowie stabile Erkrankung (SD) umfasst. Begleituntersuchungen mit molekularem Profiling bei Studieneinschluss, systematisches Biobanking, und korrelative Untersuchungen an Primärmaterial und Zelllinien sind vorgesehen. Diese Studie wird zeigen, ob die Abhängigkeit von Chordomen vom CDK4/6-Retinoblastoma 1 (RB1) Signalweg therapeutisch nutzbar ist. Basierend auf vorhergehenden klinischen Studien wird die Dosis von 125 mg Palbociclib einmal täglich über 21 Tage gefolgt von 7 Tagen Therapiepause wie bereits bei Patienten mit Brustkrebs, Liposarkomen, kleinzelligem Lungenkarzinom, hepatozellulärem Karzinom, Ovarialkarzinom, Mantelzell-Lymphom und Glioblastom eingesetzt, als sicher eingeschätzt. Der primäre Endpunkt wird in Abwesenheit eines klinisch offensichtlichen Progresses nach 6 Monaten überprüft. Für die Fallzahlkalkulation wurde eine schlechte Ansprechrate mit 10% und eine gute Ansprechrate mit 25% (power, 80%; alpha, 5%) definiert. Dies führt zu einer Fallzahl von 18 Patienten in der ersten Stufe und, bei Ansprechen von 3 oder mehr Patienten, zu weiteren 25 Patienten in der zweiten Stufe (Gesamt n=43).

Table of Contents

Protocol Synopsis

Title

CDK4/6 inhibition in locally advanced/metastatic chordoma

Phase

Phase II

Sponsor

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Financing/ Status of the Sponsor

The trial is financed by funds of Pfizer Pharma GmbH and DKFZ Heidelberg.
Study drug is provided free-of-charge by Pfizer Pharma GmbH.

Indication

Chordoma (ICD-classification code: C41.0)

Trial Population

Inclusion Criteria

1. Patients with locally advanced or metastatic chordoma with confirmed diagnosis in a reference pathology (with immunohistology for epithelial membrane antigen, S100, Brachyury, INI-1) not amenable to curative treatment with surgery or radiotherapy.
2. At least one measurable tumor lesion according to RECIST 1.1 criteria
3. Loss of p16 determined immunohistochemically or CDKN2A/B genomically, presence of CDK4/6 and RB1 determined immunohistochemically or by RNA sequencing.
4. Age ≥ 18 years, no upper age limit
5. Availability of tissue blocks preferably not older than 12 months for immunohistologic assessment (if no adequate material is available, re-biopsy should be considered before entering the study)
6. Non-pregnant and non-nursing. Women of child-bearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 72 hours prior to registration (WOCBP is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 months).
7. Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or use a highly effective method of birth control (e.g. double barrier contraceptive method (IUD, condome), tubal ligation, or partner's vasectomy) while on therapy and for 14 weeks after the last dose of therapy. Hormonal contraception alone is an inadequate method of birth control. Female patients must

agree not to donate lactation during treatment and until 14 weeks after end of treatment.

8. Men must agree not to father a child and must use a latex condom during any sexual contact with WOCBP while receiving therapy and for 14 weeks after therapy is stopped, even if they have undergone successful vasectomy. Sperm donation is not permitted for the same time interval.
9. Signed written informed consent
10. Performance status ≤ 2 according to ECOG/WHO criteria
11. Ability of patient to understand the character and individual consequences of clinical trial

Exclusion Criteria

1. Prior treatment with palbociclib or known intolerance/allergy to the compound or any ingredient (acquired or hereditary).
2. Prior treatment with other CDK4/6 inhibitors
3. Co-therapy with strong/potent CYP3A inducers and/or inhibitors, (e.g., clarithromycin, indinavir, itraconazol, ketoconazol, lopinavir/ritonavir, nefazodon, nelfinavir, posaconazol, saquinavir, telaprevir, telithromycin, voriconazol, and St. John's Wort [Hypericum perforatum]) while on treatment with study drug
4. Co-therapy with corticosteroids above 7.5 mg prednisolone/prednisone equivalent
5. Anticancer treatment less than 2 weeks prior to study treatment
6. Organ insufficiency: creatinine clearance <30 ml/min; total bilirubin >1.5x upper normal serum level; AST > upper normal serum level; abnormal blood counts; heart failure (New York Heart Association (NYHA) III/IV); uncontrolled hypertension; unstable angina; serious cardiac arrhythmia; severe obstructive or restrictive ventilation disorder
7. Clinical signs of active infection (>Grade 2 according to CTCAE version 5.0)
8. Patients with a "currently active" second malignancy other than non-melanoma skin cancer. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.
9. Severe neurologic or psychiatric disorder interfering with ability of giving informed consent
10. Known or suspected active alcohol or drug abuse
11. Known positivity for HIV, active HAV, HBV, or HCV infection
12. Cytopenia: platelets <100 G/l, neutrophils <1.0 G/l, hemoglobin <10.0 g/dl
13. Corrected QT interval (QTc_B) >470 msec (based on the mean value of triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome, or known history of QTc_B prolongation or Torsade de Pointes
14. Uncontrolled electrolyte disorders that can aggravate the effects of a QTc_B-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia)
15. Participation in other ongoing interventional clinical trials (according to AMG) within 4 weeks prior to study treatment.

Objectives

Primary objective of this phase II trial is to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastasized chordoma not amenable to curative treatment with surgery or radiotherapy.

The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of complete response (CR) or partial response (PR) or stable disease (SD) according to RECIST version 1.1.

Secondary Objectives include:

1. Tumor response rate (TRR) according to RECIST version 1.1
2. Progression-free survival (PFS)
3. Overall survival (OS)
4. Safety/tolerability
5. Patient reported outcome including Quality of life

Trial Design

Non-randomized, single-arm, open-label, multicenter phase II trial, designed to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastatic chordoma. A total of 18 (stage I) or 43 patients (stages I+II) evaluable for the primary outcome (DCR) need to be treated guided by Simon's optimal two-stage design.

Investigational Medicinal Product(s)

Palbociclib (Ibrance®) 125 mg, 100 mg or 75 mg Capsule/Tablet

Sample Size

18 in the first stage

25 in the second stage (only if first stage was positive)

Total sample size: minimum 18 patients; maximum 43 patients

Statistical Analysis

The study is a phase II trial with a standard palbociclib dose of 125 mg once daily for 21 days in a 28-day cycle.

The study needs 43 patients evaluable for the primary endpoint to complete. The sample size and power calculations were based on Simon's optimal two-stage design (Simon, 1989). The type I error was set at α = 0.05, the type II error at β = 0.2. Here, the null hypothesis that the true response rate is less or equal to p_0 = 0.1 is tested against a one-sided alternative, where the desirable level of response is 0.25.

In the first stage, n_1 = 18 patients are accrued. If there are r_1 = 2 or fewer responses in these 18 patients, the study is stopped. Otherwise, 25 additional patients are accrued for a total of n = 43 patients. In the final analysis the null hypothesis is rejected and the drug recommended for further development if 8 or more responses are observed in 43 patients.

Trial Duration and Dates

Total trial duration:	66 months
Duration of the clinical phase:	54 months
First patient first visit (FPFV):	4 Quarter 2017
Last patient first visit (LPFV):	2 Quarter 2021
Last patient last visit (LPLV):	2 Quarter 2022
Trial Report completed:	2 Quarter 2023

Protocol Activities and Forms to be completed	**Baseline**	**On Treatment Cycles (1 cycle = 28 days)**										**Primary efficacy assessment**	**Extended treatment period (ExT)[1]**	**Follow-Up Period[1,]**		
														Follow-Up after stop of treatment		**Survival follow-up**
Cycle	**≤ 28 days**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**Day 29 of last (6th) cycle** or when applicable before	**day 1 of each cycle; until progression/EOT**	**3 month after stop of study treatment**	**6 month after stopf of study tretament**	**Every 3 month**
Visit description **On treatment: +/- 2 days** **During follow up: +/- 1 week**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	11	ExT-X	F-UP-3	F-UP-6	SF-UP-X
Day	**Baseline**	**0**	**7**	**14**	**21**	**28**	**42**	**56**	**84**	**112**	**140**	**169**				
Informed consent[2]	X															
Demographics[3]	X															
General medical and Oncologic history[4a]	X															
In- and Exclusion Criteria [4b]	X															
Signs/symptoms[5]	X															
Vital signs[6]	X	X				X		X	X	X	X	X	X			
Physical examination[6]	X	X				X		X	X	X	X	X	X			
Signs and symptoms	X															
ECHO[7]	X															
ECG[8]	X	X	X	X	X											
Laboratory and Clinical Assessments																
Hematology *(local lab)*[9]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Blood chemistry *(local lab)*[10a]	X	X	X	X	X	X		X	X	X	X	X	X			
Coagulation (local lab)[10b]	X															
Urinalysis *(local lab)*[11]	X															
HAV, HBV, HCV, HIV-1 testing *(local lab)*[12]	X															
Pregnancy test and counseling as well as counseling in cryo-preservation of oocyte or sperm *(local lab)*[13]	X							X				X				
Pathology, immunohistochemistry[14]	X															
Imaging (local assessment)[15]	X								X			X	X every 12 weeks after	X	X	

													V11			
Samples for biobanking *(central lab Heidelberg)*[16]	X	X				X		X	X	X	X	X	X every 3 treatment cycles			
Enrollment[17]	X															
Treatment																
Distribution of Palbociclib[18]		X				X		X	X	X	X	X in case of benefit	X			
Assessment of Concomitant medications[19]	X	X	X	X	X	X	X	X	X	X	X	X	X			
AE assessments[20]		X	X	X	X	X	X	X	X	X	X	X	X			
PRO assessment[21]	X					X						X	X every 3 treatment cycles	X	X	
Survival Follow up assessments[22]																X

Footnotes for schedule of events:

1. Observation time for all patients is expected to be at least 12 months after entry into the study. Patients receive palbociclib for 6 cycles. At day 29 of the 6th cycle *Primary efficacy assessment* takes place. In case of clinical benefit patients may continue with palbociclib therapy and are followed until progression or end of trial (*Extended Treatment Period*). There is a regular *follow-up* of 6 months after end of treatment. During *follow-up* every 3 months patient reported outcomes including quality of life are assessed and the investigator should make an assessment on tumor development. All Patients with ongoing drug-related toxicities must be followed until all drug-related toxicities are resolved.
2. Informed consent and patient assignment: every patient must sign the informed consent to participate in this trial before starting any trial-related procedures. After signature, the patient study ID is assigned automatically when a data set of a new patient is created in eCRF.
3. Demographics: gender, year of birth, ethnicity
4. a) General Medical and oncologic history: date of first diagnosis, detailed information on pretreatment including type and composition of prior therapy as well as response to prior therapy, , detailed information on disease progression according to RECIST v1.1 criteria over the last 6 months prior to study inclusion, family history, additional medical history on concomitant diseases, prior exposure to toxic agents, prior malignancy including therapy, information on smoking; tumor staging according to UICC (TNM)

   b) Inclusion / Exclusion Criteria:

   At Baseline, all inclusion/ Exclusion criteria as defined in chapter 5.3 and 5.4 are assessed.
5. Signs/symptoms: chordoma-related and unrelated signs and symptoms
6. Vital signs: At baseline and at the start of every new cycle: weight (in kg), WHO performance status, temperature (in grade centigrade), blood pressure/pulse; at baseline additionally height (in cm).

   Physical examination at baseline and at the start of every new cycle: inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination
7. ECHO: at baseline and thereafter at investigator's discretion. If abnormal at baseline, ejection fraction (EF) to be quantified, and thereafter in case of of abnormal findings. EF should be specified according to Simpson.
8. ECG: 12-lead study, at baseline, during the first treatment cycle every week, and thereafter at investigator's discretion
9. Hematology (local lab): hemoglobin, RBC, PLT, WBC. Differential cell counts should be performed at baseline, weekly during the first treatment cycle, on Day 1 and Day 14 (+/- 2 days) of second cycle, in each first week during following cycles, at Primary efficacy assessment, and in the first week of each cycle during *Extended Treatment Period*. Clinical status and laboratory parameters are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician, which can involve more frequent testing, especially in neutropenic/aplastic patients. It is expected that patients on this protocol are cared for by physicians experienced in the treatment and supportive care.
10. a) Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid: at baseline and then once a week during the first treatment cycle, in each first week during following cycles, at Primary efficacy assessment, and in each first week during *Extended Treatment Period*, or to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician, which can involve more frequent testing.

    b) Coagulation: Prothrombin time , aPTT and fibrinogen are measured at baseline and at investigator's discretion during treatment.
11. Urinalysis (local lab): pH, glucose, proteins (qualitative, dipstick accepted): at baseline and at investigator's discretion during treatment
12. HAV, HBV, HCV, and HIV-1 testing: at baseline and thereafter at investigator's discretion
13. Serum/urine pregnancy test (local lab, sensitivity of at least 25 mIU/mL): in WOCBP, a pregnancy test must be performed at baseline (≤ 72h prior to patient registration). In addition, WOCBP and male patients must be counseled to avoid getting pregnant or to father a child within three months after the last application of therapy.

    Serum/urine pregnancy test must be repeated at cycle 3 and at the end of the 6th cycle.
14. Pathology and Immunohistochemistry at baseline: tissue blocks preferably not older than 12 months are requested either from initial diagnosis or from biopsies of locally advanced disease or metastatic sites. Re-biopsy should be performed in any case if no adequate material is available. Samples must be shipped to Central Pathology Ulm.

15. Imaging/ Local assessment: MRI/CT should be available at the time of study entry. MRI/CT scan should not be older than 2 weeks and include all known chordoma manifestations. Tumor imaging is part of the clinical routine (for assessment details see 7.3.1). The choice of either MRI or CT depends on tumor localization and is at investigator's discretion. For chordoma of the axial skeleton, including sacral or clival tumors, MRI is recommended. The imaging method should not be changed after study entry. During study treatment imaging should be performed on day 1 (+/- 2 days) of cycle 4, day 1 (+/- 2 days) after cycle 6 (primary efficacy assessment) or when progression/relapse occurs. During extended treatment Imaging should be performed every 12 (+ max. 4) weeks and during follow-up 3 month after stop of study treatmend (+/- 1 week) as well as 6 months after stop of study treatment.
16. Procurement of Samples for Biobanking at NCT Heidelberg: 40 ml blood (for details see *sample shipping instructions*) should be sent at baseline, at the beginning of each treatment cycle, every three treatment cycles in responding patients (Extended Treatment Period) and at relapse (if CR or PR was achieved)
17. Enrollment: at the end of baseline visit the investigator verifies inclusion and exclusion criteria and confirms patient enrollment with his signature.
18. Palbociclib is taken orally by the patient on days 1-21 of each treatment cycle (28 days).
19. Concomitant medications should be reported in the relevant case report form (CRF) pages, including supportive care drugs, prophylaxis with antiemetics, and drugs used for treating AEs or chronic diseases.
20. AE assessments: Events should be documented and recorded continuously. Patients must be followed for AEs from first palbociclib administration up to 28 days after last study drug administration or until all drug-related toxicities have been resolved, whichever is later, or until the investigator assesses AEs as "chronic" or "stable". However, if the patient commences alternative anti-cancer therapy < 28 days after the last dose of study drug administration, the AE reporting period ends at the time the new treatment is started. Each AE must be reported once per cycle, indicating the worst CTCAE (Version 5.0) grade. If an event stops and later restarts within the same cycle, all occurrences must be reported. A specific procedure for definition and reporting of SAEs is described in protocol section 9.3.
21. Patient reported Outcomes (PRO) including Quality of life (QoL): assessed by questionnaires of the EORTC Quality of Life Item Library (core questionnaire QLQ-C30, fatigue module QLQ-FA12, and selected symptom items), as well as the Pittsburgh Sleep Quality Index (PSQI), the Patient Health Questionnaire for Anxiety and Depression (PHQ-4), and the Functional Assessment of Cancer Therapy - cognitive function scale (FACT-cog). In addition, patient-reported information on personal traits and experiences are collected at baseline**.** Assessments are performed at the beginning of the 2nd cycle, and after the sixth cycle, during *follow-up* every 3 months, and every three treatment cycles in responding patients (*Extended Treatment Period*).
22. Follow-up assessment: further oncological treatment e.g. chemotheraphy and radiotherapy, vital status and disease status according to RECIST 1.1 criteria.

Abbreviations

AE	Adverse Event
ALT	Alanine Amino Transferase, also known as SGPT
AST	Aspartate Amino Transferase, also known as SGOT
AP	Alkaline Phosphatase
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BUN	Blood Urea Nitrogen
CDK	Cyclin-dependent kinase
CDKN2	Cyclin-dependent kinase Inhibitor 2
CI	Coordinating Investigator (LKP)
CNS	Central nervous system
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease Control Rate
DKFZ	Deutsches Krebsforschungszentrum (German Cancer Research Center)
IDMC	Independent Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research an Treatment of Cancer
EOT	End of Treatment
ExT	Extended treatment period
FDA	US Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Ordinance (GCP-Verordnung)
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator´s Brochure
IC	Informed Consent
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICD	International Classification of Disease
IIT	Investigator Initiated Trial
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INI-1	Integrase interactor 1
INN	International Nonproprietary Name
INR	International Normalized Ratio

ISF	Investigator Site File
IUD	Intrauterine device
LDH	Lactatdehydrogenase
LKP	Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)
LPI	Last Patient In
LPLV	Last Patient Last Visit
n.a.	Not applicable
NCT	National Center for Tumor Diseases Heidelberg
NYHA	New York Heart Association
OS	Overall Survival
PD	Progessive Disease
PET	Probability for Early Termination
PFS	Progression-free Survival
PHQ-4	Patient Health Questionnaire for Anxiety and Depression
p.o.	per os/ per oral/ orally
PR	Partial Response
PRO	Patient Reported Outcomes
PSQI	Pittsburgh Sleep Quality Index
PTT	Partial Thromboplastine Time
QoL	Quality of Life
QTc_B	Corrected QT interval (Bazett's formula)
RBC	Red Blood Cell
RB1	Retinoblastoma 1
RDE	Remote Data Entry
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
RT	Radio therapy
SAE	Serious Adverse Event
SAS	Statistical Analysis Systems
SD	Stable Disease
SDV	Source Data Verification
SGPT	Serum Glutamic-Pyruvat Transaminase, also known as ALT
SGOT	Serum Glutamic-Oxaloacetic Transaminase, also known as AST
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNM	TNM Classification of Malignant Tumors
TRR	Tumor Response Rate
UICC	Union for International Cancer Control
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 Introduction

1.1 Scientific Background

1.1.1 Palbociclib

Palbociclib, an orally available pyridopyrimidine, is a highly selective, reversible inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that is being studied for use in cancer treatment. The compound prevents cellular DNA synthesis by blocking progression from the G1 to the S phase of the cell cycle, as demonstrated in laboratory models and early clinical trials.

Palbociclib inhibits purified CDK4-catalyzed phosphorylation of retinoblastoma (Rb) protein with an IC_{50} of less than 20 nM. Palbociclib prevents Rb phosphorylation at serine 780 and 795, inducing a G1 arrest. Estimated steady-state plasma concentrations of 1,000 ng/mL resulted in 80% to 90% inhibition of phospho-Rb formation and 50% reduction of tumor growth. Reduction in phospho-Rb was rapidly reversible as plasma palbociclib concentrations declined. CDK6, another enzyme that also complexes with cyclin-D subunits, is also commonly expressed in mammalian cells and tumors. CDK6 is highly homologous to CDK4 and can perform the same function by phosphorylating Rb, thus potentially creating a redundant mechanism to promote cell cycle progression. Palbociclib inhibits purified CDK6 with an IC_{50} of 15 nM.[1]

In humans, the primary routes of metabolic clearance for [^{14}C]-palbociclib include multiple oxidative pathways and a single conjugative pathway (sulfonation). Minor primary routes of metabolism include glucuronidation and acylation (acetylation and formylation) pathways. Based on the sum of radioactivity in peaks from feces and urine that can be ascribed exclusively to primary and secondary oxidative metabolites, greater than 50% of the clearance mechanism can be assigned to oxidative pathways, while primary conjugative processes (sulfonation and glucuronidation) contribute approximately 26% and 2%, respectively, to the overall clearance, with acylation (formyl and acetyl) pathways contributing less than 3%.[1]

A study in 26 healthy women of non-childbearing potential evaluated drug-drug interaction with midazolam. This pharmacokinetic study was conducted to evaluate the potential of palbociclib to act as a time-dependent inhibitor of CYP3A4/5 at steady-state. Plasma midazolam C_{max} and AUC_{inf} values increased 1.37 and 1.61-fold, respectively, when single oral doses of midazolam were co-administered with multiple doses of palbociclib as compared to its administration alone. This is consistent with weak time-dependent CYP3A4/5 inhibition mediated by palbociclib at steady-state following daily 125 mg dosing.[1]

Two completed phase I studies have established dosing regimens of 200 mg daily for two weeks of three, or 125 mg daily for three weeks in a four-week cycle.[2, 3] Following repeated daily dosing to day 14 and day 21 (assumed to be steady-state), palbociclib was absorbed with a median T_{max} of approximately four hours. The mean palbociclib Vz/F was 3,103 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues. Palbociclib was eliminated slowly with a mean t½ of 27 hours. Renal excretion of palbociclib is the minor route of elimination with ~1.7% of the drug excreted unchanged in urine over the 10-hour collection period after dosing with 125 mg and 200 mg. The mean renal clearance (CLR) is ~6.6 L/hour.

In all clinical studies, neutropenia has been the most frequently reported adverse event. In each case, neutropenia was the dose-limiting toxicity and the one-week break was required for neutrophil recovery. This toxicity profile is likely to be a result of transient growth arrest in hematopoietic precursor cells.[4] Gastrointestinal toxicity, alopecia, mucositis, neutropenic fever, or infection were rare.

Palbociclib was tested in CDK4-amplified liposarcoma and promising results have been reported.[5, 6] Similarly, palbociclib has also shown promising activity in mantle-cell lymphoma.[7]

The development of palbociclib in breast cancer is most advanced; it has broad activity in breast cancer cells in vitro, especially the estrogen receptor-positive luminal type.[8] Several clinical studies from phase I to phase III showed impressive prolongation of progression-free survival by

palbociclib when given in combination with letrozole[9] which led to marketing approval in US on 03Feb2015. FDA approved IBRANCE® (palbociclib) capsules in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

The resent investigation in vivo with patient-derived chordoma cell lines demonstrated that downstream machinary of p16 can be efficiently inhibited by the CDK4/6 inhibitor palbociclib, resulting in reduced proliferation and growth of neoplastic cells[10].

1.1.2 Chordomas

Chordomas are rare tumors considered to arise from persistent notochordal remnants along in the vertebral bodies[10]. Because of their slow growth, there is no efficient standard chemotherapy: therapy of choice is surgery followed by radiotherapy. After surgical therapy of this orphan disease, chordoma recurs in up to 50% of patients and metastasizes in 20% an more[10]. Only a minority is cured by surgery, the disease-free survival is generally short[10]. The median survival is 6 to 7 years after diagnosis, although the range varies from months to 25 years. High-dose radiotherapy is administered for residual or recurrent disease[10]. Patients who have metastases and have inoperable recurrent disease are not eligible for further radiotherapy. Therefore, there is a strong unmet need for systemic pharmacologic therapy. Aggressive chemotherapy has been described to be effective in rare cases of dedifferentiated chordomas[10]. Only limited response is seen by therapy with alkylating agents (ifosfamid), anthracyclines (doxorubicin), and cisplatin[10]. In the first prospective phase II study with 9-nitrocamptothecin, one patient out of 15 achieved a partial response[10]. Recently, new targeted therapy options using erlotinib, cetuximab, gefitinib, sunitinib, thalidomide, and lapatinib have been published[10]. An activated platelet-derived growth factor receptor b (PDGFRb) was described as a basis for therapy with imatinib in patients with progressive disease[7, 8]. Because of the rarity of this tumor and only a few well characterized chordoma cell lines, there is limited experience with preclinical models[10]. Recently, systematic pharmacologic screening of our first published two chordoma cell lines U-CH1 and U-CH2 chordoma cell lines, we found that the tumor suppressor p16 (CDKN2A) is deleted and that p16 protein is not expressed in these cell lines. This deletion has been described in the majority of chordomas[10]. The downstream machinery of p16 can be efficiently inhibited by CDK4/6 inhibitors such as palbociclib[10]. Inhibition of this pathway by palbociclib is a defined mechanism to reduce the proliferation and growth of neoplastic cells[10].

1.2 Trial Rationale/Benefit-Risk Assessment

1.2.1 Trial Rationale

The aim of this phase II study is to gain first evidence of antitumor activity of palbociclib in patients with locally advanced or metastasized chordoma not amenable to surgery or radiotherapy. Currently, no standard treatment is available in this clinical situation and tumor control rates in published experimental approaches are low (<50%). Thus, there is a clear unmet medical need to evaluate new treatment approaches based on solid preclinical data.

1.2.2 Benefit-Risk Assessment

Chordoma is a rare bone tumor. The standard treatment is en bloc excision, but the site of origin of the disease often prevents complete surgery. For these patients, debulking surgery followed by radiation therapy (RT) or exclusive high-dose RT can be an alternative. However, local relapses occur in >50% of cases, while metastases affect >20% of patients. Systemic therapy is needed in patients not amenable to surgery or RT[11].

Only very limited responses are seen with chemotherapy or targeted agents, such as imatinib and lapatinib. However, no active drugs are approved to date[11]. In chordoma cell lines and patient biopsies, the p16 (CDKN2A) tumor suppressor is consistently deleted. Thus, chordomas are an example of a tumor with universal activation of the CDK4/6 pathway, and experiments with

patient-derived chordoma cell lines demonstrate aberrant CDK4/6 activity downstream of p16 loss can be efficiently inhibited by the CDK4/6 inhibitor palbociclib, resulting in reduced proliferation and growth of neoplastic cells.

Palbociclib, an orally available pyridopyrimidine, is a highly selective, reversible inhibitor of CDK4 and 6 that is being studied for use in the treatment of cancer. The most common side effects of palbociclib are reversible neutropenia, thrombocytopenia, anemia, fatigue, constipation, nausea, and diarrhea. Taking into the consideration beneficial safety profile, palbociclib may offer these patients a more specific and effective treatment option.

1.4 Reference Committees

1.4.1 Independent Data Monitoring Committee (IDMC)

An IDMC is assembled. The IDMC is composed of two independent experts, assessing the progress and safety data. The mission of the IDMC is to ensure the ethical conduct of the trial and to protect the safety interests of patients in this trial.

The IDMC meets virtually after 18 patients have finished at least one cycle of study treatment. Based on its review, the IDMC provides the sponsor with recommendations regarding trial modification, continuation or termination.

Further details including IDMC members are specified in the IDMC charter.

2 Trial Objectives

2.1 Primary Objective

Primary objective of this phase II trial is to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastasized chordoma not amenable to to curative treatment with surgery or radiotherapy.

The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of complete response (CR) or partial response (PR) or stable disease (SD) according to RECIST version 1.1 (compare Section 7.3.1 for definitions).

2.2 Secondary Objectives

Secondary objectives include further efficacy (clinical response, survival), safety and quality of life analyses.

Secondary endpoints:

- **Tumor response rate (TRR)**, defined as the sum of complete response (CR) and partial response (PR) according to RECIST version 1.1 after six cycles of study medication (compare Section 7.3.1 for definitions).
- **Progression-free survival (PFS)**, defined as the time from first administration of the IMP to progression of disease or death from any cause, whichever occurs first. Patients without the event are censored on the last date of follow-up. [time frame: up to LPLV]
- **Overall survival (OS)**, defined as the time from first administration of the IMP to time of death from any cause. Patients without the event are censored on the last date of follow-up. [time frame: up to LPLV]
- **Safety** (toxicity, tolerability); Toxic effects are graded according to CTCAE v5.0.
- **Patient reported outcomes (PRO) including QoL** is assessed by questionnaires of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Item Library (core questionnaire QLQ-C30, fatigue module QLQ-FA12, and selected

symptom items), as well as the Pittsburgh Sleep Quality Index (PSQI), the Patient Health Questionnaire for Anxiety and Depression (PHQ-4), and the Functional Assessment of Cancer Therapy - cognitive function scale (FACT-cog).

3 Trial Design

Non-randomized, single-arm, open-label, multicenter phase II trial, designed to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastatic chordoma. A total of 18 (stage I) or 43 patients (stages I+II) evaluable for the primary outcome (DCR) need to be treated guided by Simon's optimal two-stage design.

4 Trial Duration and Schedule

The duration of the trial for each patient is expected to be 12 months, including 6 treatment cycles and 6 months of follow-up. In case of clinical benefit, it will be longer.

Each patient remains on treatment until disease progression or other reasons for withdrawal. Conditions leading to patient withdrawal from the study are detailed in Section 5.5 Criteria for Withdrawal. Treatment response is assessed every 12 weeks according to RECIST version 1.1 criteria. In case of progressive disease, study therapy will be stopped. In patients showing response or stable disease, therapy within the study is intended until progression or LPLV. After 6 treatment cycles, primary efficacy assessment takes place. Patients are followed for 6 months after discontinuation of study medication. There is no further follow-up in all patients under treatment with palbociclib at LPLV. LPLV is 12 months after LPFV at the latest.

Recruitment of minimally 18 and maximally 43 patients evaluable for the primary endpoint takes place at 3 investigator sites in Germany.

A recruitment period of approximately 4 years and an overall study duration of approximately 6 years is anticipated.

The treatment duration for an individual patient is estimated to be 2-6 months, but may be prolonged in patients with sustained response (“case-by-case decision”).

After finishing all study-relevant procedures, therapy, and follow-up period, the patient is followed in terms of routine care and treated if necessary by the primary responsible hematology/oncology center.

Total trial duration:	66 months
Duration of the clinical phase:	54 months
First patient first visit (FPFV):	4 Quarter 2017
Last patient first visit (LPFV):	2 Quarter 2021
Last patient last visit (LPLV):	2 Quarter 2022
Trial Report completed:	2 Quarter 2023

5 Selection of Patients

5.1 Number of Patients and Recruitment

As described in Section 10.2, a minimum of 18 (stage I) or 43 (stage II) patients are to be enrolled in the clinical trial. Expecting a number of 15 eligible patients per year with a consent rate of > 90%, approximately 4 years are required to recruit the intended number of patients.

Recruitment and treatment of patients should be performed in 3 trial centers.

5.2 General Criteria for Patient Selection

This clinical trial can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Any questions regarding a patient's eligibility should be discussed with the Coordinating Investigator or the Scientific Coordinator.

5.3 Inclusion Criteria

Both female and male patients are included in this clinical trial as the occurrence of chordoma is independent of gender. Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Patients with locally advanced or metastatic chordoma with confirmed diagnosis in a reference pathology (with immunohistology for epithelial membrane antigen, S100, Brachyury, INI-1) not amenable to curative treatment with surgery or radiotherapy
2. At least one measurable tumor lesion according to RECIST 1.1 criteria.
3. Loss of p16 determined immunohistochemically or CDKN2A/B genomically, presence of CDK4/6 and RB1 determined immunohistochemically or by RNA sequencing.
4. Age ≥ 18 years, no upper age limit
5. Availability of tissue blocks preferably not older than 12 months for immunohistologic assessment (if no adequate material is available, re-biopsy should be considered before entering the study)
6. Non-pregnant and non-nursing. Women of child-bearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 72 hours prior to registration (WOCBP is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 months).
7. Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or use a highly effective method of birth control (double barrier contraceptive method (IUD, condome), tubal ligation, or partner's vasectomy) while on therapy and for 14 weeks after the last dose of therapy. Hormonal contraception alone is an inadequate method of birth control. Female patients must agree not to donate lactation during treatment and until 14 weeks after end of treatment.
8. Men must agree not to father a child and must use a latex condom during any sexual contact with WOCBP while receiving therapy and for 14 weeks after therapy is stopped, even if they have undergone successful vasectomy. Sperm donation is not permitted for the same time interval.
9. Signed written informed consent
10. Performance status ≤ 2 according to ECOG/WHO criteria
11. Ability of patient to understand the character and individual consequences of clinical trial

5.4 Exclusion Criteria

Patients fulfilling any of the following criteria cannot be included in the trial:

1. Prior treatment with palbociclib or known intolerance/allergy to the compound or any ingredient (acquired or hereditary).
2. Prior treatment with other CDK4/6 inhibitors
3. Co-therapy with strong/potent CYP3A inducers and/or inhibitors, (e.g., Clarithromycin, Indinavir, Itraconazol, Ketoconazol, Lopinavir/Ritonavir, Nefazodon, Nelfinavir, Posaconazol, Saquinavir, Telaprevir, Telithromycin, Voriconazol, and St. John's Wort [Hypericum perforatum])) while on treatment with study drug.
4. Co-therapy with corticosteroids above 7.5 mg Prednisolone/Prednisone equivalent

5. Anticancer treatment less than 2 weeks prior to study treatment
6. Organ insufficiency: creatinine clearance <30ml/min; total bilirubin > 1.5x upper normal serum level; AST > upper normal serum level ; abnormal blood counts; heart failure (New York Heart Association (NYHA) III/IV); uncontrolled hypertension; unstable angina; serious cardiac arrhythmia; severe obstructive or restrictive ventilation disorder
7. Clinical signs of active infection (>Grade 2 according to CTCAE version 5.0)
8. Patients with a “currently active” second malignancy other than non-melanoma skin cancer. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.
9. Severe neurologic or psychiatric disorder interfering with ability of giving informed consent
10. Known or suspected active alcohol or drug abuse
11. Known positivity for HIV, active HAV, HBV, or HCV infection
12. Cytopenia: platelets <100 G/l, neutrophils <1.0 G/l, hemoglobin <10.0 g/dl
13. Corrected QT interval (QTc_B) >470 msec (based on the mean value of triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome, or known history of QTc_B prolongation or Torsade de Pointes
14. Uncontrolled electrolyte disorders that can aggravate the effects of a QTc_B-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia)
15. Participation in other ongoing interventional clinical trials (according to AMG) within 4 weeks prior to study treatment.

No patient is allowed to enroll in this trial more than once.

5.5 Criteria for Withdrawal

5.5.1 Withdrawal of Patients

A patient must be withdrawn from the trial treatment or/and all trial-related procedures for the following reasons:

- At any time at their own request. Withdrawal of patient’s consent to continue therapy. Unresolved AEs should be followed.
- Unacceptable toxicity dictating cessation of treatment
- Changes in medical status of the patient such that the investigator believes that patient safety is compromised or that it would be in the best interest of the patient to stop treatment
- Pregnancy
- Non-compliance by the patient with protocol requirements
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome if possible.

If the patient withdraws from the trial and also withdraws consent for disclosure of future information (e.g. follow-up visits), no further evaluations are allowed to be performed and no additional data can be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.5.2 Handling of Withdrawals

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the patient’s medical records. In case of withdrawal of a patient at his/ her own request, the reason should be asked for as extensively as possible and documented.

5.5.3 Replacement of Patients

Patients are replaced to meet the goal of 43 patients evaluable for the primary endpoint.

Patients who go off study due to adverse events before final staging at 6 months are considered treatment failures, receive reponse status = PD (progressive disease), and are not be replaced. Patients going off study for other reasons (drop-outs; e.g. lost-to-follow-up, death unrelated to disease/treatment, retracted IC, etc. without assessment of the primary outcome are replaced until the goal of 18 or 43 patients (as the case may be) is met.

5.5.4 Premature Closure of the Clinical Trial or a Single Center

The trial can be prematurely closed or suspended by the Sponsor after consulting the Coordinating Investigator. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (completed, partially completed, and blank CRFs, investigational medicinal product and other material) must be returned to the Sponsor in Heidelberg or treated according Sponsor notice.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial centers and investigators.

The Sponsor after consulting the Coordinating Investigator has the right to close a center, at any time, in case of:

- Non-compliance with the protocol
- Poor data quality
- No recruitment

5.6 Prior and Concomitant Illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and are documented on the appropriate pages of the CRF. Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

5.7 Background Medication

Not applicable.

5.8 Prior and Concomitant Medication

Relevant additional treatments administered to the patients on entry to the trial or at any time during the trial are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

Directives for supportive care are outlined below.

5.8.1 Supportive Care

Antiemetics support: emesis prophylaxis is mandatory and is administered at the investigator's discretion using institutional or DGHO guidelines taking into account potential interactions (e.g. CYP3A4 inhibition/induction).

Antidiarrheal support: infectious work-up is left at the investigator's discretion using institutional guidelines. Treatment with antidiarrheal drugs is recommended once the earliest signs of diarrhea are present. Patients should be instructed to refer immediately to the center in case of such symptoms, and treatment should proceed according to institutional or DGHO guidelines.

Hematopoietic support: RBC and PLT transfusions should be administered as indicated.

Granulocyte-colony stimulating factor: primary prophylactic use of G-CSF is not permitted, but G-CSF may be used to treat therapy-related neutropenia in patients with response, including PR, CR, and SD, in subsequent treatment cycles. If neutropenic complications are observed in a previous cycle, CSFs may be given at the discretion of the investigator, but only if dose reduction or delay of palbociclib are not considered reasonable alternatives.

Antibiotic treatment: patients with neutropenic fever or systemic infection should be hospitalized promptly for i.v. antibiotic therapy.

Pain relief: analgesics can be administered as needed.

5.8.2 Other Permitted Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator, such as chronic treatments for concomitant medical conditions as well as agents required for life-threatening medical problems, analgesics, etc. Patients should be advised to contact their physician before starting any new drug.

5.8.3 Prohibited Medications During Therapy With Palbociclib and Interactions With Strong Inhibitors/Inducers of Cytochrome P450-3A4

Strong CYP3A inhibitors/inducers: palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog, and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors or inducers may change the plasma concentrations of palbociclib in humans. **The concurrent use of potent CYP3A inhibitors, including but not limited to aprepitant, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice are not allowed. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's Wort is not allowed.** Refer to the following website for additional information on CYP3A4 inhibitors, inducers, and substrates: http://medicine.iupui.edu/flockhart/table.htm
Based on in vitro data, palbociclib is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of palbociclib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g., pravastatin, rosuvastatin, sulfasalazine) may increase their therapeutic effect and adverse reactions.

Based on in vitro data, palbociclib may inhibit the uptake transporter organic cationic transporter OCT1 and then may increase the exposure of medical product substrates of this transporter (e.g., metformin).

In addition, co-medication with **corticosteroids** above 7.5 mg prednisolone/prednisone equivalent during the study period is prohibited to avoid masking of infections.

6 Investigational Medicinal Product/-s

6.1 General Information about Investigational Medicinal Product/-s

Investigational medicinal product 1:

Drug Code:	PD-0332991-00
Trade name:	IBRANCE

ATC code, if officially registered:	L01XE33
Pharmaceutical formulation:	75 mg/100 mg/125 mg capsules
Route of administration:	oral
Storage conditions:	At room temperature
Manufacturer / Importer:	Pfizer Pharma GmbH

Investigational medicinal product 2:

Drug Code:	PD-0332991-00
Trade name:	IBRANCE
ATC code, if officially registered:	L01XE33
Pharmaceutical formulation:	75 mg/100 mg/125 mg tablets
Route of administration:	oral
Storage conditions:	At room temperature
Manufacturer / Importer:	Pfizer Pharma GmbH

The pharmaceutical manufacturer Pfizer Pharma GmbH switches the formulation of palbociclib from capsules to tablets during the NCT-PMO-1601 trial. While there are no safety issues tablets are more convenient allowing intake with or without food. The active ingredient, dosage strength and administration schedule are the same. Bioequivalence is given. Patients in the NCT-PMO-1601 trial are treated with capsules from the beginning and will be switched to tablets upon availibility. Instructions in this protocol are valid without change.

6.2 Therapeutic/Diagnostic Effects

Palbociclib, an orally available pyridopyrimidine, is a highly selective, reversible inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that is being studied for use in cancer treatment. The compound prevents cellular DNA synthesis by blocking progression from the G1 to the S phase of the cell cycle, as demonstrated in laboratory models and early clinical trials.

6.3 Known Side Effects

The most common side effects of palbociclib are reversible neutropenia, thrombocytopenia, anemia, fatigue, constipation, nausea, and diarrhea.

Serious adverse events considered to be related to palbociclib included febrile neutropenia, unstable angina, diarrhea, ischemic colitis, pneumonia and bronchopneumonia, dehydration and metabolic acidosis, allergic alveolitis, and attempted suicide.

In vitro data indicate that palbociclib is primarily metabolized by CYP3A4. Potent CYP3A4 inhibitors (e.g., ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin, tilithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and grapefruit juice) are thought to represent the most significant potential for drug interaction with palbociclib. In addition, concomitant administration of agents that are strong CYP3A inducers (such as phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John’s Wort) may reduce the exposure to palbociclib and are thus not recommended. For further information, please refer to the summary of product characteristics (SPC).

6.4 Dosage Schedule

Palbociclib is given orally once per day for 21 days in a 28-day cycle.

6.4.1 Dosage

Maximum duration of treatment: in responding patients until disease progression or LPLV.

Maximum dose allowed: 125 mg/day for 21 days in a 28 days cycle

Dose level	**Palbociclib for 3 out of 4 weeks**
Starting dose	125 mg/d
-1	100 mg/d
-2	75 mg/d

Palbociclib dose reduction below 75 mg/d is not intended.

6.4.2 Dosage Adjustment

Toxicity	**Action**
Grade 4 neutropenia (ANC < 0.5 G/l)	Hold palbociclib treatment until ANC recovery to ≥ 1 G/l Reintroduce palbociclib at next lower dose level
Grade 4 thrombocytopenia (PLT count < 25 G/l)	Hold palbociclib treatment until PLT recovery to ≥ 50 G/l Reintroduce palbociclib at next lower dose level
Grade 3 neutropenia (ANC < 1 G/l) associated with documented infection or fever ≥ 38.5°C	Hold palbociclib treatment until ANC recovery to ≥ 1 G/l and no fever Reintroduce palbociclib at next lower dose level
Uncomplicated grade 3 neutropenia (ANC < 1 G/l)	Hold palbociclib treatment until ANC recovery to ≥ 1 G/l Reintroduce palbociclib at same dose level
Grade 3 thrombocytopenia (PLT count < 50 G/l)	Hold palbociclib treatment until PLT recovery to ≥ 75 G/l Reintroduce palbociclib at same dose level
Grade ≥ 3 non-hematologic toxicity, including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment	Hold palbociclib treatment until recovery to grade ≤ 1, baseline, or, at the investigator's discretion, grade ≤ 2 if not considered a safety risk for the patient Reintroduce palbociclib at next lower dose level

No specific dose adjustments are recommended for grade 1/2 treatment-related toxicity. However, physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.

6.5 Treatment Assignment

The trial medication is administered only to patients included in this trial. It is administered following the patient medication diary.

Patients withdrawn from the trial retain their identification codes.

6.6 Randomization and Blinding

Not applicable.

6.7 Packaging and Labeling

The trial medication is not labeled according to § 5 (8) of GCP-V. Pfizer Pharma GmbH provides palbociclib free of charge.

Supplies have to be obtained by sending an order form to Pfizer and the NCT Trial Center. The required amount of investigational medicinal product is shipped to the local pharmacies of the study sites by Pfizer Pharma GmbH. A pre-requisite for shipment is the full regulatory approval of the study site.

6.8 Supplies and Accountability

The investigators keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication. All trial medication must be kept in a locked area with access restricted to designated trial staff. The trial medication must be stored dry and in accordance with manufacturer's instructions at room temperature. The investigator also keeps accurate records of the quantities of trial medication dispensed, used, and returned by each patient. The documentation has to include date of dispensary, patient identification, batch/serial numbers or other identification of trial medication. After examination by the monitor, all unused trial medication and all medication containers are destroyed and this process is documented. It is assured that a final report of the drug accountability is prepared and maintained by the investigator in the Investigator's site file.

6.9 Compliance

Trial medication is dispensed/applied to the patients by the investigator or another authorized study physician. Patients are instructed to bring all trial medication to the trial site at every visit. Compliance is assessed by count of capsules/tablets. Details are recorded on the Drug Accountability Form.

7 Trial Methods

7.1 Description of Study Visits

Overviews of the course of the trial and all diagnostic and therapeutic measures are given in the trial schedule at protocol synopsis.

Baseline

- Prior to any trial specific invasive procedures, all patients provide written informed consent to participate in the study.
- A patient ID is assigned
- Assessment of general inclusion and exclusion criteria
- Assessment demographics (year of birth, gender, ethnic group)
- Assessment of general medical and oncologic history: date of first diagnosis detailed information on pretreatment including type and composition of prior therapy, response to prior therapy, date of relapse/refractory disease, detailed information on disease progression according to RECIST v1.1 criteria over the last 6 months prior to study inclusion, family history, additional medical history on concomitant diseases, prior exposure to toxic agents, prior malignancy including therapy, information on smoking; tumor staging according to UICC (TNM).
- Assessment of vital signs: height (in cm), weight (in kg), WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Assessment of child bearing potential and/or pregnancy blood test (women)
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of signs/symptoms: chordoma-related and unrelated signs and symptoms
- Assessment of Concomitant medications

- Assessment of PRO including Quality of Life assessed by questionnaires of the EORTC Quality of Life Item Library (core questionnaire QLQ-C30; fatigue module QLQ-FA12, and selected symptom items), as well as the Pittsburgh Sleep Qualitiy Index (PSQI), the Patient Health Questionnaire for Anxiety and Depression (PHQ-4), and the Functional Assessment of Cancer Therapy – cognitive function scale (FACT-cog). In addition, patient-reported information on personal traits and experiences are collected.
- ECHO and ECG
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Coagulation: Prothrombin time, aPTT and fibrinogen
- Urinalysis (local lab): pH, glucose, proteins (qualitative, dipstick accepted)
- HAV, HBV, HCV, and HIV-1 testing (local lab)
- Checking of tumor status on basis of CT/MRI scan not older than 2 weeks
- Sample shipment to Central Pathology Ulm for pathology and immunohistochemistry
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to Heidelberg

Visit 1 - Start of Therapy

- Assessment of vital signs: weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- ECG
- Assessment of Concomitant medications
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Distribution of palbociclib to patient
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to Heidelberg

Visit 2-4, weekly in first treatment cycle

- ECG
- Assessment of concomitant medications
- Assessment of AEs
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid

Visit 5, Day 1 (+/- 2 Days) of 2nd treatment cycle

- Assessment of vital signs weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of Concomitant medications
- Assessment of AEs
- Assessment of PRO including Quality of Life
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid

- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to NCT Heidelberg
- If applicable, distribution of palbociclib to patient

Visit 6, Day 14 (+/- 2 Days) of 2nd treatment cycle

- Assessment of Concomitant medications
- Assessment of AEs
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts

Visit 7, Day 1 (+/- 2 Days) of 3rd treatment cycle

- Assessment of vital signs: weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of Concomitant medications
- Assessment of AEs
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to NCT Heidelberg
- If applicable, distribution of palbociclib to patient
- Assessment of child bearing potential and/or pregnancy blood test (women)

Visit 8 Day 1 (+/- 2 Days) of 4th treatment cycle

- Assessment of vital signs: weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of Concomitant medications
- Assessment of AEs
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to NCT Heidelberg
- MRI/CT
- If applicable, distribution of palbociclib to patient

Visit 9 / 10 Day 1 (+/- 2 Days) of 5th / 6th treatment cycle

- Assessment of vital signs: weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of Concomitant medications
- Assessment of AEs
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts

- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to NCT Heidelberg
- If applicable, distribution of palbociclib to patient

Visit 11 Day 1 (+/- 2 Days) after 6th treatment cycle - Primary efficacy assessment or whenever applicable before in case of premature end of study treatment

- Assessment of vital signs: weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of Concomitant medications
- Assessment of AEs
- Assessment of PRO including Quality of Life
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to NCT Heidelberg
- MRI/CT
- If the patient benefits from treatment, this is the starting day of the next treatment cycle and beginning of the “Extended Treatment Period”
- In case of clinical benefit distribution of palbociclib to patient
- Assessment of child bearing potential and/or pregnancy blood test (women)

If patient continus treatment with study medication: Extended Treatment Period

Visit 10+X Day 1 (+/- 2 Days) of each treatment cycle after Primary efficacy assessment

- Assessment of vital signs: weight, WHO performance status, temperature (in grade centigrade), blood pressure/pulse
- Physical examination (inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination)
- Assessment of Concomitant medications
- Assessment of AEs
- Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts
- Blood chemistry (local lab): BUN, creatinine, albumin, AST/SGOT, ALT/SGPT, total bilirubin, AP, LDH, sodium, potassium, magnesium, calcium, serum uric acid
- Taking samples for biological characterization (40 ml blood; for details see sample shipping-manual) and shipment to NCT Heidelberg every 12 weeks (= every three treatment cycles)
- Assessment of PRO including Quality of Life every 12 weeks (= every three treatment cycles)
- MRI/CT every 12 weeks (+ 4 weeks)

Visit F-UP-3: 3 months after stop of study treatment (+/- 1 Week) – Follow-up

- Assessment of PRO including quality of life
- Assessment of tumor status with MRI/CT

Visit F-UP-6: 6 months after stop of study treatment (+/- 1 Week) – End of follow-up

- Assessment of PRO including quality of life
- Assessment of tumor status with MRI/CT

Visit SF-UP-X: Survival Follow-up

Patients are followed until death every 3 months by phone, unless they are seen in the center regularly anyway. Survival-Follow-up is continued until end of clinical trial (LPLV).

7.2 Methods of Data and Sample Collection

7.2.1 Data Collection and Handling

All findings including clinical and laboratory data are documented by the investigator or an authorized member of the study team in the patient's medical record and in the case report form (CRF). The investigator at the clinical site is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. The CRF has to be filled out according to the specified CRF Completion Guidelines. The correctness of entries in the CRF is confirmed by dated signature of the responsible investigator.

All data is reported pseudonymized.

7.2.2 Sample Collection and Handling

Tumor biopsy

Tissue blocks preferably not older than 12 months are requested either from initial diagnosis or from biopsies of locally advanced disease or metastatic sites. A corresponding pathology report should be included along with the archival sample.

In case of re-biopsies before study entry, also fresh material could be send by courier in provided standard medium to the central pathology lab.

Biopsies are analyzed for p16 (CDKN2A) tumor suppressor expression level at:

Institute of Pathology, M23
University of Ulm
Albert-Einstein-Allee 11
89075 Ulm

Blood samples

Blood samples of 40 ml blood (for details see sample shipping-manual) taken at every dedicated visit are used for biobanking.

Blood samples for biobanking are sent to:

Biobank des Nationalen Centrums für Tumorerkrankungen (NCT) Heidelberg
Im Neuenheimer Feld 460
69120 Heidelberg

7.3 Measurement of Efficacy Parameters

7.3.1. Tumor Response

Tumor assessment is evaluated by MRI or CT and progression or response is based on RECIST v1.1 criteria[12] as well as Choi criteria[13]. Tumor imaging is done according to clinical routine. The first measurement is performed during study entry and subsequent scans are performed on the

first day of the 4th cycle, at primary efficacy assessment, every 12 weeks (+ 4 weeks variance) in the extended treatment phase and in F-up-3 and F-up-6. All lesions are assessed locally and reported at each scheduled scan. The same imaging technique used to characterize each identified and reported lesion at baseline is employed in the following tumor assessments.

Target Lesions

Complete response (**CR**) is defined as the 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**) is defined as a ≥30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Progressive disease (**PD**) is defined as a ≥20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded while on study, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (**SD**) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

Complete response (**CR**) is defined as the disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD is defined as a persistence of 1 or more non-target lesions.

Progressive disease **(PD)** is defined as unequivocal progression of existing non-target lesions, or the appearance of 1 or more new lesion.

7.4 Measurement of Safety Parameters

The following laboratory parameters are used to monitor safety:

Hematology (local lab): hemoglobin, RBC, PLT, WBC and differential cell counts should be performed at baseline, weekly during the first treatment cycle, in each first week during following cycles (including ExT), Visit 6 and 11. Clinical status and laboratory parameters are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician, which can involve more frequent testing, especially in neutropenic/aplastic patients. It is expected that patients on this protocol are cared for by physicians experienced in the treatment and supportive care of patients with acute leukemia.

Blood chemistry (local lab): including creatinine, albumin, BUN, AP, AST/SGOT, ALT/SGPT, serum uric acid, total bilirubin, sodium, potassium, magnesium, calcium, and LDH, are performed at baseline and then once a week during the first treatment cycle, in each first week during following cycles (including ExT), at primary efficacy assessment, and during follow-up while ongoing treatment, or following individual institutional guidelines and the best clinical judgment of the responsible physician, which can be more often.

Prothrombin time, aPTT, and fibrinogen are measured at baseline and at appropriate times during treatment cycles at the investigator's discretion.

Urinalysis (local lab), pH, glucose, proteins [qualitative, dipstick accepted] are performed at baseline and at appropriate times during treatment cycles at the investigator's discretion.

Serum/urine pregnancy test (local lab, sensitivity of at least 25 mIU/mL) is performed at baseline (≤ 72 hours prior to patient registration), at day 1 cycle 3, at the end of study treatment and repeated if clinically indicated.

Hepatitis A, B, and C as well as HIV-1 testing (local lab) is performed at baseline and thereafter at the investigator's discretion.

7.5 Measurement of Further Parameters

Vital signs

Height, weight, temperature, WHO performance status, and blood pressure/ pulse are collected. Height (in cm) is measured at baseline only. Weight (in kg), WHO performance status, temperature (in grade centigrade), and blood pressure/pulse are measured at baseline and before the start of every new cycle.

Echocardiography

Cardiac ultrasound is performed at baseline as safety assessment and thereafter at the investigator's discretion. Ejection fraction must be specified in case of abnormalities and quantified.

Electrocardiogram (ECG)

A 12-lead ECG is performed at baseline and during the first treatment cycle every week as well as additionally at the investigator's discretion.

For the purpose of this study, QTc_B intervals are calculated according to the formula of Bazett:

$$QTc = \frac{\overline{QT}\,(ms)}{\sqrt{RR\,(sec)}}$$

For QTc_B intervals > 450 ms and ≤ 470 ms, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication that may prolong the QTc_B interval. Continue palbociclib.

For QTc_B intervals > 470ms and ≤ 500 ms, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication that may prolong the QTc_B interval. Reduce palbociclib to the next lower dose level or, if the lowest dose level is reached, discontinue palbociclib.

For QTc_B intervals > 500 ms, immediately stop palbociclib, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication that may prolong the QTc_B interval. Re-start palbociclib if the QTc_B interval is < 470ms. If QTc_B interval is not improved (QTc_B remains > 470 ms for more than three weeks), discontinue palbociclib until QTc_B improves to < 470 ms, then resume palbociclib. Missed doses of palbociclib are not made up.

8 Ancillary and Post Trial Care

After the end of the 6 months follow-up phase, patients are routinely followed-up usually including visits every 3 months, and treated regarding standard of care according to the discretion of the treating physician.

9 Assessment of Safety

9.1 Specification of Safety Parameters

9.1.1 Adverse Events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/ diseases existing before inclusion into the trial
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom is not considered an adverse event unless there is an untoward change in its intensity, frequency or quality. This change is documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have cause death if it was more severe)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or
- Results in a congenital anomaly/ birth defect
- Any other important medical event may be considered serious when, based upon medical judgement, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.1.3 Expectedness, Reference Safety Information (RSI)

An ‘unexpected’ adverse event is one the nature or severity of which is not consistent with the applicable reference safety information (RSI) included in the Investigator’s Brochure (IB) or Summary of Product Characteristics (SPC). In this trial the current version of the SPC is considered RSI.

Furthermore, reports which add significant information on specificity or severity of a known adverse reaction may be counted as ‘unexpected’ events (cf. 9.4 Expedited Reporting).

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP, and ‘unexpected’, i.e. the nature and/ or severity of which is not consistent with the RSI are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case if either the investigator, who primarily reported the SAE, or the second assessor classify the SAE as 'suspected' (*i.e. as 'definitely', 'probably', 'possibly' related to IMP)* and the SAE is also 'unexpected', it is categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority (BfArM), and to all participating investigators.

9.2 Period of Observation and Documentation

All AEs reported by the patient or detected by the investigator are collected during the trial, and must be documented on the appropriate pages of the CRF. AEs must also be documented in the patient's medical records.

In this trial, all AEs that occur after first administration of the IMP are documented on the pages provided in the CRF. The individual period of observation ends 28 days after the last dose of the IMP for chordoma. All patients who have AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE is followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

9.2.1 Grading of AEs

The grading of AEs in this trial is carried out on the basis of the 5-grade scale defined in the CTCAE v5.0.

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The grading of all AEs listed in the CTCAE v5.0 is based on the information contained therein. The grading of all other AEs, i.e. those which are not listed in the CTCAE v5.0 are performed by a responsible investigator, based on definitions of CTCAE v5.0 shown in the table above.

9.2.2 Coherence between AEs and the IMP

The investigator evaluates each AE that occurred after administration of investigational medicinal product regarding the coherency with the administration of the investigational medicinal product according to the definitions of the WHO:

Definitely related:	There is a reasonable possibility that the event may have been caused by IMP. A certain event has a strong temporal relationship and an alternative cause is unlikely.
Probably related	An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a timely relationship and follows a known pattern of response, but a potential alternative cause may be present.

Possibly related:	An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a timely relationship to the IMP; however, the pattern of response is atypical, and another cause seems more likely.
Unlikely related:	Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
Not related:	An AE that does not follow a reasonable temporal sequence related to IMP and is likely to have been produced by the patient's clinical state, other modes of therapy or other known etiology.
Unassessable/Unclassified:	A report suggesting an AE which cannot be judged because of insufficient or contradictory information, or a report which cannot be supplemented or verified.

9.2.3 Outcome of AEs

The outcome of an AE at the time of the last observation is classified as:

Recovered/ resolved	All signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation.
Recovering/ resolving	The intensity of signs and symptoms has been diminishing and/or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/ not resolved	Signs and symptoms of an AE are mostly unchanged at the time of the last interrogation.
Recovered/ resolved with sequel	Actual signs and symptoms of an AE disappeared but there are sequels related to the AE.
Fatal	Resulting in death. If there are more than one AE only the adverse event leading to death (possibly related) is characterized as 'fatal'.
Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

9.2.4 Action taken with the IMP

The action taken with IMP is assigned to one of the following categories:

Dose not changed	No change in the dose of IMP.
Dose reduced	Reduction in the dose of IMP.
Temporary discontinuation	Temporary discontinuation of IMP.
Drug withdrawn	Discontinuation of IMP.
Unknown	The information is unknown or implausible and it cannot be supplemented or verified.
Not applicable	The question is implausible (e.g. the patient is dead).

9.2.5 Treatment of SAE

The term 'Treatment of SAE' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequelae. The following categories are used to categorize this treatment:

None	No action taken

Drug treatment	Newly-prescribed medication or change in dose of a medication
Others	Other countermeasures, e.g. an operative procedure

9.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the KKS Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" (SAE)-form. The initial report must be as complete as possible, including details of the (serious) adverse event as well as an assessment of the causal relationship between the event and the trial medication. The reporting is performed by faxing of a completed 'SAE Form' to the KKS Heidelberg.

Fax-number: + 49 (0)6221 56 33687

9.4 Expedited Reporting

SUSARs are to be reported to the ethics committee(s), regulatory authorities (BfArM) and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting.

All SAEs are forwarded by e-mail immediately (not later than 24 hours after receipt) by the responsible person at KKS Heidelberg to the coordinating investigator or the scientific coordinator in order to perform a second assessment. The coordinating investigator or the scientific coordinator fills out a 'Second Assessment Form' for each SAE and returns it by e-mail to the KKS Heidelberg within 48 hours.

E-mail: V-KKS.SAE@med.uni-heidelberg.de

The 'Second Assessment Form' contains the following information:

I) Assessment of relationship between SAE and IMP
II) Assessment of expectedness of SAE (derived from IB which serves as RSI)
III) Statement if the benefit/ risk assessment for the trial did change as a result of SAE, and

The expedited reporting is carried out by a responsible person of KKS Heidelberg. Only SUSARs occurring after administration of IMP undergo expedited reporting.

9.5 Emergency Treatment

During and following a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to a patient for any AE, including clinically significant laboratory values. The investigator should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

9.6 Reporting Requirements for Pregnancies

9.6.1 Pregnancies in Female Patients

Female patients of childbearing potential are instructed to immediately inform the investigator if they become pregnant during the study. A pregnancy should primarily be reported using an SAE-form. The investigator has to send the SAE-form immediately (i.e. no more than 24 hours after learning of the pregnancy).

Fax-number: + 49 (0)6221 56 33 687

The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Medical monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an

event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF and additionally in accordance with the requirements defined for all other SAEs (see above).

9.6.2 Pregnancies in Female Partners of Male Patients

Male patients are instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the last dose of study drug. The SAE-form has to be completed by the investigator immediately (i.e. within 24 hours after becoming aware of the pregnancy) and submitted to KKS Heidelberg. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner needs to sign an authorization for use and disclosure of pregnancy health information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator updates the information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision.

10 Statistical Considerations

10.1 Study Design and Research Hypothesis

Non-randomized, single-arm, open-label, multicenter phase II trial, designed to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastatic chordoma. The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib.

Formally, the null hypothesis that the true response rate p is less or equal to a reference rate p_0 is tested against a one-sided alternative:

$$H_0: p \leq p_0 \quad vs. \quad H_1: p \geq p_1$$

where p is the true response probability, p_0, the (uninteresting) reference response rate, and p_1 the (desirable) target level.

10.2 Sample Size Calculation

The sample size and power calculations were based on Simon's optimal two-stage design[14], which minimizes the expected sample size under the null hypothesis subject to the error probability constraints. The type I error was set at $\alpha = 0.05$, the type II error at $\beta = 0.2$. Here, the null hypothesis that the true response rate is less or equal to $p_0 = 0.1$ is tested against a one-sided alternative, where the desirable level of response is 0.25.

The study needs 43 patients evaluable for the primary endpoint to complete. In the first stage, $n_1 = 18$ patients are accrued. If there are $r_1 = 2$ or fewer responses in these 18 patients, the study is stopped and the drug rejected. This occurs with a probability of early termination under H_0 of $PET(p_0) = 0.73$. Otherwise, 25 additional patients are accrued for a total of $n = 43$ patients. In the final analysis the null hypothesis is rejected and the drug recommended for further development if 8 or more responses are observed in 43 patients. This design yields a type I error rate of ≤ 0.05 and power of $\geq 80\%$ when the true response rate is $p = 0.25$.

Impact on Secondary Analyses
A sample size of 43 patients is deemed adequate for all secondary/exploratory analyses.

Replacements
Patients who go off study due to adverse events before final staging at 6 months are considered treatment failures, receive response status = PD (progressive disease) and are not replaced. Patients going off study for other reasons (drop-outs, e. g. lost-to-follow-up, death unrelated to disease/treatment, retracted IC, etc.) without assessment of the primary outcome are replaced until the goal of 43 is met.

Drop-outs
The rate of patient drop-out is estimated at 5%.

10.3 Analysis Variables

10.3.1 Primary analysis

The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of at least one confirmed complete response (CR) or confirmed partial response (PR) or stable disease (SD) according to RECIST version 1.1.

10.3.2 Secondary analyses

Tumor response rate (TRR)

The TRR is defined as the presence of at least one complete response (CR) or partial response (PR) according to RECIST version 1.1 after six cycles of study medication.

Progression-free survival (PFS)

PFS is defined as the time from first administration of the IMP to progression of disease or death from any cause, whichever occurs first. Patients without the event are censored on the last date of follow-up. [time frame: up to LPLV]

Overall survival (OS)

OS is defined as the time from first administration of the IMP to time of death from any cause. Patients without the event are censored on the last date of follow-up. [time frame: up to LPLV]

10.3.3 Safety

This endpoint includes all AEs, their severity, SAEs, the relation of AEs to the study treatment, dose modifications for toxicity and discontinuation of study treatment during the trial phase. Toxic effects are graded according to the National Cancer Institute Common Toxicity Criteria (CTCAE) version 5.0.

10.3.4 Patient Reported Outcomes (PROs) including Health-related quality of life (QoL)

- Patient Reported Outcomes (PROs) are calculated as the new EORTC QLQ-C30 Summary Score recommended by the EORTC Quality of Life Group, which has been recently developed and and evaluated.[15] In addition, the EORTC QLQ function and symptom scores are calculated according to the actual EORTC Scoring Manual.[16]
- **Fatigue** is calculated from the EORTC QLQ-FA12 according to the EORTC Scoring Manual.[16]
- **Sleep problems** are calculated from the PSQI according to the corresponding scoring guidelines.[17]

- **Perceived cognitive impairments** and **impact of cognitive changes** are calculated from the FACT-cog according to the corresponding scoring manual.
- **Anxiety** is calculated from the PHQ-4 according to the corresponding scoring manual.[18]
- **Depression** is calculated from the PHQ-4 according to the corresponding scoring manual.[18]

PROs are assessed using questionnaires (EORTC QLQ-C30, EORTC QLQ-FA12, PSQI, FACT-cog, PHQ-4) at baseline, at the beginning of the second and after the sixth 28-day treatment cycle, every 3 treatment cycles during the extended treatment period.

10.4 Analysis Populations

10.4.1 Full Analysis Population

All enrolled patients who have finished at least one cycle of the study medication and who are evaluable for the primary endpoint are included in the full analysis set under the ITT principle.

Untreated patients are identified and described separately.

10.4.2 Per Protocol Population

No per protocol analysis is planned for the present study.

10.4.3 Safety Population

All enrolled patients who have received any amount of the study medication are subject to the safety analysis.

Patients' disposition and reasons for ending the study are presented in frequency distribution tables and individual data listing. Patients not meeting the eligibility criteria and who are considered protocol violations are also described. Descriptive statistics of the baseline characteristics are generated across all treated patients. Frequency distributions are presented for the categorical categorized variables. Summary statistics including mean, standard deviation, median, minimum, maximum, and the number of assessed patients is calculated, as appropriate, for the quantitative variables. Individual data are presented in listings.

10.5 Statistical Methods

10.5.1 General Considerations

The statistical analysis is carried out by the responsible biostatistician at the National Center for Tumor diseases (NCT) Heidelberg using SAS statistical software (SAS Insitute Inc., Cary, NC, USA). The details of the analysis are specified in the statistical analysis plan (SAP), which is finalized and approved prior to the database lock.

10.5.2 Demographic and other Baseline Characteristics

Categorical baseline characteristics, like sex, age, detailed history of cancer, performance status (ECOG), relevant previous anticancer treatment, tumor staging according to UICC (TNM), concomitant illness at trial initiation, and concomitant treatment maintained, are summarized by frequency tables. Summary statistics are provided for quantitative variables like age, weight, laboratory values.

10.5.3 Study Therapy, Treatment Compliance, and Follow-up

Summary statistics are presented for the dosage of palbociclib received at each cycle, dose modifications for toxicity, discontinuation and withdrawal from study treatment, as well as drop-out from the follow-up during the post-study phase.

The number of cycles administered, actual and total doses administered, dose modifications, delays and omissions, as well as reasons for deviation from planned therapy and overall duration of treatment, are described.

10.5.4 Analysis of the Primary Endpoint

Descriptive statistics and patient data listing are used for the presentation of all response data. Treatment efficacy is evaluated considering the disease control rate (DCR) and best overall response achieved according to RECIST criteria, for which an unbiased estimate and exact 95% CI is computed. Exploratory efficacy analyses may be performed if deemed of clinical relevance.

10.5.5 Analysis of the Secondary Endpoints

Tumor response

Descriptive statistics and patient data listing are used for the presentation of all response data. Treatment efficacy is evaluated considering the tumor response rate (TRR), for which an unbiased estimate and exact 95% CI is computed. Exploratory efficacy analyses may be performed if deemed of clinical relevance.

Survival Analysis

Standard methods for right-censored data are used for analyzing PFS and OS. Cox Proportional Hazards Regression is used to examine the influence of covariates on PFS/OS if deemed clinically relevant.

Safety Analysis

The assessment of safety is based mainly on the frequency of adverse events (see Section 9) and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline during the study phase (up to cycle 6 + 4 weeks). Adverse events are summarized by presenting the number and percentage of patients having any adverse events or serious adverse events, and having each individual adverse event, and by determining and summarizing the maximum individual toxicity grade (over all forms of toxicity) for each treatment cycle during the study phase. Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) are determined. Any other information collected (e.g. severity or relatedness to study drug) is summarized as appropriate. Laboratory data is summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges). All proportions are given along with exact Pearson-Clopper 95% confidence intervals.

Patient Reported Outcomes Analysis

The scales are scored and analyzed according to the corresponding EORTC guidelines. The Quality of Life subscales and single item sub-scores are summarized by the mean, standard deviation, median, minimum and maximum, and plotted by time. The change from baseline for all domains is examined descriptively.

Other Analyses

Patients Disposition is tabulated. In addition, the number of patients who withdrew from the study and reasons for discontinuation are summarized. The number and percentage of patients with

normal and abnormal ECG results are summarized. Summary statistics for baseline values and Follow-up are displayed for QT and QTc_B correction methods.

10.5.6 Handling of Missing Data

Missing values are not replaced or imputed. For patients with incomplete follow-up, time to last follow-up date is used as the censoring time in the analysis of time-to-event data.

10.6 Interim Analyses

As defined in section 10.2, one interim analysis of efficacy is performed at the end of the first stage. After accrual of 18 patients, recruitment is interrupted, if necessary, until a decision according to the first stage of Simon's design has been reached. Evaluation takes place after response evaluation of the last patient of the first stage is available.

The objective of the interim analysis is to allow the early stopping of the trial in case of an insufficient number of responders ($\leq$2).

10.7 Safety Monitoring

Safety monitoring is performed by the IDMC after 18 patients have finished at least one cycle of the study treatment. Safety assessments consist of evaluating AEs and SAEs. The IDMC provides the sponsor with recommendations regarding trial modification, continuation or termination.

11 Data Management

11.1 Data Collection

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to an electronic data record.

All findings including clinical and laboratory data are documented by the investigator or an authorized member of the study team in the patient's medical record and in the CRF except the data on PRO. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and entries can be verified by source data. The CRF has to be filled out according to the specified CRF Completion Guidelines.

Data collection can only be done by authorized persons. All study data are password-protected. The electronic CRF provides several checks for completeness and consistency. Each entry or change of data is tracked with name and exact date. The investigator signs the CRF electronically as per agreed project process. A copy of the electronic CRF is archived at the study site.

PRO questionnaires, which are paper-based, are completed by the patient and serve as source data. Upon completion the questionnaires are sent by the trial site to the NCT trial centre for tracking. Thereafter, they are forwarded to the central unit responsible for Patient-Reported Outcomes. The questionnaires are recorded using the TELEFORM® system (Cardiff) and undergo a computer assisted manual verification.

11.2 Data Handling

Data entries undergo an automatic online check for plausibility and consistency.

Further checks for plausibility, consistency, and completeness of data are performed after completion of the study. Queries are generated on the basis of these checks, combined with a visual control by a responsible monitor/data manager.

The investigator has to resolve and clarify all queries.

All data management activities are done according to the current Standard Operating Procedures (SOPs) of the NCT Trial Center.

11.3 Storage and Archiving of Data

According to §13 of the German GCP-Regulation all important trial documents (e.g. CRFs) are archived for at least 10 years after the trial termination.

The CI is responsible for archiving the TMF including protocol, CRFs, report etc.

The investigator(s) archives all trial data (source data and Investigator Site File (ISF) including Patient Identification List and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations. The Patient Identification List is archived for at least 15 years after trial termination.

If the investigator relocates, retires, or for any reason withdraws from the study, the NCT Trial Center should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the NCT Trial Center. The investigator must obtain CIs written permission before disposing of any records, even if archiving requirements have been met.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the current version of the Declaration of Helsinki. The trial is carried out in keeping with local legal and regulatory requirements.

12.2 Patient Information and Informed Consent

Before being admitted to the clinical trial, the patient must consent in written form to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The original personally signed and dated Informed Consent Form must be kept on file by the investigator(s), and documented in the case report form.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language easily understandable to the patient and must clearly state who informed the patient, which is confirmed by the dated signature of the responsible investigator

If new safety information results in significant changes in the risk/benefit assessment, or if changes are made in the protocol, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue the study.

12.3 Confidentiality

The data obtained in the course of the trial is treated pursuant to the applicable Data Protection Law as well as § 40 (2a) AMG.

During the clinical trial, patients are identified solely by means of an individual identification code (Patient ID). Storage of trial findings on a computer is done in accordance with local data protection law and is handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation are fulfilled in its entirety.

The patient consents in writing to relieve the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors,

auditors, inspectors) may inspect the patient-related data collected during the trial, ensuring the data protection law.

The investigator maintains a patient identification list (Patient IDs with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data are not included into the trial.

12.4 Responsibilities of Investigator

The Principal Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol and any amendments, the trial treatments, and their trial-related duties and functions.

The Principal Investigator should maintain a list of investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties (Log of Staff).

The investigator(s) should support monitoring, auditing and inspections as described in sections 13.1 and 13.2.

12.5 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents are submitted to the independent Ethics Committee (EC) as well as to the competent federal authority (BfArM). A written favourable vote of the EC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of the clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation) are submitted to EC and the competent higher federal authority in writing as amendments. They have to be approved by the EC and the competent higher federal authority.

The Coordinating Investigator or the NCT Trial Center, and if applicable the investigator(s) keep a record of all communication with the EC and the regulatory authorities.

12.6 Continuous Information to Independent Ethics Committee

Pursuant to the German Drug Law (AMG) and the GCP Regulation, the EC and the competent higher federal authority are informed of all suspected serious unexpected adverse reactions (SUSARs). Both institutions are informed in case the benefit-risk assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) is submitted once a year (Development Safety Update Report (DSUR)).

The EC and the regulatory authorities must be informed of the end of the trial. They are provided with a summary of trial results within one year after the end of clinical phase (LPLV).

12.7 Notification of Regulatory Authorities

The local regulatory authorities as responsible for each particular investigator and the competent higher federal authority are informed before the beginning, during and at the end of the trial according to §67 AMG and §13 GCP-V. Each investigator is obliged to notify his/ her local regulatory authority and the competent higher federal authority according §67 AMG and §12 (1, 2, 6) GCP-V.

12.8 Registration of the Trial

Prior to the beginning of the clinical phase (FPI) the coordinating / principal investigator registers the trial at a public accessible clinical trial register having the status of a primary register according to the International Clinical Trials Registry Platform (ICTRP) and correspondingly is listed at the International Clinical Trials Registry Platform of the World Health Organization (WHO,

http://www.who.int/ictrp/en/). The requirements are fulfilled by the European Clinical Trials Register and submission of EMA Module 1 (Clinical Trial Application Form).

The registration is a prerequisite for a publication in many peer-reviewed journals (see Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors; (http://www.icmje.org/ publishing_10register.html).

12.9 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy which covers in its terms and provisions its legal liability for injuries caused to participating persons. The insurance policy also covers any damage done to the patient, even if the harm done arises out of strictly following the procedures described in this protocol and abiding as applicable law and professional standards. The insurance was taken out at HDI Global SE (insurance number: 57 010310 03018, maximum limit: € 500.000 per participating person).

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person must agree to help clarify the cause and the extent of damage with all appropriate measures. He is also obliged to take measures himself to reduce damage as much as possible. During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance must be delivered to the patient.

The insurance company has to be informed about all amendments that could affect patients' safety, and must also receive the actual version of the informed consent.

13 Quality Assurance

13.1 Monitoring

Monitoring is done by personal visits from a clinical monitor and by centralized monitoring. The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor. Monitoring is done in a risk based manner.

By frequent communications (e-mails, letters, telephone, fax), the site monitor a ensure that the trial is conducted according to the protocol and to regulatory requirements.

13.2 Inspections/ Audits

Regulatory authorities and an auditor authorized by the sponsor may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14 Agreements

14.1 Financing of the Trial

The trial is financed using funds of Pfizer Pharma GmbH and DKFZ.

The study drug is provided free-of-charge by Pfizer Pharma GmbH.

14.2 Declaration of Interests

Before the start of the trial, the investigator discloses to the sponsor any proprietary or financial interests he or she might hold in the sponsors/ a funding company, in the investigational product(s), or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

14.3 Dissemination Policy

Trial results are published in medical journals, and via the chordoma foundation (https://www.chordomafoundation.org/).

14.3.1 Access to data

After the trial has been completed and published, it is planned to make the trial available for re- and meta-analyses. An appropriate repository is defined at the end of the trial.[19]

14.3.2 Reports

The biostatistician prepares the final trial report together with the Coordinating Investigator within 12 months after the end of the study (database lock).

Interim safety reports (DSURs) are prepared by the pharmacovigilance officer together with the Coordinating Investigator in accordance with legally required timeframes; data reconciliation is carried out where necessary and possible together with the data management of the NCT Trial Center based on already available CRF-AE data.

14.3.3 Publication

All information concerning the trial is confidential before publication. Trial results are published in medical journals.

15 Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- The current benefit-risk assessment of the investigational medicinal product
- Moral, ethical, and scientific principles governing clinical research as set out the principles of GCP and in the applicable version of Declaration of Helsinki.

The investigator is supplied with details of any significant or new finding, including relevant safety information relating to treatment with the investigational medicinal product.

Date: _____ Signature: _____

Prof. Dr. Richard F. Schlenk
Function: Coordinating Investigator

Date: _____ Signature: _____

Lisa-Marie Rother
Function: Biostatistician

16 Declaration of Investigator

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enrol the first patient only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all patients before enrolment.

I know the requirements for accurate reporting of serious adverse events, and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described.

Date: _____ Signature: _____

Name (block letters): _____

Trial Center (address): _____

_____

_____

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