Clinical Trial Protocol

Doc. No.: c02332639-05

EudraCT No.:	2014-002123-10
BI Trial No.:	1200.120
BI Investigational Product(s):	Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution
Title:	Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology
Clinical Phase:	I/II
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Phone: Fax:
Status:	Final protocol (based on global amendment 3)
Version and Date:	**Version: 4** **Date: 02 June 2017** Version: 1 (initial protocol) 12 December 2014

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution			
Name of active ingredient: Afatinib			
Protocol date: **12 Dec 2014**	**Trial number:** 1200.120		**Revision date:** **02 June 2017**
Title of trial:	Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology		
Co-ordinating Investigator:			
Trial site(s):	International, multi-centre trial with participation of ITCC trial sites specialized in paediatric oncology and new drug development		
Clinical phase:	I/II		

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Name of finished product: Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution			
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Protocol date: **12 Dec 2014**	**Trial number:** 1200.120		**Revision date:** **02 June 2017**

Objective(s):

Dose finding part

- To determine the maximum tolerated dose (MTD) of afatinib in patients ≥2 to <18 years by assessing dose limiting toxicity (DLT). The MTD will be determined as the highest dose at which no more than 1/6 patients experienced DLT.
- To assess safety
- To describe the pharmacokinetics (PK) after first dose and at steady state in children.
- To investigate objective response (OR) to treatment

MTD expansion cohorts/Phase II part

- Patients aged ≥1 year to <18 years included into the MTD expansion cohorts/Phase II part will be selected by biomarker(s) for ErbB deregulation, which were previously identified in the biomarker prevalence study outside of this clinical trial protocol, i.e. fulfil at least two of the below criteria:
    - EGFR gene amplification (FISH) *and/or*
    - HER2 gene amplification (DDISH) *and/or*
    - EGFR protein expression (H score >150) *and/or*
    - HER2 protein expression (H-score > 0)

  Patients aged ≥1 year to <18 years with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined above will be included in an exploratory cohort (for further information see section 5.6)
- To investigate objective response (OR) to treatment, progression free survival (PFS) and duration of objective response (DoR)
- To collect further safety, PK and efficacy data

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Protocol date: **12 Dec 2014**	**Trial number:** 1200.120		**Revision date:** **02 June 2017**

Methodology:	Open-label, dose escalation, monotherapy trial with biomarker specific MTD expansion cohorts/ Phase II part. The trial will consist of 2 parts: 1) Dose finding part to determine the MTD 2) MTD expansion cohorts/Phase II part to assess clinical anti-tumour activity in patients selected by any two of the above detailed biomarkers for ErbB deregulation; i.e. EGFR FISH positive and/or EGFR H-score >150 and/or HER2-DDISH positive and/or HER2 H-score >0. Patients with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined above will be included in an exploratory cohort.
No. of patients:	
total entered:	Approximately up to 550 patients will need to be screened to allow for up to55 patients who are entered and evaluable for response/MTD
each treatment:	- Dose finding part: 17 patients were entered to determine the MTD (c09990672-01) - MTD expansion cohorts/Phase II part: Up to 38 patients evaluable for OR will be entered. ▪ A minimum of 5 patients in each of the four following cohorts, i.e. high grade glioma (HGG), diffuse intrinsic pontine glioma (DIPG), ependymoma (EM) and a mixed histology agnostic cohort of patients with refractory tumours, will be accrued. All patients must fulfil two of the biomarker screening criteria, i.e. EGFR FISH positive *and/or* EGFR H-score >150 *and/or* HER2-DDISH positive *and/or* HER2 H-score >0. ▪ An exploratory histology agnostic patient cohort with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined above will be added.
Diagnosis :	Paediatric patients with recurrent/refractory HGG, DIPG, low grade astrocytoma, neuroblastoma, EM, medulloblastoma/primitive neuroectodermal tumours (PNET), rhabdomyosarcoma (RMS) and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology will be included during the dose finding part. From the MTD expansion cohorts/phase II part onwards, patients with either HGG, DIPG, EM or any other solid tumour selected by biomarkers for ErbB deregulation; i.e. EGFR FISH positive and/or EGFR H-score >150 and/or HER2-DDISH positive and/or HER2 H-score >0 and patients regardless of tumour indication but with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined above will be included.

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Name of finished product: Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution			
Name of active ingredient: Afatinib			
Protocol date: **12 Dec 2014**	**Trial number:** 1200.120		**Revision date:** **02 June 2017**
Main criteria for inclusion:	- Paediatric patients - presenting with recurrent/refractory disease after they received at least one prior standard treatment regimen and for whom no effective conventional therapy exists Dose finding part - aged ≥2 years - <18 years at the time of informed consent - Patients with a diagnosis of HGG, DIPG, low grade astrocytoma, neuroblastoma, EM, medulloblastoma/PNET, RMS, and/or solid tumours with known ErbB pathway deregulation regardless of tumour histology. MTD expansion cohorts/phase II part: - aged ≥1 year to <18 years at the time of informed consent - patients with HGG, DIPG, EM and any other solid tumour which fulfil at least two of the below criteria: o EGFR gene amplification (FISH): Either EGFR/Cen7 ≥ 2.0 or ≥10% of cells with ≥15 copies or ≥40% of cells with ≥ 4 copies or gene cluster in ≥10% of cells *and/or* o HER2 gene amplification (DDISH): Her2/CEP17 ≥ 2.0 *and/or* o EGFR protein expression: H-score > 150 (membrane staining) *and/or* o HER2 protein expression: H-score > 0 (membrane staining) - patients with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined above regardless of tumour histology		
Test product(s):	Giotrif®, Gilotrif®, Afatinib		
dose:	Once daily dosing of afatinib using film coated tablets 20, 30, 40 or 50mg afatinib or age appropriate oral liquid dosage form at a concentration of 4mg/ml. The dose will be calculated by allometric scaling per m^2BSA. Dose escalation starts at 80% of recommended adult dose (40mg once daily) based on allometric scaling per m²BSAwith escalation levels to 100%, 125% and 150%; in case 80% is exceeding the MTD, dose level "-1" will allow dose de-escalation to 50%		
mode of admin.:	Oral		

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Comparator products:	Not applicable		
Duration of treatment:	Therapy with afatinib will continue as long as the individual patient benefits from therapy, does not develop secondary malignancy and does not meet one of the criteria requiring withdrawal from treatment		
Criteria for efficacy:	- Anti-tumour activity measured as objective response (OR) assessed by the investigator according to the institution's tumour response evaluation criteria for the given tumour type - Duration of objective response (DoR) for those patients with a response (CR or PR) - Progression free survival (PFS)		
Criteria for pharmacokinetics	- PK parameters of afatinib based on noncompartmental analysis (NCA) after 1st dose and at steady state ($AUC_{\tau(,ss)}$, $C_{max(,ss)}$, $t_{max(,ss)}$ and accumulation (or effective) half-life) for patients with extensive PK sampling - PK parameters of afatinib based on population PK modeling ($C_{max,ss}$, $AUC_{\tau,ss}$, CL/F, Vd/F) for all patients with sparse and extensive PK sampling		
Criteria for safety:	- Evaluation of safety and tolerability of afatinib by incidence and severity of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE v3.0) - Assessment of the MTD of afatinib in the dose finding part The recommended safe paediatric dose will take all safety assessments during dose finding part and MTD expansion cohorts/phase II part into consideration		
Statistical methods:	Descriptive statistics, frequency tables for DLTs Objective response rate will be calculated with exact 95% confidence interval. DoR for patients with response and PFS will be evaluated using Kaplan-Meier estimate. The analyses will be exploratory and descriptive in nature		

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FLOW CHART

Trial periods	**screen**	**Treatment Course 1**					**Treatment Course 2**[1]		**Treatment Course 3 and onwards**[1]			
Day of period	-28 to 0	1	2	8 ±2	15 ±2	22 ±2	1 ±2	15[1] ±2	1 ±2	**EOT**[2]	**FU**[3]	**OP**[4]
Visit		1		2	3	4	1	2	1			
Informed consent /patient assent	x[5]											
Demographics	x											
Medical history	x											
Physical examination including neurological exam in patients with brain tumours	x	x	x	x	x	x	x	x	x	x		
Ophthalmologic examination	x									x		
Pulmonary examination[6]	x	x					x		x	x		
Performance score[22]	x	x					x		x	x		
Vital signs	x	x	x	x	x	x	x	x	x	x		
Height [7]	x								x[7]			
Weight	x	x		x	x	x	x	x	x			
Safety laboratory tests[8-9]	x	x[8]		x[9]	x[9]	x[9]	x	x[9]	x	x[8]		
Pregnancy test (if appl.)[10]	x									x		
12 lead-ECG[11]	x			x					x[11]	x		
LVEF echo	x						x		x[12]	x		
Disease assessment imaging[13]	x								x[13]	x		
Tumour marker(s) [14]	x						x		x	x		
Tumour sample tissue availability[23]	x											
Review in-/ex- criteria	x											
Dose assessment	x						x[15]	x[15]	x[15]			
Dispense trial drug[16]		x					x		x			
Afatinib administration		Continuous oral once daily, fasted										
Pharmacokinetics		x[17]	x[17]	x[17]	x[17]							
Adverse events	x	x		x	x	x	x[18]	x	x	x	x	x[19]
Concomitant therapies	x	x		x	x	x	x	x	x	x	x	
Compliance check				x			x		x	x		
Patient diary check			x	x	x	x	x		x	x		
Eligibility for treatment continuation							x		x			
Conclusion of treatment										x		
Conclusion of patient participation											x	
Survival status												x

1 All courses are of 4 weeks duration (28 days). Day 1 of a new course should take place on day 29. Patients may continue on treatment for unlimited courses until the criteria for stopping medication are met (see Section 3.3.4). Visits are performed weekly for the first course. At course 2, visits will take place every 2 weeks (Visit 2 day 8 and visit 4 day 22 are no longer requested). From course 3 onwards, only visits "1" are required.

2 EOT= end of treatment – When the decision is taken to permanently discontinue the study medication, the EOT visit must be performed within 7 days after last administration of afatinib. If the decision is taken at a scheduled visit, the EOT visit will be performed instead of the scheduled visit. Examinations performed at this time may need to be renamed for the actual visit conducted.

3 FU= safety follow-up 28 to 30days after last afatinib administration. With the FU visit the patient will have completed his/her trial participation.

4 OP= observation (post-trial) period. Collection of information on vital status every 3 months. Information could be collected from the patient's notes or by telephone contact. A formal visit is not required.

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5 Before any trial procedure, both the patient and/or parent/legal guardian have to give informed consent/assent according to the local regulatory requirements. At each moment along the trial, the site staff must disclose and discuss any new information that might affect willingness to continue trial participation with the patient and/or parent/legal guardian. For the MTD expansion cohorts/phase II part a high rate of screening failures is expected. Therefore a pre-screening informed consent may be used to allow collection and testing of tumour tissue for ErbB deregulations (see section 3.3.2). Upon confirmation of positivity for selection biomarkers and before to proceed with trial procedures the informed consent/assent for trial entry, as mentioned earlier in this footnote, must be signed.
6 Pulmonary examination must include transdermal O2 saturation at screening, at visit 1 of each course and EOT. It should be repeated as clinically indicated during the trial and may be supplemented by a chest X-ray if clinically indicated.
7 Measurement of height (in cm) will be performed on day1 every other courses.
8 Safety lab tests should not be repeated if previous tests are not older than 48 hours.
9 Safety lab test at visits 2, 3, 4 of courses 1 and 2 to be limited as described in Section 5.2.3.
10 Mandatory for female patients of child bearing potential (post menarchal) within 7 days prior to first treatment and at EOT. To ensure early detection of pregnancy, test might be repeated as necessary during the treatment period depending on the local law.
11 ECG is required at screening, at C1V2, V1 every third course thereafter (i.e. C4V1, C7V1…) and EOT.
12 Left ventricular ejection fraction (LVEF) at screening, at end of course 1 (C2V1 visit) and to be repeated C4V1, every 3rd course thereafter (C7V1…) and EOT.
13 Imaging (CT or MRI for CNS tumours or soft tissue lesions) assessment is to be performed every 8 weeks until progression of disease. In case of objective response, the latter has to be confirmed 4 to 6 weeks after initial OR observation. Consecutive imaging assessment will be performed every 8 weeks. In exceptional cases when patients have been stable on treatment for at least 2 consecutive images (i.e. 16 weeks), imaging intervals may be extended to 12 weeks upon discussion between the investigator and the sponsor.
14 Tumour marker(s) in urine or blood as indicated depending on tumour type (e.g. catecholamines (VMA/HVA, dopamine), NSE in neuroblastoma)
15 Intra-patient dose escalation might be allowed as soon as the next higher dose tier is completed and considered safe (applicable to dose finding part only). A dose reduction can also be applied in case of drug-related toxicity (see Section 4.1.4.3)
16 New kit(s) of trial drug must be dispensed at visit 1 of each course. If needed (e.g. in case a dose adaptation has to be applied during treatment course), new kit(s) of trial drug might be dispensed outside of the planned visit schedule
17 A full PK profile (extensive PK sampling) is to be taken at course 1, day 1: pre-dose before afatinib administration then 1h, 2h, 3h, 4h, 5h, 6h, 8h and 24h after administration and to be repeated at steady state on day8. In exceptional cases where extensive PK sampling is not possible, a limited sampling approach must be applied with blood sampling before, 1h and 3 h after afatinib administration. An additional trough sample is to be taken on day 15 to confirm steady state exposure to afatinib. In addition, trough CSF sampling (from Rickham, Ommaya reservoirs or from lumbar puncture performed for clinical reasons not related to the trial) may be taken on day 8 or later. This CSF sampling is optional. Each trough CSF sample has to be accompanied by a trough plasma sample taken at the same time-point. For further details on time points and sampling volumes, see Section 5.5.2 and Appendix 10.3 .
18 During the dose escalation part, a DLT confirmation fax has to be sent to the sponsor before start of course 2.
19 AE/SAE after the 28-30 days FU period have to be reported only if considered relevant by the investigator.

22 Lansky for patients ≤ 12 years or Karnofsky for patients older than 12 years at time of informed consent
23 Tumour samples must be assessed for ErbB deregulation with start of recruitment into the MTD expansion cohorts/phase II part see Section 3.3.1. For patients with proven genomic, transcriptomic or proteomic ErbB alterations a confirmatory analytical laboratory report has to be provided to the sponsor. Inclusion will be dependent on ErbB deregulation from that time point onwards, for details see Section 4.1.2 and Section 5.6.

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TABLE OF CONTENTS

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ABBREVIATIONS

ADL	Activity of Daily Life
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BA	Bio-Availability
BSA	Body Surface Area
CA	Competent Authority
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CNS	Central nervous system
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical research organization
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DFS	Disease free survival
DILI	Drug Induced Liver Injury
DIPG	Diffuse intrinsic pontine glioma
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic Acid
DoR	Duration of Objective Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event free survival
EGFR	Epidermal Growth Factor Receptor
EM	Ependymoma
EMA	European Medicines Agency
ErbB	Erythroblastic leukaemia viral oncogene homolog of the human EGFepidermal growth factor family of receptors
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set

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FDA	Food and Drug Administration
FDG-PET	Fluoro-2-desoxy-D-glucose positron emission tomography
FF tablet	Film-Coated Tablet
FISH	Fluorescence In Situ Hybridation
FU	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration
GGT	Gamma-Glutamyl Transferase
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HER2	Human epidermal growth factor receptor 2
HGG	High grade glioma
HIV	Human immunodeficiency virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPC	Human Pharmacology Centre
HPLC-MSMS	High performance liquid chromatography tandem mass spectrometry
HVA	Homovanillic acid
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IRB	Institutional Review Board
ISF	Investigator Site File
ITCC	Innovative Therapies for Children with Cancer
i.v.	intravenous
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
Mab	Monoclonal antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
MIBG	Meta-Iodbenzylguanidine
MIC2	Synonyme for CD99 (Cluster of differentiation 99)
µm	Micrometer
MRI	Magnetic resonance imaging
MST	Medical Subteam
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
NSE	Neuron specific enolase
OPU	Operative Unit
OR	Objective Response
ORR	Objective response rate
OS	Overall Survival
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PFS	Progression Free Survival
P-gp	P-glycoprotein

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PK	Pharmacokinetics
PNET	Primitive neuroectodermal tumour
PR	Partial response
RECIST	Response evaluation criteria in solid tumours
RMS	Rhabdomyosarcoma
RNA	Ribonucleic acid
RPIID	Recommended Phase II dose
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time from (last) dosing to the maximum measured
TMM	Team Member Medicine
TMW	Trial Medical Writer
TMZ	Temozolomide
TSAP	Trial Statistical Analysis Plan
TTP	Time to Progression
ULN	Upper Limit of Normal
VMA	Vanillylmandelic acid
WBC	White blood cells
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Afatinib (Giotrif®, Gilotrif®) is an ErbB-family blocker. It binds to and efficaciously blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4. It was approved by EMA in 2013 for the indication of "GIOTRIF monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s)" and for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002280/WC500152392.pdf) and by US FDA as "GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test" and for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy.
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/201292s010lbl.pdf).

Neuroectodermal tumours and their aetiology: The neural crest which consists of a unique transient embryonic cell population was initially identified by the Swiss embryologist in 1868, as a group of cells localized in between the neural tube and the epidermis in the vertebrate embryo. Neural crest cells after a phase of epithelial mesenchymal transition and extensive migration, settle down in different parts of the body to contribute to the formation of a plethora of different tissues and organs. Neural crest derivatives originate from four major segments of the neuraxis: Cranial, cardiac, vagal, and trunk neural crest. The cranial neural crest gives rise to the majority of the head connective and skeletal structures, nerves and pigment cells (R13-0505, R13-0511).

An extensive line of research has revealed that 'neuregulins', a family of EGF-like ligands, are keys to nervous system development in mice (R13-0502, R13-1286). ErbB signalling also plays an important role in neural crest-derived melanophore differentiation during embryogenesis in zebra fish suggesting that this signalling system is conserved over species. Indeed, the picasso mutant zebra fish which lacks most metamorphic melanophores results from a homozygous deletion of the ErbB gene erbb 3b, which encodes an EGFR-like receptor tyrosine kinase (R13-0513).

With a limited capacity for self-renewal and a wide range of differentiation fates, neural crest cells bear many of the hallmarks of stem cells and persist throughout embryonic and adult development. These stem cells bear the potential for tissue-specific repair. Overall many ontogenetic studies have established the crucial role of ErbB-family signalling on neural crest cell development and homeostasis and it is thus not surprising that deregulation of the ErbB network can lead to proliferation and survival defects and thus can result in cancer.

The ErbB pathway: Ontogenetically the ErbB pathway is highly conserved (R13-1286) and was associated with ectodermal and also with mesenchymal development at certain stages. Neuroectodermal tumours or tumours of neuroepithelial tissue per WHO classification (R14-

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1466) are originally derived from the ectoderm of the early embryo that gives rise to the central and peripheral nervous systems and comprise malignant neoplasms including a large variety of paediatric and adult malignancies (R13-1189, R13-1286, R13-0502, R13-0650) . These lineages give rise to astrocytomas, glioblastoma multiforme including diffuse intrinsic pontine glioma (DIPG) and high grade glioma (HGG), ependymomas (EM), medulloblastomas, primitive neuroectodermal tumours (PNET) and neuroblastomas (R13-1286). For these tumours and also for rhabdomyosarcoma (RMS), a mesenchymal tumour, ErbB deregulation has been sparsely described in the literature. A recent study on ectomesenchymomas which are believed to arise from the widely distributed, pluripotential, migrating neural crest cell, or remnants thereof, the so-called ectomesenchyme, showed that these pluripotential cells form not only neuroectodermal tissues but also various mesenchymal tissues. Aside from primitive neuroblastic/neuroectodermal elements, mesenchymal elements which usually consist of rhabdomyosarcoma tissue (RMS) can be found (R13-4400).

For years various molecular profiling programmes enriching trials with patients of certain molecular subtypes (R14-4092) have been integrated into adult oncology clinics. Similar programmes like MOSCATO (R14-4191; R14-4189) or INFORM (R14-4190; R14-4233; R14-4104) are now also being implemented into paediatric oncology and reshape the trial scene (R17-1692; R17-1805). The latter allow more targeted patient selection into future paediatric clinical trials with targeted agents. In line with the above, clinical trial 1200.120 will recruit paediatric patients suffering from tumours with ErbB pathway deregulations regardless of tumour histology into the MTD expansion cohorts/Phase II part.

Tumours to be considered for treatment within this trial are recurrent or refractory

1. HGG
2. DIPG
3. Low grade astrocytomas
4. Neuroblastoma
5. EM
6. Medulloblastoma/PNET
7. RMS
8. Other solid tumours with known ErbB pathway deregulation regardless of tumour histology

This group of tumours shares common aetiological features as described above and a poor prognosis once refractory or recurrent disease is diagnosed, i.e. the tumours progressed or relapsed despite initial anti-cancer treatment. A high unmet medical need requires new treatment options. Based on afatinib's mode of action and the descriptions of ErbB pathway deregulations in paediatric tumours, it is expected that afatinib as an irreversible ErbB family blocker renders its maximum therapeutic effect in the condition of neuroectodermal paediatric tumours, rhabdomyosarcomas and other solid tumours with ErbB deregulation and may add a valuable choice to the treatment armamentarium of these tumours.

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A brief description of all diseases is included below. For further details on clinical tumour presentation, diagnosis and treatment please refer to Table 10.5:1, Appendix 10.5.

High grade gliomas (HGG) include astrocytomas with histological documentation of either a WHO III or IV pathology, either of pure astroglial or mixed glial neuronal lineage, radiographically diagnosed diffuse intrinsic pontine gliomas (DIPGs) and others. Median age at diagnosis varies between 4-8 years (R13-0762, R13-0393). Malignant high grade gliomas account for 15% of all paediatric CNS tumours. Utilizing multimodality treatment with surgery, radiotherapy and chemotherapy, the 5-year survival increased over time from 47% (1975-1984) to 57% (1985-1994). At the time of relapse or recurrence treatment regimen to be considered are largely experimental. Prognosis and outcome tremendously deteriorate upon relapse. Gruber et al reported survival times of 4-6 months from relapse (R13-1360). Responses are very infrequently observed. Narayana et al report 16.7% of their patients experienced a partial response after the first MRI (R13-0403). No complete radiographic responses were seen. New treatment options combining the EGFR-targeting MAb nimotuzumab and radiotherapy, or using BRAF inhibitors and others are currently under investigation and show interesting results (R13-4931, R17-1805).

Diffuse intrinsic pontine glioma (DIPG) due to its location is one of the most devastating paediatric malignancies and one for which no effective therapy exists (R12-3163). Incidence rates are still largely unclear. Reports vary with between 5-10% (R13-0421) and 10-20% of all brain tumours (R13-0405) in children being DIPGs. Children are diagnosed between ages 5 to 10 years (R13-5168). The use of hyper-fractionated radiotherapy, pre-irradiation chemotherapy, adjuvant chemotherapy, high dose chemotherapy, concurrent chemo-radiotherapy and radio-sensitizers has not increased long-term OS (R12-1172). The 2-year OS-rates from relapse were 3.6% and 2.5%, respectively (R13-1355). Several AKT/mTOR and MEK pathway inhibitors are currently under clinical trial investigation (R17-1691; R17-1690).

Astrocytoma (low grade) occurs with 2 peaks at median ages of 5 years and 12 years. Despite an increase in incidence from $4/10^6$ to $19/10^6$ over the past 30 years (R13-0762), 5-year survival improved and was between 70%-80% (R12-3186; R13-0360, R13-0762). Overall these tumours have a very good prognosis (P13-01488). Grade I and II astrocytomas are curable by gross total resection. Recurrence-free survival is greater than 95% at 10 and 20 years and extent of resection is strongly correlated with survival. Upon recurrence of disease or progression, however, treatment is challenging and several studies reported 4-year PFS and OS-rates of 17% (95% CI, 1 to 33%) and 71% (95% CI, 43 to 100%), partial or minimal response in only 12% of the patients, stable disease not requiring additional treatment in 30% of the patients (P13-01488).

Neuroblastoma is the most frequent extra cerebral solid tumour in children with a total of 1240 children newly diagnosed in Germany over the past 10 years and 650 patients/year in the US (R13-0393; R13-0762). The peak incidence is observed in children between 0-5 years of age (R13-0393). Patient survival is dependent on age at diagnosis with a better prognosis in younger children (R13-0393). Multimodality treatment includes chemotherapy combinations, radiotherapy, MIBG treatment, high dose chemotherapy with bone marrow

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rescue and immunotherapy with anti-GD2 antibodies. Despite all these treatments, high risk stage patients with metastatic and recurrent disease face a 5-year survival of only 30-40% (R13-0491, R13-1190, R13-0762, R13-0468). According to Cole et al, high-risk neuroblastoma accounts for 12% of paediatric cancer deaths but only for 4% of all paediatric cancer diagnoses. New therapies are clearly needed (R13-0472). Lately encouraging results were published for the ALK inhibitor crizotinib in a subset of neuroblastoma patients carrying ALK oncogenic mutations (R13-5080).

Ependymoma (EM) is the third most common neuroepithelial tumour in children (R13-0435). The incidence of ependymoma lies between 0.2 and 0.34/100000. It comprises approximately 9% of all childhood brain tumours with approximately 200 cases per year in the US (R12-1174, Central Brain Tumour Registry of the United States (CBTRUS) 2011). Median age at diagnosis ranges from 51 to 71 months (R13-1648, R12-1159, R12-3173, R13-1524) and 25-40% are diagnosed in children less than 3 years of age. The majority of paediatric ependymomas is of intracranial location. This tumour remains difficult to treat due to the high frequency of chemotherapy and radiation resistance (P13-04039). Surgery, if feasible, remains the approach with the most curative potential. Patients frequently experience multiple recurrences with a median 5-year PFS-rate of 18–55% (R13-0410). Zacharoulis et al. report that survival is very poor (0%-25%) after relapse post primary treatment (R13-0388). Data for chemotherapy of recurrent ependymomas are limited to few small retrospective series and results vary significantly as do PFS and OS (R13-0412; R13-0418). Median Time to Progression (TTP) in several series is between 4.4 months and 10 months (R13-0388). Recent molecular characterization ependymoma subtypes may give way to new and more effective targeted treatments (R17-1689).

Medulloblastoma and primitive neuroectodermal tumours (PNET): Medulloblastomas are derived from primitive neuroectodermal cells and as such are grouped together with PNETs occurring in the CNS. They account for 10-20% of primary CNS neoplasms (R13-0388). Overall the incidence increased from $4/10^6$ to $18/10^6$ over past 30 years (R13-0762) and in the US an incidence of 462 patients/year with an age peak between 0-4 years is described for both tumours (R13-0393). Standard treatment includes surgery, radiation and chemotherapy. Although the five-year survival increased over time, and was 80% in Germany and 50-55% (1985-1994) in the US per SEER database (R13-0393, R13-1190, R13-0414), patients with metastatic or recurrent disease have a 5-year survival of approximately 20%. New treatment options targeting the Wnt and sonic hedgehog pathway, like LDE 225 are currently under investigation in medulloblastoma (R13-4458).

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood, accounts for approximately 3.5% of the cases of cancer among children aged 0 to 14 years and 2% of the cases among adolescents and young adults aged 15 to 19 years (R13-0392). The incidence is 4.5 per one million children and 50% of cases are seen in the first decade of life (R13-1401). Like other sarcomas RMS tumours are molecularly diverse. Treatment is largely relying on chemotherapy (R13-1190, R13-0432), surgery and radiotherapy. The presence of distant metastases defines high-risk RMS which has a poor prognosis and treatment options are very limited. Patients with primary metastatic disease have a 5-year EFS of 20-30% with conventional treatment despite chemotherapy, surgery and radiotherapy.

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Tumours with known ErbB pathway deregulation regardless of tumour histology will be included into this trial. Various molecular profiling programmes have been integrated into adult oncology clinics aiming at enriching trials with patients of certain molecular subtypes (R14-4092). Similar programmes are now being implemented into paediatric oncology, e.g. MOSCATO (R14-4191; R14-4189) or INFORM (R14-4190; R14-4233; R14-4104) and reshape the trial scene (R17-1692; R17-1805). These programmes, like the biomarker prevalence study conducted in parallel to the dose finding part of this trial (c09990672-01) aim at more targeted patient selection into paediatric oncology clinical trials and may support early inclusion of patients suffering from tumours with known ErbB pathway deregulation.

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1.2 DRUG PROFILE

Afatinib (BIBW2992) is a small molecule, selective and irreversible ErbB family blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4. Due to its wide spectrum of inhibition across the ErbB family and the irreversible nature of this inhibition, afatinib belongs to the new generation ErbB TKIs.

Afatinib is being developed in mutation positive non-small cell lung cancer (NSCLC), and head and neck squamous cell carcinoma (HNSCC). Marketing Authorisations have been granted by several regulatory authorities including the US FDA and the European Commission in patients with non-small cell lung cancer (NSCLC) with (certain) activating EGFR mutation(s) and for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib has a moderate to high apparent clearance (CL/F= 1050 mL/min for single dose treatment and 898 mL/min at steady state) and a high apparent volume of distribution (Vz/F= 1940 L for single dose treatment and 2770 L at steady state), suggesting that it is highly distributed out of the blood into tissues. However, values for CL/F and Vz/F should be considered with caution as the absolute bioavailability (F) of afatinib in humans is not known. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken

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simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for AUC0-∞ and Cmax when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % (AUC0-∞) and 22 % (Cmax), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators, for further information see Appendix 10.4 .

Afatinib exposure is expected to be comparable for the film-coated tablets and the capsule and solvent for oral solution (both formulations are to be used in this trial).

In pre-clinical studies afatinib is not irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

In adult cancer patients, the choice of the starting dose of 40 or 50 mg daily with afatinib monotherapy was based on the expected balance between patient's tolerability and the required level of target inhibition. A dose of 40 mg daily has been used in patients with NSCLC or HNSCC not previously exposed to EGFR-targeted treatments. A dose of 50 mg

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has been largely limited to EGFR TKI pre-treated NSCLC patients with tumours that are expected to harbour resistant mutations.

In clinical studies, the pattern of AEs was as expected from EGFR inhibitors, including predominantly GI and dermatological AEs which were dose-dependent. Early and effective management of these AEs is mandated in ongoing and forthcoming clinical trials with the opportunity to reduce the dose where appropriate. The typical AEs associated with afatinib treatment are diarrhoea (which in severe cases may lead to dehydration with or without renal insufficiency) and effects on skin and its appendages: rash/acne/folliculitis, paronychia, pruritus, dryness and eczema. Besides diarrhoea, GI AEs include stomatitis, mouth ulceration, dry mouth, and oral pain. Other AEs seen in clinical trials of afatinib include general disorders such as fatigue/asthenia; mucosal inflammation; respiratory disorders such as epistaxis and rhinorrhoea; eye disorders such as conjunctivitis and keratitis.

Hepatic failure, including fatalities, has been reported during treatment with afatinib in less than 1% of patients.

Afatinib does not appear to have an adverse effect on cardiac contractility or QTcF parameter. The frequency of interstitial lung disease (ILD) -like AEs in all afatinib treated patients was low (approximately 1.5%) and similar to that observed with other EGFR TKIs (c01802941). Considering reports of suspected cases of ILD on afatinib, afatinib trials exclude patients with known pre-existing ILD from treatment with afatinib and request assessment of all patients with acute onset and/or unexplained worsening of pulmonary symptoms (see Table 4.1.4.3:1).

Afatinib has been combined with various anti-cancer agents including chemotherapy and targeted treatments. The pattern of AEs displayed in combination was consistent with the respective monotherapy safety profiles and tolerable doses of afatinib in these combination regimens varied between 20 to 50 mg (c01802941).

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2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Several Phase I or Phase II studies on EGFR and/or HER2 inhibitors in paediatric cancers have been conducted (R10-4924, R10-4926, R11-4989, P11-14451, R10-4917, R11-5022, R10-4960, R10-4920, R11-5046, R11-4988) or are still ongoing (R10-4921, R11-5021). These trials established the safety profile, pharmacokinetics and MTDs for gefitinib (Iressa ®) and erlotinib (Tarceva®, OSI-774) and lapatinib in children (R11-5022, R10-4926, R11-4989). Overall, gefitinib, erlotinib and lapatinib were reported to be well tolerated in children, with a safety profile similar to that observed in adults and paediatric MTDs comparable with those associated with anti-tumour activity in adults (R11-5022, R10-4926, R11-4989).The clinical pharmacokinetics of gefitinib in children were similar to those observed in adults (P11-14451, R11-4987). Some signs of clinical anti-tumour activity were observed (R11-4989, R11-5022).

Although the ErbB pathway ontogenetically is highly conserved (R13-1286) and is associated with ectodermal and mesenchymal development at certain stages (R14-1466), and despite ErbB deregulation being sparsely described in the literature, none of the above trials was dedicated to the in-depth assessment of the role of ErbB family deregulation neither (i) in the aetiology of paediatric cancers nor (ii) trying to make use of ErbB deregulation for the development of targeted treatment options.

Limited reports of clinical efficacy for ErbB pathway inhibitors in paediatric cancer patients may be due to the following: (1) ErbB network aberrations observed in the various tumour entities tested are contributing to tumour proliferation but are not essential to maintaining tumour growth. As most of these clinical studies were not conducted in pre-selected patients, it is possible that signs of clinical efficacy were diluted in the total patient population. (2) The tested drugs may only partially silence the ErbB network. Indeed, the mechanism of ErbB signalling relies on ligand-induced stabilization of homo- or heterodimers formed by the various ErbB-receptor tyrosine kinases. Currently available ErbB directed therapies do not inhibit all ErbB-family receptor members and possibly fail to block both partners in an active receptor complex.

ErbB-family blockers, like afatinib, bind to and block signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4. This complete and irreversible blockage by afatinib may achieve greater efficacy than reversible inhibitors with selective ErbB1 (EGFR) and/or ErbB2 (HER2) inhibitory activity.

The proposed trial 1200.120 attempts to address the following questions:

1. Can afatinib be safely administered to paediatric patients with neuroectodermal tumours, rhabdomyosarcomas and/or solid tumours with known ErbB pathway deregulation regardless of tumour histology?

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2. Will the observed degree of ErbB receptor expression render the tumour types included in this trial a suitable condition for treatment with the ErbB family blocker afatinib? Thus will deregulated ErbB receptors be drugable targets, and as such will patients treated with afatinib show increased benefit from treatment?

3. Will patients' benefit obtained from treatment with afatinib be considered meaningful by experts in the field of paediatric oncology?

4. Will the biomarker selected patient population included in the MTD expansion cohorts/phase II part render a further biomarker driven development suitable and beneficial for patients?

2.2 TRIAL OBJECTIVES

The objective of the **dose finding part** is to determine the maximum tolerated dose (MTD), safety and pharmacokinetics of afatinib. The MTD of afatinib as single agent will be determined in the paediatric patient population across all applicable tumour entities, based on the occurrence of dose limiting toxicities (DLTs).

The **MTD expansion cohorts/Phase II part** will provide insight into the clinical anti-tumour activity of afatinib, i.e. efficacy of afatinib evaluated by objective response (OR), duration of objective response (DoR), progression free survival (PFS) and more data on safety and pharmacokinetics in a larger number of patients suffering from HGG, DIPG, EM and other solid tumours with ErbB pathway deregulation regardless of tumour histology will be generated.

In case the observed degree of efficacy in any of the above mentioned tumour indications within this phase I/II trial renders further development of afatinib in paediatrics suitable, additional trial(s) with single agent or combination therapy may proceed.

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2.3 BENEFIT - RISK ASSESSMENT

Standard treatment regimens for newly diagnosed neuroectodermal tumours, rhabdomyosarcomas and/or other tumours for which ErbB deregulation may play a role, do exist and result in acceptable disease free survival periods. Once patients develop recurrent/refractory disease, however, treatment options are limited and outcome dismal. The European Paediatric Medicine Regulation implemented by EMA in 2006 ((EC) No 1901/2006) (R09-2583) and Written Requests issued by US FDA attempt to improve access to new treatment modalities for paediatric patients, but little has changed for paediatric oncology (R13-1146).

At the start of this trial no safety or efficacy data for afatinib in paediatric patients existed, but in analogy to observations made for the reversible EGFR-inhibitors gefitinib and erlotinib in children, the safety profile of afatinib in paediatric patients was not expected to deviate from what was observed in adults. The safety and efficacy of afatinib is well described in adults. The known side effects of afatinib in adults are similar to EGFR inhibitors and largely consist of gastrointestinal side effects, mostly diarrhoea and stomatitis and skin related side effects. Side effects proved to be manageable with early and proactive concomitant treatment. Implementation of similar measures to control afatinib related side effects in this paediatric trial are expected to limit early treatment discontinuations due to toxicity, and thus positively impact compliance and efficacy. The dose finding part of this trial was completed; the MTD was established in children between ≥2 years to <18 years and the paediatric safety data were consistent with the known safety profile of afatinib in adults (c09990672-01).

The proposed paediatric phase I/II trial is following suggestions made by PDCO during the review of afatinib's initial paediatric development plan and the FDA's written request issued April 2017 (ra00865826). The MTD expansion cohorts /Phase II part will accrue patients with HGG, DIPG, EM and any other solid tumour with ErbB deregulation as defined in sections 3.3.2 and 5.6. In addition patients with proven genomic, transcriptomic or proteomic ErbB alterations in their tumours will be recruited to an exploratory cohort. Such biomarker driven, histology agnostic development is innovative for paediatric oncology and only little precedence exists in adults (SHIVA (R14-4174), MOSCATO (R14-4191; R14-4189)). More recently, however, genomic screening programs were implemented in paediatric oncology (INFORM (R14-4190; R14-4233; R14-4104)), allowing patients' early assignment to targeted treatment regimen. To enable assessment of afatinib's anti-tumour activity in this biomarker driven, largely histology agnostic approach, nevertheless a defined/ small number of patients per indication needs to be included (ra00865826). Assessment of antitumour activity for afatinib at the end of this phase I/II trial will determine future trial activities in close alignment with regulatory agencies and specialists in the field.

The trial medication is available as oral formulations, i.e. film coated tablets of various strengths for older children and an oral liquid formulation at 4 mg/ml dose strength for younger children. These oral formulations will grant patients and their parents the advantage of out-patient treatment and increase flexibility to move on with their lives. A resulting increase in quality of life, with hopefully increased efficacy should impact positively on treatment compliance.

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The proposed treatment with the ErbB family blocker afatinib targets a deregulated ErbB pathway. If the latter proves as a suitable target in this phase I/II trial, afatinib may become a valuable choice in the treatment armamentarium of children suffering from recurrent/refractory tumours with ErbB deregulation. Although biomarkers of ErbB deregulation were successfully identified in the biomarker prevalence study, which was conducted outside of this clinical trial (c09990672-01), it still has to be established if the observed degree of efficacy in paediatric patients suffering from certain tumour indications (HGG, DIPG, EM) and other solid tumours with ErbB pathway deregulation or proven genomic, transcriptomic or proteomic ErbB alterations, render afatinib a suitable agent for further clinical evaluation.

Finally, even if the hypothesis described above cannot be confirmed, the phase I dose finding part has established the maximum tolerated dose for afatinib in children and safety data in children will be available to the paediatric oncology community (c09990672-01).

As this trial is a "first in child" trial with afatinib, a data monitoring committee (DMC) will continuously monitor the benefit /risk for all patients participating in the trial (for details, refer to section 3.1.1). For an early detection of rare but potential toxicities, the patients will also be assessed for the following:

- Potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety. For details refer to Section 5.2.2.

- Keratitis and ulcerative keratitis that have been reported following treatment with currently approved EGFR inhibitors for cancer. Although rarely observed with afatinib thus far, special safety precautions are provided in Section 4.2.1.

- Left ventricular dysfunction that has been associated with HER2 inhibition in adults. Although stringent monitoring in adults did not demonstrate any impact of afatinib on cardiac function (c01802941), LVEF will continuously be monitored in this trial in children and precautions are given in Section 4.2.1.

- Interstitial lung disease (ILD) is a rare and serious (potentially fatal) AE that has been reported with EGFR TKIs. Patients with known ILD are therefore excluded from trial participation. In case of suspected ILD on treatment please refer to Section 4.2.1.

Following the determination of a safe dose of afatinib in paediatrics, the goal of this study is to bring a new and efficacious treatment to paediatric patients who suffer from solid tumours with ErbB deregulation. Considering the (i) well established side effect profile in adult patients, (ii) the established concomitant treatment algorithms for afatinib related side effects, (iii) close safety monitoring by a DMC, (iv) participating paediatric phase I sites with experience in new drug development and (v) planned consultations with regulatory agencies at decision points (see figure in Appendix 10.1), the expected benefits from afatinib treatment for the paediatric patients will outweigh its risks.

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I/II open-label, dose escalation study to determine the MTD of afatinib as single agent and to assess its anti-tumour activity in children with recurrent or refractory malignant neuroectodermal tumours, RMS and/or other solid tumours with ErbB pathway deregulations.

This phase I/II trial is connected to a translational biomarker prevalence study which is informative for the identification of possible biomarkers which are considered suitable for inclusion of patients in the MTD expansion cohorts/Phase II part. The biomarker prevalence study was conducted outside of this clinical trial. For details refer to Section 2.1 and Section 5.6. Results of the biomarker prevalence study are partially reported (c09990672-01).

This clinical trial has 2 parts (see Figure 3.1:1):

1. A dose finding part
2. A biomarker specific MTD expansion cohorts/Phase II part

The trial will end when the last patient has completed the 28-30 day safety follow-up (FU) visit. For additional information on trial termination, see also Section 3.3.4.2 and Section 8.6.

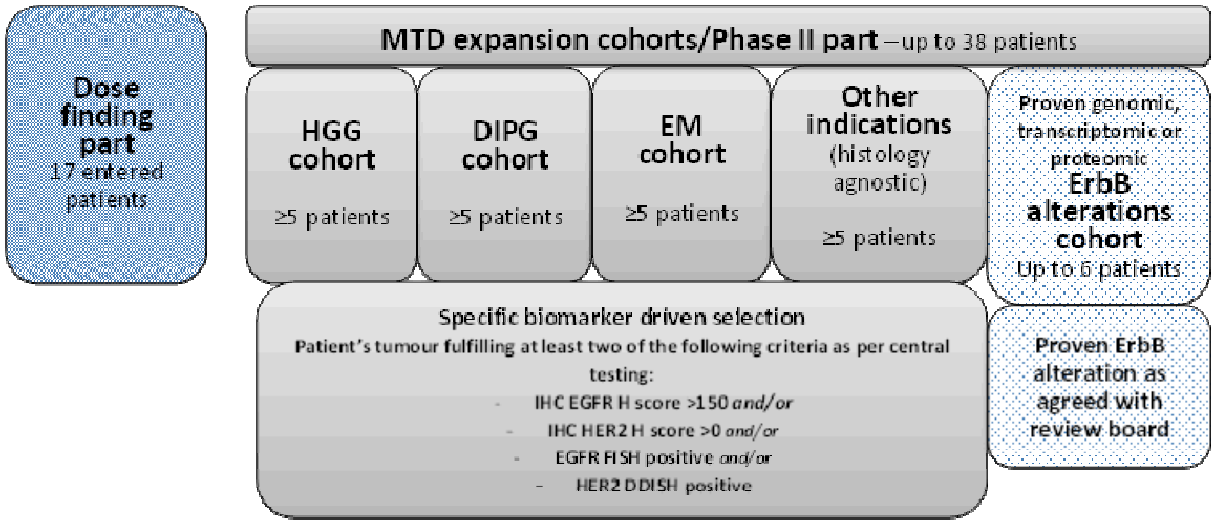

Figure 3.1:1 Trial design

1. **Dose finding part**: Accounting for the low incidence of each paediatric tumour entity within the above group and the heterogeneity of ErbB pathway deregulations described, the dose finding part of the trial will be conducted in paediatric patients with recurrent/refractory neuroectodermal tumours, and RMS, for whom no further treatment option exist and who are likely to derive benefit from treatment as their tumours are known to show ErbB deregulation in literature. In addition, patients with other solid tumours (regardless of histology) with known ErbB deregulations,

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assessed by institutional standards, may be included into this part of the trial. All of these patients will be included to determine the MTD. A rolling-6 design will be used for patients' assignment to dose cohorts (see Table 4.1.4.1:1).

Patients in Phase I dose finding part will undergo retrospective testing for ErbB deregulation.

This part was completed (c09990672-01).

2. **MTD expansion cohorts/Phase II part**: Once the MTD is determined, patients will be tested and recruited only if they fulfil at least two of the following biomarker criteria (i) EGFR gene amplification (FISH) *and/or* (ii) HER2 gene amplification (DDISH) *and/or* (iii) EGFR protein expression (membrane staining): H-score > 150 *and/or* (iv) HER2 protein expression (membrane staining): H-score > 0 (see section 5.6). A minimum of 5 patients in each of the four following cohorts, i.e. HGG, DIPG, EM and a mixed histology agnostic cohort of patients with refractory tumours, will be accrued to confirm a safe recommended Phase II dose (RPIID) and to be assessed for response. An exploratory cohort of a maximum of 6 patients with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined above will also be included. This part of the trial will allow the collection of further safety and PK data to limit failure due to dosing issues in further clinical development, but also give insight if the "targeted" patient selection increases the level of clinical efficacy.

3.1.1 Administrative structure of the trial

The coordinating investigator is an expert in paediatric oncology with experience in new drug development. The coordinating investigator has been designated by Boehringer-Ingelheim and will sign the clinical trial report. Selected investigators from the network of "Innovative Treatments for Children with Cancer (ITCC)" and other participating investigators are likewise experts in the paediatric oncology with experience in this type of trial and investigations and in new drug development.

A steering committee including the coordinating investigator, selected ITCC investigators in different EU countries, non-ITCC in non-EU countries and BI representatives, will monitor the study on a regular basis (recruitment issues, data quality, decisions on dose escalation, etc.).

A data monitoring committee (DMC) will be appointed by BI. The DMC will consist of an independent, multidisciplinary group who have expertise in paediatric oncology and new drug development trials in children. A statistician must be part of this group. The DMC's responsibility will be the continuous assessment of the trial data to ensure the overall benefit/risk of the patients treated and to monitor the quality of the trial. The DMC will advise BI and the steering committee about the conduct of the trial and the integrity of the data. Regular safety review and benefit/risk assessment will be performed by the DMC as described in the DMC charter. The latter defines but is not limited to e.g. a regular DMC meeting schedule, adhoc meetings in case of unexpected SAE, regular AE listings to be provided by the sponsor, etc.. The DMC will guide the sponsor throughout the trial.

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3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Since the implementation of the Regulation (EC) No 1901/2006 of the European Parliament (R09-2583) numerous paediatric development programs on new oncology compounds started but Paediatric Investigation Plans (PIPs) were driven by adult indications, which were not waived for children, rather than by a paediatric unmet medical need (R13-1146). Where pursued, paediatric development is frequently hampered by an early focus on rare indications with lack of feasibility of patient recruitment. In contrast, trials set up too broadly provided scattered evidence of clinical activity but were neither evaluable for effect size per indication examined, nor for a biomarker enriched population, as biomarkers were frequently introduced retrospectively to help explaining an observed effect. Different compounds targeting similar pathways in relatively few paediatric cancer patients compete for patient accrual into clinical trials. If no clear working hypothesis/rationale for the assessment of a certain compound in a particular population is generated, it is difficult to convince cooperative groups and patients' guardians to recruit into these trials. BI proposes to conduct a Phase I trial in patients with relapsed and or poor prognostic neuroectodermal tumours, which are embryologically and ontogenetically derived from the same germinal sheet, and for which therefore some rationale for ErbB deregulation in tumour genesis can be hypothesized and evidence in the literature exists. In addition, the dose finding part of this trial allowed to include patients with solid tumours (regardless of histology) with known ErbB pathway deregulations, assessed by institutional standards– this part is completed (c09990672-01). The above described paediatric patients don't have further treatment options outside of clinical trials, but are likely to derive benefit from treatment with the ErbB family blocker afatinib as their tumours are known (i) to show ErbB deregulation per literature review , or (ii) demonstrated ErbB deregulation by institutional standards. Patients in the MTD expansion cohorts/Phase II part will be recruited based on ErbB pathway deregulations, defined in the biomarker prevalence study (c09990672-01), see also Section 5.6. With the proposed design, three questions can be addressed at the same time: (i) identifying the right dose during the dose finding, (ii) hitting the right target, and (iii) the impact of targeted patient selection on efficacy. The basket approach will address feasibility of patient recruitment and the biomarker driven patient selection will address unanswered questions on ErbB deregulation. For patients' benefit refer to Section 2.3.

Dose finding Part: A rolling 6 design will be used to determine the MTD. The MTD will be assessed by DLT as described in Table 4.1.4.1:2. The MTD will be determined as the highest dose at which no more than 1/6 patients experienced DLT. The rolling 6 design was chosen to limit the waiting period for paediatric patients seeking treatment, as depicted below.

MTD expansion cohorts/Phase II part will recruit a minimum of 5 patients in each of the four disease specific cohorts for HGG, DIPG, EM and other solid tumours fulfilling ErbB biomarker selection criteria (see Section 3.3.2) and an exploratory cohort of patients with proven genomic, transcriptomic or proteomic ErbB alterations. Efficacy will be assessed by objective response (OR) and the OR rate must be considered meaningful by experts in the field of paediatric oncology and regulatory agencies to pursue further clinical development.

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Tumour material from all patients entered into this clinical trial must be available for retrospective testing of an ErbB pathway deregulation (for DIPG in dose finding part, see section 3.3.2) or prospective patient screening into the MTD expansion cohorts/Phase II part.

Intra-patient dose escalation: No clear exposure-efficacy correlation for afatinib has been identified in adult cancer patients yet. Conventional dosing in oncology trials is based on the MTD, or a recommended Phase II dose close to the MTD, dependent on overall safety. Treatment at lower dose tiers may be hampered by a presumed lack of efficacy. Assessment of the MTD or the recommended Phase II dose in oncology trials is based on a frequency of patients with DLTs. Trial 1200.120 will allow intra-patient dose escalation. As soon as the next higher dose tier is considered safe by standard DLT incidences in course one, patients of the lower dose tier, who benefit from treatment may resume treatment at the next higher dose. Although these patients will not be counted into MTD dose cohorts – see rolling 6 design- the safety database at the MTD level/ higher dose tiers and hopefully patients' benefit from participation in Phase I dose finding will be increased.

This part has been completed (c09990672-01).

3.3 SELECTION OF TRIAL POPULATION

17 patients were treated in the dose finding part to determine the MTD according to a rolling 6 design Skolnik et al (R12-4744). Once the MTD was determined, MTD expansion cohorts/Phase II part will include up to 38 additional patients who must be evaluable for OR. It is expected that up to 550 patients will need to be screened to treat 55 patients who will be evaluable for MTD/OR in the trial.

About 30 trial sites in EU/US/Canada are expected to recruit in this trial. The sites will have experience in paediatric oncology and in new drug development. All sites are willing to deliver tissue samples from recruited patients.

A log of all patients included into the study will be maintained in the ISF at the investigational site irrespective of whether they commenced trial drug or not.

The MTD expansion cohorts/Phase II part will provide biomarker specific efficacy data to establish proof of concept of anti-tumour activity of afatinib in ErbB deregulated paediatric cancer patients.

3.3.1 Main diagnosis for study entry

The proposed Phase I/II trial will include paediatric patients with refractory or recurrent HGG, DIPG, lower grade astrocytoma, neuroblastoma, ependymoma, medulloblastoma and PNET, rhabdomyosarcoma (R13-0506, R12-3164), and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology.

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3.3.2 Inclusion criteria

Phase I dose finding part

1. Patients with a histological diagnosis of high grade glioma (HGG), diffuse intrinsic pontine glioma (DIPG), low grade astrocytoma, medulloblastoma/PNET, ependymoma (EM), neuroblastoma, rhabdomyosarcoma and/or patients with other solid tumours (regardless of histology) but with known ErbB pathway deregulation
2. Patients must have recurrent or refractory disease following at least one prior standard treatment regimen
3. Patients aged between ≥2 to < 18 years*
4. Patients must have recovered (to CTCAE grade 1 or baseline) from any acute toxicity resulting from any prior anti-cancer treatment (except alopecia)
5. No effective conventional therapy exists
6. Patient assent and parent(s)/legal guardian(s)' written informed consent that is consistent with local law and ICH-GCP guidelines
7. Archival and/or fresh tumour tissue available. For DIPG, if the latter is not available, biopsy data on tumour histology and tumour profiling (if applicable) must be made available
8. Performance status: Lansky ≥ 50% for patients ≤ 12 years of age or Karnofsky ≥ 50% for patients older than 12 years of age assessed within two weeks prior to enrolment
9. Patients with CNS malignancies must be neurologically stable for at least 7 days before inclusion into the trial as per investigator judgement
10. Patients, both males and females, with reproductive potential (girls post menarche and males after 1st ejaculation) and sexually active must agree to practice highly effective contraceptive measures for the duration of study drug therapy and for at least 28 days after completion of study drug therapy (see Section 4.2.3.3 for highly effective contraceptive measures)
11. Patients must be able and willing to swallow/take afatinib orally once daily (tablets or oral solution) as per investigator judgement
12. LVEF ≥50%

* In special cases where a patient / guardian(s) signed a pre-screening consent when the patient was 17 years old and the patient turns 18years before the trial consent was signed, the patient can be included in the trial.
In any case, the rate of patients >18years at treatment start must not exceed 19% of the whole trial population

Inclusion criteria for MTD expansion cohorts/ Phase II part:

- Inclusion Criterion 1: Patients with HGG, DIPG, EM and other solid tumours than aforementioned which fulfil at least two of the below criteria:

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- EGFR gene amplification (FISH): Either EGFR/Cen7 ≥ 2.0 or ≥10% of cells with ≥15 copies or ≥40% of cells with ≥ 4 copies or gene cluster in ≥10% of cells *and/or*
- HER2 gene amplification (DDISH): Her2/CEP17 ≥ 2.0 *and/or*
- EGFR protein expression: H-score > 150 (membrane staining) *and/or*
- HER2 protein expression: H-score > 0 (membrane staining)

Inclusion will be based on biomarker assessment prior to inclusion, as detected by central laboratory analysis of tumour biopsy material

- Inclusion criterion #3: Patients aged between ≥1 to < 18 years
- Inclusion criterion #7: Archival and/or fresh tumour tissue available.

Inclusion criteria 2, 4, 5, 6, 8-12 apply as above

- Inclusion criterion #13: Patients with proven genomic, transcriptomic or proteomic ErbB alterations which are not defined in the above inclusion criterion #1 regardless of tumour histology (See Section 5.6, tables 5.6:1 to 5.6:4).
- Inclusion criterion#14: Patients must have at least one measurable lesion according to the institutional response criteria for the given tumour type.

3.3.3 Exclusion criteria

1. Chemotherapy within 3 weeks prior to the start of study treatment, biological therapy or investigational agents within 4 weeks prior to the start of study treatment or prior to passing 5 half-lives, i.e. systemic clearance, whatever comes first
2. Radiotherapy within 2 weeks before starting study treatment (palliative radiotherapy is allowed if not focused on a target lesion)
3. Surgery within 4 weeks before starting study treatment or planned surgery during the projected course of the study which compromises patient's trial participation by investigator judgement
4. Known hypersensitivity to afatinib or its excipients
5. History or presence of clinically relevant cardiovascular abnormalities as per investigator judgement
6. Female patients of childbearing potential, who are nursing or are pregnant
7. Any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug

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8. Requirement of treatment with a prohibited concomitant medication listed in the CTP that cannot be stopped for the duration of trial participation
9. Known pre-existing interstitial lung disease (ILD), or signs and symptoms indicative of the latter as per investigator judgement (see Section 4.2.1)
10. Any history or presence of poorly controlled gastrointestinal disorders that could affect the intake/absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) as per investigator judgement
11. Active hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier
12. Known keratitis
13. Inadequate liver function (AST/ALT>2.5xULN, Bilirubin>1.5xULN adjusted for age)
14. Inadequate kidney function, i.e. creatinine>1.5xULN adjusted for age and/or creatinine clearance <70 ml/min/1.73m² estimated by institutional standard formula for estimation of GFR in paediatric patients
15. Inadequate bone marrow function (ANC ≤1000/mm³, platelets ≤100000/mm³)

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

The Investigator, patient and/or parent/legal guardian may stop study treatment at any time for safety or personal reasons.
If a patient is entered in violation of inclusion/exclusion criteria, the sponsor, in discussion with the investigator and if needed DMC, will determine the medical benefit/risk on a patient-by-patient basis and can require such a patient be discontinued from the study treatment.

A patient is to discontinue study medication if:

1 The patient and/or parent/legal guardian withdraw assent/consent to continue therapy without the need to justify.

2 The patient is no longer receiving benefit from treatment, in the opinion of the investigator.

3 In the investigator's medical judgment, further participation would not be in the best interest of the patient, or might be injurious to the health and well-being of the patient

4 The patient is no longer able to participate for other medical reasons (e.g. surgery, adverse events, secondary malignancy, or other diseases)

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5 A female post-menarchal patient becomes pregnant (Section 5.2.2.3)

6 The patient is diagnosed with ILD, keratitis or heart failure (including clinically relevant LVEF reduction) (Section 4.2.1)

7 The patient needs further dose reductions considered necessary but not allowed according to the protocol (Section 4.1.4.3)

The sponsor may remove patients from the study after completion of the primary analysis and grant access to afatinib via an alternative source e.g. through an expanded-access program, named patient use program, or compassionate use protocol.

Patient discontinuation of study participation:

A patient, who has discontinued study medication, will complete a follow-up (FU) visit 28-30 days after the last intake of the trial drug. After this FU visit, no further study procedure will be performed and the patient will enter the observation period during which only data collection on (S)AE(s) considered relevant by investigator, vital status and further anti-cancer treatment will be requested.

For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

If the patient and/or parents and/or legal guardian withdraw assent/consent to continue further trial procedures and the follow-up visit activities, no additional study assessments will be completed. In this event patients and parents or legal guardians will be asked whether they agree to allow continued further data collection of associated clinical outcome parameters during the observation period. If the patient/parents do not permit further contact/data collection this will be documented in the eCRF and in the source data.

Patients who withdraw from the trial after entering active treatment phase may be replaced if the primary endpoint of the respective trial phase is not achieved (see Section 5).

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The recommendation of the DMC that would require discontinuation of the trial due to an imbalance in benefit/risk
5. Discontinuation of the clinical development programme with afatinib in paediatrics.

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6. The primary analysis has been completed and all patients have either experienced progressive disease or are eligible to receive afatinib under the conditions indicated in Section 3.3.4.1

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

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4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will be treated with once daily oral dosing of afatinib.
Oral solid single-unit dosage forms represent stable and convenient formulation approaches and are therefore proposed for treatment of paediatric patients that are able to swallow them.
For younger children who cannot swallow the film-coated tablets, and for doses which cannot be achieved by the film-coated tablets, capsules and solvent for oral solution have been developed. This oral liquid formulation may also serve as alternative formulation for older paediatric patients who do not accept the film-coated tablets.

4.1.1 Identity of BI investigational product

Substance (INN) (Brand name):	**Afatinib (Giotrif®, Gilotrif®)**
Pharmaceutical form:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20, 30, 40 and 50 mg film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent to afatinib)
Route of administration:	Oral
Posology:	Once daily

Substance (INN) (Brand name):	**Afatinib**
Pharmaceutical form:	Capsules and Solvent for Oral Solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100ml solvent), i.e. 4 mg/ml
Route of administration:	Oral
Posology:	Once daily

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4.1.2 Method of assigning patients to treatment groups

Patients who have given their informed assent/written consent and whose parent(s)/legal guardian(s) gave written consent will be enrolled sequentially. A **screening form** must be faxed or emailed to the sponsor as soon as written informed consent has been obtained. Recruitment will be competitive.

Patients who meet all eligibility criteria will be entered into the study. A **registration form** will be faxed or emailed to the sponsor for patients who meet the eligibility criteria prior to starting study treatment.

The screening form and the registration form will be used by the sponsor for tracking purposes (overall recruitment, dose cohort assignment, tumour type information)

During the dose finding part, a rolling 6 statistical design will be used for dose escalation (R12-4744). Treatment slots are assigned by the sponsor in close collaboration with the recruiting sites according to Table 4.1.4.1:1. The sponsor will return the registration form for cohort confirmation.
The MTD expansion cohorts/Phase II part will recruit patients in a biomarker specific approach, see section 3.3.2. For cohorts 1 to 4, ErbB deregulation in each patient's tumour sample must be confirmed centrally. For cohort 5, an analytical laboratory report to prove genomic, transcriptomic or proteomic ErbB alterations (which are not defined in Tables 5.6:1 - 5.6:4) must be provided prior to study entry. For the MTD expansion cohorts/Phase II part a high rate of screening failures is expected. Therefore a pre-screening informed consent may be used to allow collection of tumour tissue samples and minimum data for central assessment of ErbB deregulation (further details are explained in the pre-screening informed consent. Upon confirmation of positivity for selection biomarkers (see Section 3.3.2) and before to proceed with trial procedures, the informed consent/assent for trial entry must be signed.

Recruitment will be closely monitored by the sponsor and sites will be informed of global patient enrolment numbers on an ongoing basis. Recruitment will continue until confirmation is received that patients included are evaluable for MTD (dose finding part) and the minimum number of patients required for assessment of OR (MTD expansion cohorts/Phase II part) is reached (see Section 3.3).

Following registration, patients should begin protocol treatment within 7 days.

4.1.3 Selection of doses in the trial

The choice of afatinib dose levels for this trial follows current clinical development practice and regulation (P96-1356) taking into account the available strengths of the tablet formulation. Five dose levels are planned in this trial. They are based on the approved dose for adults of 40 mg and described in Table 4.1.3:1.
(http://www.ema.europa.eu/docs/en_GB/document_library/EPAR -_Product_Information/human/002280/WC500152392.pdf)
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/201292s010lbl.pdf)

A recently published comparative analysis of paediatric dose finding trials of molecularly targeted agents with adults' dose finding trials by Paoletti et al (R13-4734) showed that the

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recommended Phase II dose for paediatric patients ranged between 90% to 130% of the BSA-adjusted adult dose for 70% of the trials. Due to conventional dose escalation, 63% of paediatric patients did not receive an optimal dose during Phase I. Toxicity profiles were very similar between children and adults. For EGFR targeted agents and dual HER2/EGFR inhibitors BSA adjusted paediatric MTDs ranged between 100% and 180% of RPIID or FDA approved dose (R13-4734). However, as afatinib has shown anti-tumour activity at doses between 20 – 50 mg in adults a starting dose at 80% level of the adult dose is chosen for safety reasons. Allometric scaling of the dose, based on BSA (R13-5168, R13-5170, R13-5167, P13-15789), is proposed in the dose finding part to take allometric differences between children and adults into account. The dose escalation will start at 80% of the approved adult dose (estimated by allometric scaling) with escalation levels to 100%, 125% and 150%; in case 80% is exceeding the MTD, dose level -1 will allow dose de-escalation to 50%. For obese patients BSA may be derived based on ideal body weight per institutional standard.

Table 4.1.3:1 Target dose in child as a function of efficacious dose in adult and dose level

Dose level	Percentage of adult dose (%)	Equivalent pediatric dose mg/m²*
-1	50	12
0	80	18
1	100	23
2	125	29
3	150	35

* for actual dose, please refer to Table 4.1.4:1

The dose finding part has been completed and the MTD was determined at 80% of the approved adult dose (estimated by allometric scaling based on BSA) (c09990672-01).

4.1.4 Drug assignment and administration of doses for each patient

Patients will be administered a single oral dose of afatinib each day. Treatment will be applied continuously until the development of progressive disease or unacceptable adverse events.

The medication should be taken at the same time each day (± 2 hours) without food (at least one hour before or at least three hours after a meal). If above time intervals cannot be adhered to in patients ≥1year and <2 years, time and type of food consumed within the critical application window for afatinib has to be recorded in the patient diary.

Missed doses of afatinib can be made up during the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the dose must be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis must not take a replacement dose.

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Depending on age, BSA (see Appendix 10.7), dose strength and individual preference, afatinib film-coated tablets or liquid formulation prepared from afatinib capsules and solvent for oral solution may be applied.

Assuming comparable exposure for both formulations (see Section 1.2), the oral solution and the film-coated tablets may be used interchangeably when determining the MTD, in case of matching doses (deviation -/+ 10%) as specified in Table 4.1.4:1. However, individual patients shall not switch between formulations as long as this is not necessitated by dose adaptations due to changing weight or BSA, or changes in the clinical health status or if patient adherence to treatment is otherwise endangered. **In any case, it must be attempted to keep all patients on their starting formulation for their first treatment cycle. This will be crucial for MTD determination**.

BSA has been recommended as the principal basis for drug dosage in the majority of chemotherapy regimens in adults and children (R13-1191; R13-1141; P13-03365).

For the current afatinib development in paediatric patients, allometric scaling was used to support estimation of a starting dose for different age groups based on the approved adult dose (40 mg).

Table 4.1.4: 1 Proposed afatinib dosing schedule for the Phase I/II

	Dose levels									
	Level -1 (50%)		**Level 0 (80%)**		**Level 1 (100%)**		**Level 2 (125 %)**		**Level 3 (150%)**	
BSA range (m^2)	AOS (mL)	Tablet (mg)	AOS (mL)	Tablet (mg)	AOS (mL)	Tablet (mg)	AOS (mL)	Tablet (mg)	AOS (mL)	Tablet (mg)
<0.40	1.0	-	2.0	-	2.5	-	3.0	-	3.5	-
[0.40 - 0.50[	1.5	-	2.5	-	3.0	-	3.5	-	4.5	-
[0.50 - 0.65[	1.5	-	2.5	-	3.5	-	4.0	-	5.0	-
[0.65 - 0.71[	2.0	-	3.0	-	3.5	-	4.5	-	5.5	-
[0.71 - 0.79[	2.0	-	3.5	-	4.0	-	5.0	-	6.0	-
[0.79 - 0.86[	2.5	-	3.5	-	4.5	-	5.5	-	7.0	-
[0.86 - 0.93[	2.5	-	4.0	-	5.0	-	6.0	-	7.5	-
[0.93 - 1[	2.5	-	4.5	-	5.5	20	6.5	-	8.0	30
[1 - 1.08[	3.0	-	4.5	20	5.5	-	7.0	30	8.5	-
[1.08 - 1.16[	3.0	-	5.0	20	6.0	-	7.5	30	9.5	40
[1.16 - 1.28[	3.5	-	5.5	20	6.5	-	8.5	-	10	40
[1.28 - 1.38[	3.5	-	6.0	-	7.5	30	9.0	40	11	-
[1.38 - 1.49[	4.0	-	6.5	-	8.0	30	10.0	40	12	50
[1.49 - 1.56[	4.5	-	7.0	30	8.5	-	10.5	40	13	50
≥1.56*	-	20	-	30	-	40	-	50	-	2 x 30

AOS: afatinib oral solution, 4 mg/mL
*Patients with a BSA ≥1.56, who are not able to swallow film coated tablets can also receive oral solution

Study drug will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy. Afatinib oral solution (capsules and solvent for

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oral solution) will be prepared preferably at the investigational site. After preparation, afatinib oral solution is stable for 4 weeks. At each course, the dose level of the drug must be checked and the patient will be re-supplied with a new bottle of freshly prepared afatinib oral solution.

Feeding tubes made of PVC and PUR have successfully been tested with Afatinib oral solution, i.e. they showed no negative influence on the intended dose of afatinib. The oral syringe (see Section 4.1.6) must not be used for rinsing the feeding tube.

Afatinib film-coated tablets should be swallowed with a glass of water and should not be chewed or crushed.

4.1.4.1 Dose escalation of afatinib for MTD determination

The MTD will be determined as the highest dose at which no more than 1/6 patients experienced DLT. The MTD will be determined when the last patient included into the dose finding part completed his/her 1st treatment cycle and is evaluable for DLTs.

The dose finding part will use a rolling six design (R12-4744).The dose escalation and de-escalation and the MTD determination will be performed as described in Table 4.1.4.1:1

Table 4.1.4.1:1 Dose escalation and de-escalation schedule and determination of MTD

	DLT data among the enrolled patients			Enrolling dose level for the next patient	
No. of enrolled patients per dose cohort	No. with DLT	No. without DLT	No. with DLT data pending	MTD not exceeded	MTD exceeded **
2	0 or 1	Any	Any	d	--
	2	0	0	d – 1	--
3	0	3	0	d + 1	d
	1	Any	Any	d	--
	>=2	Any	Any	d – 1	--
4	0	4	0	d + 1	d
	0	Other	Other	d	d
	1	Any	Any	d	d
	>=2	Any	Any	d – 1	d – 1
5	0	5	0	d + 1	d
	0	Other	Other	d	d
	1	Any	Any	d	d
	>=2	Any	Any	d – 1	d – 1
6	0	5, 6	1, 0	d + 1	MTD
	0	Other	Other	Suspend***	Suspend
	1	5	0	d + 1	MTD
	1	Other	Other	Suspend	Suspend
	>=2	Any	Any	d – 1	d – 1

Table adapted from Skolnik et al JCO 2008 Table 1 pp 191 (R12-4744.)
Note this table does not take into account unevaluable patients.
* d is the current dose level; d + 1 and d – 1 represent dose escalation and de-escalation, respectively.

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** MTD exceeded means that the 'd + 1' dose level has >=2 out of 3 to 6 patients with DLT (which is why there is no escalation in any of the listed scenarios).
*** 'Suspend' means there is not enough information to determine the next patient's dose level, one needs to wait until pending DLT data become available.

Note that the Rolling 6 design allows enrolling up to 6 patients on each dose cohort. The first cohort of patients will start with dose level 0 (i.e. 80% of adult dose) as listed in Table 4.1.3:1. As soon as at least two patients are treated at dose level 0, the dose level for the third and subsequent patients will be determined based on the number of patients determined to have experienced DLT, those determined without DLT, and those with DLT data pending for the first treatment course, as illustrated in the first row of Table 4.1.4.1:1. For illustration purpose, an example (considering 4 patients treated on dose level 0) is given below:

1) If DLT data of all 4 patients are available and none of them observed with DLT, the dose level may be escalated and the 5th patient will be enrolled to dose level 1

2) If data is not yet available for one or more of the first 4 patients, or if one patient with DLT is observed, then the 5th patient will remain on dose level 0; the decision on further dose escalation or de-escalation will be made based on the rules illustrated for a 5-patient cohort

3) If more than 2 patients are observed with DLTs, the dose will be de-escalated and the 5th patient will be enrolled to dose level -1

If scenario 1) occurs, dose level 1 becomes dose 'd' in Table 4.1.4.1:1. The process repeats after two patients are enrolled on dose level 1.

If scenario 3) occurs, dose level 0 exceeds the MTD, and dose level -1 is the lowest dose level allowed in this trial. Up to six patients will then be treated on this level, if <=1/6 patients with DLT, then dose level -1 will be the MTD; if >=2 patients with DLT, then there will be no MTD.

Similarly, suppose the trial has been escalated to higher dose levels, e.g. dose level 3, and >=2 patients had DLT, and if dose level 2 treated less than 6 patients previously, then the dose will be de-escalated to level 2 to fill up to 6 patients and the decision will be made according to the last column in Table 4.1.4.1:1.

As shown in Table 4.1.4.1:1, in order for a dose level to be the MTD, there must have been 6 patients treated on the dose level (at most one patient can have DLT) and the next higher dose level exceeded MTD (>=2 patients with DLT). The exception to this rule is if none of the 4 dose levels exceeds MTD, then dose level 3 will be MTD.

If a patient experiences DLT (for definition refer to Table 4.1.4.1:2), therapy may be continued at a reduced dose (for dose reduction, refer to Table 4.1.4.3:1) after recovery of the respective adverse event(s) to pre-dose CTCAE grade(s). The investigator shall liaise with BI and ask for confirmation of the dose of the trial drug before a new treatment course is started for any patient. In questionable cases, the DMC might be involved in decision making. If a patient is not eligible for further therapy, the patient has to discontinue further treatment with the trial drug.

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Table 4.1.4.1:2 Dose limiting toxicities

Dose limiting toxicity (DLT)
DLTs are defined as any of the following events that are considered related to afatinib: 1. CTCAE grade 4 hematologic toxicity lasting for 7 days 2. CTCAE Grade 3 or 4 non-hematologic toxicity (except fever grade 3). 3. CTCAE Grade 2 or higher decrease in cardiac left ventricular function 4. CTCAE Grade 2 or higher worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate 5. CTCAE Grade 2 diarrhoea persisting for 7 or more days, despite supportive treatment (loperamide treatment or other effective anti-diarrhoeal medication) 6. CTCAE Grade 2 nausea and/or vomiting persisting for 7 or more days despite antiemetic treatment 7. CTCAE grade 5 events

4.1.4.2 Intra-patient dose escalation of afatinib

For the patients included in the dose finding part, retreatment and intra-patient dose escalation to the next dose tier may be allowed when this dose tier was considered safe (for dose tiers, refer to Table 4.1.3:1; for dosing, refer to Table 4.1.4:1). This will allow all patients remaining on treatment to maximize their benefit from treatment, and prevent under-dosing patients in the initial dose cohorts (Section 3.2).
The decision on when to consider the next higher dose tier safe will be based on a thorough assessment by the steering committee and, if required, by the DMC. Intra-patient dose escalation still needs to be confirmed with the sponsor.

4.1.4.3 Dose reduction of afatinib

Treatment related toxicities will be managed by treatment interruptions and subsequent dose reductions of afatinib according to the schedule described in Table 4.1.4.3: 1. Dose reductions will apply to individual patients only. Once the treatment dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhoea, nausea and vomiting or rash should be managed early and proactively as described in Section 4.2.

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Table 4.1.4.3:1 Dose reduction scheme for afatinib

AE type and CTCAE Grade	Action	Dose reduction scheme
Events related to study drug: • **Diarrhoea** Grade 2 persisting for 7 or more consecutive days despite adequate anti-diarrhoeal medication/hydration • **Reduced renal function** to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline • **Any drug related AE Grade ≥3**	Pause treatment until patient has recovered to Grade ≤1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to Grade ≤1 or baseline[1] within 14 days, study treatment must be permanently discontinued[2].	If patient was treated at dose level 3, resume treatment at dose level 2 If patient was treated at dose level 2, resume treatment at dose level 1 If patient was treated at dose level 1, resume treatment at dose level 0 If patient was treated at dose level 0, resume treatment at dose level -1 If patient was treated at dose level -1, discontinue afatinib.
Acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea requiring supplementation of oxygen with cough and/or fever)	Pause afatinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume afatinib at current dose. If ILD is confirmed, discontinue afatinib.
Acute onset of symptoms indicative of keratitis	Pause afatinib while clinical assessment of keratitis is ongoing.	If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be discontinued. Unless the treatment benefit for the patient outweighs the risks of worsening keratitis (blindness) in the opinion of the investigator.
Acute onset of symptoms indicative of cardiac failure and/or CTCAE Grade ≥ 2 LVEF decrease and/or ≥20% decrease of LVEF from baseline	Pause afatinib while clinical assessment is ongoing and until patient recovers to Grade≤1 or baseline[1]	If patient has not recovered despite appropriate treatment to Grade ≤1 or baseline[1] within 14 days, study treatment must be permanently discontinued[2]

1 Baseline is defined as the CTCAE Grade at the start of treatment
2 In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

In the event of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction should occur once treatment is resumed.

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If the medication is interrupted for more than 14 days, the decision to continue with afatinib will be made by the BI clinical monitor in agreement with the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

Trial drug packages will have unique medication numbers which will be used for tracking purposes only. The medication numbers will not be linked to randomisation numbers.

Afatinib will be supplied:

- As film-coated tablets with available dosage strengths of 20 mg, 30 mg, 40 mg and 50 mg in child resistant plastic bottles. Each bottle containing 30 tablets.

- As capsules and solvent for oral solution. Afatinib solution will be prepared at site: two 200mg capsules must be dissolved in the co-supplied bottle of 100mL of solvent resulting in a concentration of 4mg/mL. See details in reconstitution instruction provided in the ISF. Dosing and administration is planned to be performed by the parents/caregivers with a co-supplied oral syringe suitable for the intended volume. The syringe can be connected to the bottle via an adapter plug. See details in handling instruction (illustration of administration procedure) provided in the ISF (also to be provided to parents/caregivers). The oral solution is stored in child resistant solvent bottles.

4.1.7 Storage conditions

Trial medication, which will be provided by the sponsor and/or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined below until supplied/administered to patient. Temperature logs must be maintained to make certain that the drug supplies are stored at the correct temperature. In case temperature would be out of range, this has to be reported in the ISF and the sponsor be notified.

Afatinib tablets:

Afatinib must be stored in the original package in order to protect from light. Film-coated tablets are humidity-sensitive; therefore, bottles must be kept tightly closed to protect from moisture. Tablets must be stored according to label instructions.

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Afatinib capsules and solvent:

Afatinib capsules must be stored in the original container in order to protect from moisture.

Solvent for Oral Solution must be stored according to label instructions.

After preparation, the solution is stable for 4 weeks at 25°C (date of preparing the oral solution has to be reported on the bottle label). The solution must be stored in the original solvent container/ amber glass bottle.

4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator or delegate (e.g. pharmacist or study drug storage manager) will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol,
- where applicable, availability of the proof of a medical licence for the principal investigator,
- for USA, availability of the Form 1572.

The investigator or delegate must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator or delegate will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of destruction at site or return (if applicable) to the sponsor and/or appointed CRO, the investigator or delegate must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining unused supplies are in the investigator's possession.

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4.1.9 Drug acceptability

Acceptability of the drug formulations in children per EMA/CHMP/QWP/805880/2012 Rev2 will be assessed using drug acceptability questionnaires for patients, parents/caregivers and investigator/site staff. Drug acceptability will be assessed after completion of the first course of treatment with the given formulation.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. Potential adverse events should be treated symptomatically. In cases of suspected overdose, afatinib should be withheld and supportive care initiated. If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage.

Common adverse events of afatinib treatment observed in adults with specified management recommendations and/or requirements include diarrhoea, mucositis and rash/acne. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described below.

Concomitant treatments

Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After study enrolment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area must not be used for tumour response assessment. During palliative radiotherapy, study treatment should be paused and be resumed once the patient has recovered from any radiation associated toxicity. If medication is interrupted for more than 14 days, the decision to continue will be made by the BI clinical monitor in agreement with the investigator. Continuous interruption of >28 days due to palliative radiotherapy will not be allowed.

All concomitant therapies, including anaesthetic agents (except pre-planned anaesthetic agents e.g. related to imaging exams), vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent for trial participation, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib around one week prior to the surgery, and to restart treatment after complete

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wound healing. If afatinib is interrupted for more than 14 days, the decision to continue will be made by the BI Clinical Monitor in agreement with the investigator.

Emergency procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever and demand for oxygen supplementation) should be performed to exclude interstitial lung disease (ILD). Study drug should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

In case the patient develops acute onset of symptoms indicative of cardiac failure and/or CTCAE Grade ≥2 LVEF decrease and/or ≥20% decrease of LVEF from baseline, study drug should be interrupted pending investigation of symptoms. The patient should be monitored closely for recovery. If patient has not recovered despite appropriate treatment to Grade ≤1 or baseline within 14 days study treatment must be permanently discontinued.

4.2.2 Management of expected adverse events

At occurrence of a drug related AE:

- Pause the drug if applicable, refer to Table 4.1.4.3:1
- Treat the side effect
- Dose reduce at reintroduction if applicable

Dermatologic adverse events and diarrhoea are the most common side-effects associated with treatment with afatinib in the adult population. Treatment of these side-effects should be proactive and should be started as early as possible after onset of symptoms.

4.2.2.1 Management of diarrhoea and hydration status following treatment with afatinib

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 4.2.2.1:1). At the time of initiation of treatment with afatinib, patients/ parents/legal guardian should be given a supply of loperamide (if applicable) to keep with them at all times or access to loperamide (if applicable) should be confirmed; and patients/ parents/legal guardian(s) should be counselled on the appropriate use. In cases where loperamide is not available or approved

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for the age group institutional standards for treatment of "chemotherapy-associated diarrhoea" must be followed.

Maintaining fluid balance in children developing diarrhoea is crucial at all times to avoid dehydration and renal insufficiency. Investigators need to assure that parents are alerted to this and must describe early signs and symptoms of dehydration (dry mucosal membranes, crying without tears, fever, decrease in urine output) clearly to caregivers/patients. Also assure that caregivers understand diarrhoea is an afatinib associated side effect which requires treatment. Caregivers/patients must seek medical advice on occurrence of initial signs and symptoms of diarrhoea and complications thereof.
To maintain fluid balance, the patient's fluid deficit must be assessed according to clinical standards. In addition daily fluid requirements may be estimated as 1.8L/m2/day, or more precisely 100 mL/kg/day can be calculated for the first 10 kg (1-10 kg). 50 mL/kg/day will be added for each kg body weight from 11-20 kg and 25 mL/kg/day can be calculated for each kg body weight from 20-30 kg. In addition estimated fluid deficits should be replaced within 36 hours, replacing the initial third of estimated fluid loss within 8-10 hours. CAVE: special rules apply for hypertonic dehydration (R14-2337).

Table 4.2.2.1: 1 Grade specific treatment recommendations for afatinib related diarrhoea

Severity (CTCAE Grading)	**Description**	**Intervention concerning afatinib treatment**	**Specific intervention**
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives if any. Oral rehydration can be attempted, but i.v. fluid replacement should start quickly if oral rehydration is not effective. For oral rehydration, advice the patient/caregiver to assure fluid consumption of at least 1.8L/m² electrolyte balanced fluids per day; in addition loperamide and racecadotril are preferred drugs for the treatment of diarrhoea. Treatment is to be started immediately according to the age-specific label instructions, i.e. for loperamide 0.4-0.8 mg/kg/24 h po should be applied at dose intervals of 6-12 hours until diarrhoea resolves; for chronic diarrhoea

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Table 4.2.2.1: 1 Grade specific treatment recommendations for afatinib related diarrhoea-(cont'd)

			0.5-1.5 mg/kg/24h po, given at dose interval of 6-12 hours, for maintenance reduce to 0.25-1 mg/kg/24 h po given at dose interval of 6-12 hours (R14-2354, R14-2355) For racecadotril, where available, a dose of 1.5 mg/kg 3 times per day** proved very effective in stopping chronic diarrhoea (P13-10876, P14-08260)
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose **unless Grade 2 diarrhoea continues for ≥ 7 days** in which case treatment must be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Continue loperamide/ racecadotril as described above; assess degree of dehydration and electrolyte imbalance and consider i.v. fluid and electrolyte replacement early; an infectious process should be ruled out with stool cultures
Severe (Grade 3)	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids > 24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 2; plus aggressive i.v. fluid replacement until fluid balance is restored; hospitalization to monitor progress; consider prophylactic antibiotics if patient is also neutropenic.
Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTC AE Grade ≤ 1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.
** Recommended for children of >3 months

4.2.2.2 Management recommendations for dermatological AEs following treatment with afatinib

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform and dry skin. General recommendations for prophylaxis are summarized in Table 4.2.2.2: 1 and treatment recommendations specified by CTCAE grade are summarized in Table 4.2.2.2: 2. For dose adjustment of afatinib refer to Table 4.1.4.1:2.

Specific interventions should be reassessed at each visit or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered. (Adapted from R11-0826)

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Table 4.2.2.2: 1 General recommendations for prophylaxis while receiving afatinib

Personal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. Use of very mild shampoos for hair wash. Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. Fine cotton clothes should be worn instead of synthetic material. Shaving (if applicable) has to be done very carefully. Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections
Sun protection	Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PAPA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended Patients should be encouraged to consequently stay out of the sun. Protective clothing for sun protection, sunglasses and wearing a hat should be recommended.
Moisturizer treatment	It is important to moisturize the skin as soon as anti-ErbB therapy with afatinib is started. Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications
Prevention of paronychia	Patients should keep their hands dry and out of water if possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.2.2: 2 Grade specific treatment recommendations of skin reactions to afatinib

Severity (CTCAE Grading)	**Description**	**Specific intervention**
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Consider referral to dermatologist. Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream or metronidazole 0.75% or topical nadifloxacin 1% as available, applicable and appropriately dosed for respective age group; Isolated scattered lesion: cream preferred Multiple scattered areas: lotion preferred
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of	Consider referral to dermatologist. Topical treatment as for Grade 1 as available and applicable per age group plus short term topical steroids, e.g.

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Table 4.2.2.2: 2 Grade specific treatment recommendations of skin reactions to afatinib- (cont'd)

	BSA	prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. erythromycin, clindamycin, minocycline hydrochloride as available, applicable and appropriately dosed for respective age group.
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	Consult a dermatologist. Topical and systemic treatment as for Grade 2. Consider systemic steroids appropriately dosed for respective age groups. Assess fluid loss and replace fluid.
Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	Consult a dermatologist, hospitalize the patient, see also Grade 3 above. Systemic steroids are recommended appropriately dosed for respective age group. Assess fluid loss and replace fluid.
EARLY AND LATE XEROTIC SKIN REACTIONS – PRURITUS		
Mild (Grade 1)	Mild or localized	Consider referral to dermatologist Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine) as available, applicable and appropriately dosed for respective age groups
Moderate (Grade 2)	Intense or widespread	Consider referral to dermatologist See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone as available, applicable and appropriately dosed for respective age group
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Consider referral to dermatologist Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics as available,

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Table 4.2.2.2: 2 Grade specific treatment recommendations of skin reactions to afatinib- (cont'd)

		applicable and appropriately dosed for respective age group
FISSURES		
Mild (Grade 1)	Asymptomatic	Consider referral to dermatologist. Consider topical treatment as available, applicable and appropriately dosed for respective age group: e.g. petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths); Topical application of aqueous silver nitrate solutions to fissures
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. Consider oral antibiotics as available, applicable and appropriately dosed for respective age group.
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.
If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 4.1.4.3:1		

4.2.2.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.2.3:1. For dose adjustment refer to Section 4.1.4 and for restrictions on concomitant therapies refer to Sections 4.2.3, 10.5 and 10.6.

Mucositis and associated pain may lead to fluid loss and hypo-alimentation. Therefore maintaining fluid balance and appropriate pain control are crucial. Please assure that parents are alerted to this and describe early signs and symptoms of mucositis and fluid loss clearly to caregivers/patients. Caregivers/patients should quickly seek medical advice on occurrence of initial signs and symptoms. In addition below measures may be useful.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non-irritating foods like ice-creams/sorbet as tolerated, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional

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support may be needed. Examples of some of the agents suggested in Table 4.2.2.3:1 include: topical analgesics –viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (Adapted from P11-09424)

Table 4.2.2.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description	Treatment recommendations*	Intervention concerning afatinib treatment/ dose modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution.	No change.
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4

*Also consider Rugo et al. (R17-1688)

4.2.3 Restrictions

4.2.3.1 Restrictions regarding concomitant treatment

Concomitant medications, or therapy to provide adequate supportive care, may be given as clinically necessary.

Palliative radiotherapy may be given as described in Section 4.2.1.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment, or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.

Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with strong P-gp modulators including, but not limited to strong P-gp inhibitors ritanovir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone. Conversely, strong P-gp inducers such as rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort may decrease the plasma concentrations of afatinib. Co-administration of P-gp modulators must be avoided

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during course 1 of Phase I dose finding. In addition P-gp modulators should be avoided within 14 days or at least 5 half-lives of the drug (whichever is longer) prior to the first dose of afatinib. For use of strong P-gp inhibitors after course 1 of the dose finding part and during the MTD expansion cohort, staggered dosing must be considered. For use of strong P-gp inducers after course 1 of the dose finding part and during the MTD expansion cohorts/Phase II part, afatinib daily dose should be increased based on tolerability and discussion with the sponsor. For a list of potent P-gp inhibitors and inducers see Appendix 10.4.

4.2.3.2 Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhoea.

To prevent skin related adverse events it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 4.2.2.2.

4.2.3.3 Boys and girls with reproductive potential – contraception and pregnancy prevention

Patients who are not of reproductive potential (i.e. pre-pubertal) do not need to use contraception to be eligible for the trial.

All other patients are considered to have childbearing potential (had 1st menarche or 1st ejaculation) and must use adequate contraception throughout the trial if sexually active (from screening until 28 days after last dose of trial medication). Highly effective methods of birth control per ICH M3 (R2) are methods that result in a low failure rate of less than 1% per year when used consistently and correctly (R09-1400). These include hormonal contraception associated with inhibition of ovulation, IUD, intrauterine hormone-releasing system, bilateral tubal occlusion, partner vasectomy (if vasectomized partner is sole sexual partner) (R16-0373). When using hormonal contraceptives, or with partners using hormonal contraceptives, patients must also be using an additional approved barrier method of contraception, i.e. condom or occlusive cap with spermicide, or vasectomised partner.

A method of contraception which is not considered highly effective (> 1% failure rate) is the double barrier method. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Use of male and female condom together, partner vasectomy (if different sexual partners), natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

Female patient who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in Section 5.2.2.3.

4.3 TREATMENT COMPLIANCE

The appropriate number of afatinib tablets/ afatinib liquid formulation for 4-weeks of treatment will be provided to the patients to be self-administered at home. An appropriate number of syringes will be co-supplied with afatinib oral liquid formulation. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary

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will be returned to clinic staff at the end of each course. During the first treatment course, compliance may also be verified by pharmacokinetic assessment.

Patients will be asked to bring the remaining trial medication at the end of each 4-week period to the investigational site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and the remaining volume of afatinib oral liquid formulation will be estimated as well (for details refer to ISF) and recorded at the investigational site. Discrepancies between the number of tablets/amount of liquid formulation remaining and the calculated amount of medication the patients should have taken must be documented and explained. An early compliance check at course 1 day 8 will be done by the investigator/site for ensuring that the medication is being taken correctly. At the end of each 4-week period, any remaining medication will be collected. If the patient is eligible for further treatment, new bottle(s) of study medication must be dispensed.

The investigator and/or the sponsor should discuss patient's withdrawal from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or renders study results for this patient unacceptable. Patients who do not attend a minimum of 75% of scheduled study visits, unless due to exceptional circumstances, should be discussed with the BI trial monitor and be evaluated for compliance. For afatinib, a maximum of 25% of the dispensed afatinib doses may be missed for other reasons than drug-related AEs. For details, see section 7.3. Patients who miss afatinib treatment more frequently are considered non-compliant.

During the first course of the dose finding part, patients should not miss more than 25% of afatinib doses (regardless of the reason of missed doses) to render patients evaluable for MTD. For details, see section 7.3.

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5. VARIABLES AND THEIR ASSESSMENT

For details on time points of evaluation and specific assessments, refer to the following Sections 5.1, 5.2 and 5.5.1.

The endpoints are categorised as follows and explained in more detail in the sections below:

Primary Endpoint

- In dose finding part
  - DLT measured during the first course of treatment
  - Pharmacokinetics ($AUC_{\tau,ss}$, $C_{max,ss}$)
- In MTD expansion cohorts/Phase II part
  - Objective Response by investigator assessment according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression of disease.

Secondary Endpoints

- In dose finding part
  - Objective Response by investigator assessment according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression of disease.
  - Pharmacokinetics (AUC_{0-24}, C_{max}, $t_{max(,ss)}$ and accumulation (or effective) half-life)
- In MTD expansion cohorts/Phase II part
  - Progression free survival (PFS)
  - Duration of objective response (DoR)
  - Pharmacokinetics ($AUC_{\tau(,ss)}$, $C_{max(,ss)}$, $t_{max(,ss)}$ and accumulation (or effective) half-life)

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5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoint(s) of efficacy

5.1.1.1 Primary endpoint

For the dose finding part, a primary endpoint of efficacy is not applicable. The primary endpoint for safety is described in Section 5.2.1.

In the MTD expansion cohorts/Phase II part, the primary endpoint will be objective response by investigator assessment according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression of disease.

5.1.1.2 Secondary endpoints

In the dose finding part of this trial, the objective tumour response (OR) assessed by investigator assessment according to the institutional response evaluation criteria for the given tumour type will represent a secondary endpoint.

In the MTD expansion cohorts/Phase II part, progression free survival (PFS) and duration of objective response (DoR) will be secondary endpoints for efficacy. PFS is defined as the duration of time from the date of first treatment until the date of the first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of last adequate tumour assessment. Duration of overall objective response (DoR) is defined only for those patients with a response (CR or PR) as the interval between the date of randomization and the earliest date of disease progression.

5.1.2 Assessment of efficacy

Response and progression will be evaluated in this study by investigator assessment according to the institutional response evaluation criteria for the given tumour type.

Each tumour type should be assessed using appropriate techniques. The method used at baseline must be continuously used throughout all consecutive tumour assessments.

In addition, all image data will be sent to a central imaging unit for digitization, quality control and archiving. If deemed necessary, a retrospective independent review of radiographic images may be performed. All procedures will be done according to the specifications provided in the investigator site file.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Primary endpoint: DLT

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The primary objective of the dose finding part is to determine the MTD as defined by patients with DLT in a paediatric population. It will be reported as primary endpoint of safety in this part of the trial.

For the purpose of dose escalation, patients with DLT events that occur during the first treatment course will be considered. Decisions on dose escalation/dose de-escalation will be made only after discussion between the sponsor and the investigators/steering committee, and in consideration of all the available toxicity and pharmacokinetic data. For details on the determination of MTD and definition of DLT, please refer to sections 4.1.4.1 and 7.3.1.

Once the MTD will be obtained, the MTD expansion cohorts/Phase II part will allow further collection of safety data and efficacy data. DLT will be monitored throughout the whole trial and all safety data will be collected in order to confirm the safety of the recommended Phase II dose.

Other safety endpoints will include:

- The overall incidence and CTCAE grade of adverse events, as well as relatedness of adverse events to treatment
- Events leading to dose reduction
- Events leading to permanent treatment discontinuation
- AESI
- Causes of death

The safety of afatinib will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to US NCI CTCAE Version 3.0 (R04-0474).

5.2.2 Assessment of adverse events

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) and include periodic physical examinations, measurement of vital signs, assessment of performance status, monitoring of laboratory tests (i.e. haematology, chemistry, coagulation, urine analysis), assessment of cardiac function with periodic ECGs and echocardiograms, pregnancy test(s) as outlined in the Schedule of Procedures/Assessments (Section 6.2.1).

If the investigator becomes aware of an SAE or AESI after the FU visit (28-30 days after the last dose of study drug), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

A diagram of the Adverse Event/Serious Adverse Event reporting requirements is provided in Table 5.2.2.2:1

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a

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pharmaceutical product. The event does not necessarily have to 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 product, whether or not considered related to the medicinal product.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Cancers with new histology are always considered serious.

The following hospitalizations are not considered to be serious adverse events (SAEs) because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol (including anaesthesia for imaging exams)
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug

Intensity of adverse event

The intensity of the AE should be judged based on the following:

- The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 in the (e)CRF.

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

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The reason for the decision on causal relationship needs to be provided in the eCRF and on the SAE form (if applicable).

Worsening of the underlying disease or other pre-existing conditions

Worsening of pre-existing conditions other than underlying disease will be recorded as an (S)AE in the (e)CRF.

Exemptions to SAE Reporting

Disease Progression is a study endpoint for analysis of efficacy. Disease progression is exempted from reporting as a (S)AE. Progression of the patient's underlying malignancy, including death due to progression of the underlying malignancy, will be recorded in the appropriate pages of the (e)CRF as part of efficacy data collection.

Examples of exempted events of PD are:

- Progression of underlying malignancy (Progressive disease PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

However, when there is evidence suggesting a causal relationship between the drug and the progression of the underlying disease, the event must be reported as (S)AE in the eCRF and on the SAE Form.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

Adverse Events of special interest (AESIs)

Protocol-specified AESIs

The following are considered as Protocol-specified AESIs:

- *Hepatic injury* defined by the following alterations of liver parameters:
  1. For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT $\geq$3 fold ULN combined with an elevation of bilirubin $\geq$2 fold ULN measured in the same blood draw sample and/or a marked peak aminotransferase (ALT, and/or AST)

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elevations ≥ 10 fold ULN. Patients showing these lab abnormalities need to be followed up according to APPENDIX 10.2 of this clinical trial protocol and according to the "DILI checklist" provided in the ISF

2. For patients with abnormal liver function at baseline an elevation of AST and/or ALT ≥5 fold ULN combined with an elevation of bilirubin ≥2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to APPENDIX 10.2 of this clinical trial protocol and according to the "DILI checklist" provided in the ISF.

Although rare, drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified AESI. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes are important for patient safety.

- *Dose limiting toxicity*. The definition of DLT is given in Section 4.1.4.1

Protocol-specified AESIs need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.2.2.2.

If the investigator determines any protocol-specific AESI is related to study drug, the administration of the study drug must be managed according to Section 4.1.4.3 of the protocol.

Expected Adverse Events

For expected (listed) AEs of afatinib, see the current version of the IB (c01802941).

5.2.2.2 Adverse event and serious adverse event reporting

The residual effect period (REP) for afatinib is 28 days after last intake of afatinib.

All adverse events, serious and non-serious, occurring from signing of the informed consent/patient assent for trial participation onwards until the FU visit i.e.28-30 days after last administration of study medication, regardless of relatedness and listedness, will be collected, documented and reported to the sponsor by the investigator.

SAEs and AESIs occurring after the FU visit (28-30 days after last administration of study medication) will be reported in case they are considered relevant by the investigator.

All AEs, including those persisting after end of study medication must be followed up until they have resolved or have been sufficiently characterised, unless the sponsor and the investigator agree not to pursue them further. Reporting will be done according to the specific definitions and instructions detailed in the adverse event reporting section of the ISF. A summary of the AE reporting requirements is given in Table 5.2.2.2:1.

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Table 5.2.2.2:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
From signing of informed consent for trial participation* to the FU visit (≤28-30 days after last trial drug administration) *Does not apply to pre-screening consent	Report all AEs and SAEs regardless of relatedness or whether the trial drug was administered. This includes all deaths.
Post-treatment: after the FU visit (>28-30 days after last trial drug administration)	Report only SAEs which are considered relevant by the investigator

The investigator must report the following events via fax using the SAE form immediately (within 24 hours) to the sponsor:

- SAEs
- non-serious AEs which are relevant for the reported SAE/AESI
- protocol-specified AESIs

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", a query will be raised if a non-serious AE is identified to be serious per BI definition. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system and in the ISF.

SAEs occurring in patients after having discontinued in the trial due to screening failures. i.e. after the screening period and who did not receive any trial medications, are to be reported if the investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedure.

5.2.2.3 Pregnancy reporting

In very rare cases, pregnancy might occur in paediatric clinical trials. Once a female patient has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (consists of Part A and Part B).

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5.2.3 Assessment of safety laboratory parameters

Safety laboratory samples will be analyzed at the investigator's local laboratory. Safety laboratory examinations will include hematology, biochemistry and urine examinations. Table 5.2.3: 1 presents the laboratory tests to be performed at screening, Day1 of each course and/or EOT whatever applies.

Table 5.2.3:1 Clinical Laboratory Tests

Category	**Parameters**
Haematology	Haemoglobin (Hb), platelet count, white blood cell count (WBC), with differential (neutrophils, lymphocytes, monocytes)
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	
Electrolytes	sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO_3)
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine; Creatinine clearance estimate by institutional standard formula for estimation of GFR in paediatric patients.
Category	**Parameters**
Other	glucose, albumin, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatine phosphokinase (CK); in case of pathological CPK further evaluation (e.g by determination of isoenzymes, troponin assays, ECG exam) should be performed as clinically indicated, CRP
Urinalysis	pH, protein, glucose, erythrocytes, leucocytes, nitrite and, if clinically indicated ketones, urobilinogen, specific gravity; in case of pathological finding(s) further evaluation should be performed and results of the latter must be documented
Pregnancy test	β-HCG testing in urine or serum in girls of childbearing potential (WOCBP)

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Limited lab tests (Hb, WBC, ANC, thrombocytes) will be required at intermediary visits

The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal findings from these investigations need to be reported as an Adverse Event. For confirmation of laboratory findings indicative for drug induced liver injury (DILI), local laboratories will be used

5.2.4 Electrocardiogram

12-lead ECG will be taken at the time points specified in the Flow Chart. The investigator will review the ECG recording, comment on any clinical significance and if applicable record any ECG abnormality that meets AE criteria.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination, vital signs, height and weight, performance score

A full physical exam must include: vital sign measurements blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, temperature, cardiopulmonary examination, examination of the regional lymph nodes, and examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination must be clarified. Wherever possible the same investigator should perform this examination.

A complete physical examination will be done at Screening, Day 1, every visit on study, and at the End-of-Treatment visit.

Measurement of height (in cm), body weight (in kg) and the evaluation of the performance score (Lansky for patients ≤ 12 years or Karnofsky for patients older than 12 years at the time of informed consent) will be conducted at the times specified in the Flow Chart.

5.2.5.2 Left ventricular function

LVEF will be assessed by echocardiography (ECHO) at time points specified in the Flow Chart.

5.2.5.3 Ophthalmologic examination

Standard ophthalmological examination to exclude keratitis will be conducted at time points specified in the Flow Chart.

5.2.5.4 Pulmonary examination

Pulmonary examination must include transdermal O2 saturation at time points specified in the Flow Chart and may be supplemented by a chest X-ray if clinically indicated.

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5.3 OTHER

5.3.2 Other assessment(s)

5.3.3 Pharmacogenomic evaluation

Not applicable

5.4 APPROPRIATENESS OF MEASUREMENTS

The US NCI CTCAE criteria version 3.0 (R04-0474) are used in the assessment of adverse events in cancer patients.

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5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.5.1 Pharmacokinetic endpoint(s)

Pharmacokinetics will be a primary endpoint for the dose escalation part and a secondary endpoint for the biomarker specific MTD expansion cohorts/Phase II part. Extensive plasma PK sampling is therefore crucial in this trial. Whenever possible, a full plasma PK profile will be taken after first dose and at steady state (e.g. after 8 days of treatment with afatinib). An additional trough sample will be taken on day 15 to confirm steady state exposure to afatinib. In exceptional cases and only if paediatric patients are by no means able to undergo extensive plasma PK sampling a limited sampling approach should be applied.

In addition, in patients carrying a Rickham- or Ommaya reservoir, or undergoing lumbar puncture for clinical reasons not related to the trial, trough CSF sampling may be performed on day 8 or later to investigate CNS exposure to afatinib. This procedure is optional. The trough CSF PK sample must be accompanied by a trough plasma PK sample taken at the same time-point.

In any case, it must be attempted to keep all patients on their starting formulation for the first treatment course. This will be crucial for the MTD determination and PK assessment during first course.

In case patients' switch from tablet to liquid formulation or vice versa becomes necessary during treatment or if for any other reason (e.g. AE) plasma PK sampling cannot be performed as planned, plasma PK profiles may be obtained within treatment course 1 as deemed appropriate by the investigator and after consultation with the sponsor.

All details with respect to sampling procedures and time points are described in Section 5.5.2 and tabulated in Appendix 10.3.

Pharmacokinetics (PK) will be evaluated as follows:

- Non-compartmental analysis: PK parameters will include AUC, C_{max}, t_{max} and accumulation (or effective) half-life will be performed for all patients with extensive PK sampling

- Model-based analysis will be performed for all patients with sparse as well as extensive PK sampling

For further details regarding the PK analysis, please refer to Section 7.3.5.

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5.5.2 Methods of sample collection

For quantification of afatinib plasma concentrations, 1 mL of venous blood will be taken in a K-EDTA (potassium ethylendiamine tetraacetic acid)-anticoagulant blood drawing tube at the blood sampling times indicated in Appendix 10.3.

Determination of afatinib CSF concentrations will be performed from optional 1 mL samples taken via puncture of a Rickham- or Ommaya reservoir, or lumbar puncture conducted for clinical reasons not related to the trial, at the time-points specified in Appendix 10.3. The type of the respective reservoir or lumbar puncture will be recorded in the eCRF.

Blood will be processed to plasma and all samples (plasma and CSF) further handled as described in the laboratory manual. This document gives all details about sample collection, preparation, storage and shipment.

All PK samples will be uniquely labelled with study number, subject number, visit number, and protocol (planned) time according to the time schedule in Appendix 10.3. Would a patient discontinue treatment at the time of a PK sampling, the sample(s) taken at this visit may need to be renamed for the EOT visit.

Pharmacokinetic samples will only be used for the analyses as described in the Clinical Trial Protocol. The plasma and CSF samples will be discarded at the latest when the CTR has been signed.

Correct sample handling as well as correct and complete documentation of drug administration and blood/CSF sampling is mandatory to obtain data of adequate quality for the pharmacokinetic analysis.

Date and time of pharmacokinetic sampling should be recorded on the eCRF. In addition, the dose, date and time of afatinib administration and time of food intake before and after medication for the four (4) days prior to pharmacokinetic sampling should be recorded in the eCRF.

5.5.3 Analytical determinations

Plasma and CSF concentrations of afatinib will be determined by validated HPLC-MS/MS assays (high performance liquid chromatography, tandem mass spectrometry) at an appropriate bioanalytical laboratory e.g.
. If necessary individual patient plasma samples may be analyzed on an „ad hoc" basis.

5.6

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5.6.1 Endpoints based on biomarker(s)

The objective response level obtained from the biomarker selected MTD expansion cohorts/Phase II part must be considered meaningful by experts in the field of paediatric oncology. For further details refer to Section 7.6.

5.6.2 Methods of sample collection

Sample analyses and logistics will be performed by a certified central laboratory, after validation of assay procedures.

Tissue sample from archived tumour blocks is preferred. Alternatively, a minimum of 15 up to 20 slides of 4 µm thickness should be provided. Further details are provided in the ISF.

Data transfer agreements, data storage and analysis will be handled by BI.

5.6.3 Analytical determinations

Refer to section 5.6.1

5.7 PHARMACODYNAMICS

Not applicable

5.7.1 Pharmacodynamic endpoints

Not applicable

5.7.2 Methods of sample collection

Not applicable

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Correlation between drug concentration and response may be made if appropriate data are available. In addition, exploratory correlation will also be made between drug concentration and AEs.

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

After the screening visit, patients will have to come to the investigational site on the days provided in the Flow Chart. More visits can be performed if deemed necessary by patient, caregivers and/or investigator. As soon as the treatment with afatinib will be permanently discontinued, the patient has to undergo the end of treatment visit (i.e within 7 days of last afatinib administration). A last visit will be performed at the end of the residual period (i.e. 28-30 days after the last afatinib administration) for safety follow-up. This last safety follow-up visit will represent the end of trial visit for the patient. Thereafter, regular contacts (every 12 weeks) after the end of trial visit will be done either via phone/correspondence to collect information whether the patient is still alive.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

The screening period may be as long as 28 days between signing informed consent and first administration of the trial drug. The screening period may be longer in case of administrative issues and/or if the patient would have to recover from an intercurrent disease.

During the screening period, the following actions will be performed:

Before screening period	*Applies only to MTD expansion cohorts/Phase II part*: Where requested, a pre-screening informed consent may be used **allowing only for collection and testing of tumour tissue for ErbB deregulation** (see Section 4.1.2). If tested positive for ErbB selection biomarkers, parents /legal guardian have to sign an informed consent –and patients have to assent in order to be entered into this trial and proceed with trial procedures (see below).
Informed consent	An informed consent has to be given by the parents /legal guardian and assent by the patient by using a suitable informed consent for the respective age group.
Demographics	
Medical and oncological history	For details refer to Section 5.2.5
Vital signs and physical examination	Preferably be done by the same person throughout the trial for a respective patient if feasible
Ophthalmological examination	To exclude keratitis
Pulmonary examination	To exclude ILD
Height and weight	Height in cm and weight in kg
Performance score	To be assessed using Lansky score for the patients aged ≤ 12 years and the Karnofsky score for the patients aged >12 years at time of informed consent
Planned hospital stay	Any stays in hospital that are planned to be performed during the trial shall be reported
Check of inclusion and exclusion criteria	To assess eligibility of the patient
Pregnancy test	To be performed in post-menarchal female patients who are of childbearing potential and within 7 days prior to first treatment.
Cardiac assessment	• LVEF echocardiography shall be performed and the results must be

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	documented in source data and eCRF • 12 lead-ECG as detailed in Section 5.2.4
Blood sampling for safety lab	Blood collection for assessment of the parameters as described in Section 5.2.3. In case the safety lab parameters as outlined in Section 5.2.3 have been collected within the past 7 days prior signing informed consent, the data may be reported in the eCRF and no new blood needs to be collected during screening
Assessment of the tumour disease	Depending on the tumour type, an assessment of the tumour disease has to be reported in the eCRF based on: o imaging findings o tumour markers in blood or urine if indicated o bone marrow if indicated Tumour assessment does not need to be repeated at the screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within the allowed time window (within 28 days prior to start of treatment).
Tumour tissue	-Dose finding part: confirm tumour tissue availability for retrospective biomarker testing or provide evidence of ErbB pathway deregulation -MTD expansion cohort: provide tumour tissue for prospective biomarker testing of ErbB pathway deregulation – see Section 5.6
Concomitant therapies	See Section 4.2.1
Adverse events	All AEs occurring since the signature of the informed consent - See Section 5.2.2
Dose assessment	Confirmation of dose according to dose level and BSA

6.2.2 Treatment period(s)

COURSE 1

Visit 1 (day 1)

The very first intake of afatinib will take place on day 1 of course 1. Patients may stay in hospital for the day 2 assessments such as blood sampling for safety laboratory and pharmacokinetics if applicable and if considered necessary by the investigator.

Before the first intake of afatinib, the following assessments shall be done:	
Vital signs and physical examination	Preferably be done by the same person throughout the trial for a respective patient if feasible
Weight	
Performance score	Lansky for patients ≤ 12 years or Karnofsky for patients older than 12 years at time of informed consent
Quality of life questionnaire	For MTD expansion cohorts/Phase II part only
Blood sampling for safety lab	Not to be older than 48 hours before the trial drug intake
Blood for the baseline pharmacokinetic	Pre-dose sample to be collected about 5 minutes before afatinib intake, see Appendix 10.3
Concomitant therapies	Update if applicable
Adverse events	Update if applicable
Dispense trial drug	The allocated treatment kit(s) should be dispensed to the patient/parent(s)/caregiver for the first drug intake at site followed by the daily intake along this treatment course.

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After first drug intake:	
Blood for pharmacokinetics post dose	To be collected on day 1 at 1, 2, 3, 4, 5, 6, 8 hours after afatinib intake as described in Section 5.5.2 and at the time points tabulated in Appendix 10.3. It is of utmost importance to report the exact clock time of the first trial drug intake and the actual sampling date and time for blood samples in the eCRF. In exceptional cases and only if patients are by no means able to undergo extensive PK sampling, a limited sampling approach should be applied with blood sampling before, 1h and 3 h after afatinib administration. For further details see Section 5.5.2 and Appendix 10.3.

Visit 1 (day 2)

Repeated procedures	Physical examination and vital signs; update on concomitant therapies and adverse events
Blood for pharmacokinetic	For extensive PK sampling, samples to be collected 24 hours after afatinib intake. Patients (or parents and/or legal guardian) should be instructed not to take the trial medication prior to the 24h blood sample. The trial medication must be taken after the last PK blood sample has been drawn
Drug intake	Intake of the trial drug should take place at the same time as previous day
Patient diary	Check for completion

Visit 2 (day 8)

Repeated procedures	Physical examination and vital signs; weight; blood sampling for safety lab (limited); update on concomitant therapies and adverse events
Cardiac assessment	12 lead-ECG as detailed in Section 5.2.4
Blood for pharmacokinetics pre-dose at steady state	Pre-dose sample to be collected about 5 minutes before afatinib intake, see Appendix 10.3
Drug intake	
blood for pharmacokinetic post dose at steady state	Extensive PK sampling: blood has to be collected at 1,2,3,4,5,6,8 and 24 hours after afatinib intake (refer to Appendix 10.3). Patients (or parents and/or legal guardian) should be instructed not to take the trial medication prior to the 24h blood sample (day 9). The trial medication must be taken after the last PK blood sample has been drawn. In exceptional cases and only if patients are by no means able to undergo extensive PK sampling, a limited sampling approach should be applied with blood sampling before, 1h and 3 h after afatinib administration. For further details see Section 5.5.2 and Appendix 10.3.
Patient diary	Check for completion
Compliance check	Check on trial drug compliance

Visit 3 (day 15)

Repeated procedures	Physical examination and vital signs; weight; blood sampling for limited safety lab; update on concomitant therapies and adverse events
Blood for pharmacokinetics pre-dose to confirm steady state	Pre-dose sample to be collected about 5 minutes before afatinib intake, see Appendix 10.3

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Patient diary	Check for completion

Visit 4 (day 22)

Repeated procedures	Physical examination and vital signs; weight; blood sampling for limited safety lab; update on concomitant therapies and adverse events
Patient diary	Check for completion

COURSE 2

Visit 1 (day 1)

This visit should take place at day 29 from start of treatment and should serve for confirming patient's eligibility for treatment continuation

- Depending on the patient status, the investigator has to perform a disease assessment on patient's eligibility for the next treatment course. This might include but is not limited to:
    - Imaging findings (requested only every 2 courses: course 3 visit1, C5V1, C7V1…)
    - Tumour markers in blood or urine if indicated
    - Bone marrow if indicated

In case treatment discontinuation is required at this visit, please complete the EOT visit instead of this visit.

For patients included in the dose escalation part, a DLTs evaluation should be provided before to start a new course of treatment.

C2V1 visit should include:

Patient acceptability	Completion of acceptability questionnaires by patients, parents/caregiver and investigator/site staff *Special note*: at any time, if the patient switches from his/her initial formulation to the other, the questionnaires should be completed again after 28 days of intake of the new formulation.
Quality of life questionnaire	For MTD expansion cohorts/Phase II part only
Repeated procedures	Physical examination and vital signs; weight; blood sampling for safety lab; update on concomitant therapies and adverse events
Performance score	Lansky for patients ≤ 12 years or Karnofsky for patients older than 12 years at time of informed consent
Cardiac assessment	LVEF echocardiography shall be performed and the results must be documented in source data and eCRF for DLT evaluation
Patient diary	Check for completion
Compliance check	Check on trial drug compliance
Eligibility for treatment continuation	Confirm eligibility for further treatment
If the patient eligibility for further treatment is confirmed:	
Dose assessment	Assess appropriateness of the afatinib dose
Dispense trial drug	New afatinib kit(s) must be dispensed to the patient/parent(s)/legal guardian

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	(recalculate BSA for allocation of dose) for a daily drug intake along this treatment course

Visit 2 (day 15)

Repeated procedures	Physical examination and vital signs; weight; blood sampling for limited safety lab; update on concomitant therapies and adverse events
Dose assessment	Assess appropriateness of the afatinib dose

COURSE 3 AND ONWARDS

Visit 1 (day 1)

Repeated procedures	Physical examination and vital signs; weight; height (every other course); blood sampling for safety lab; update on concomitant therapies and adverse events
Quality of life questionnaire	For MTD expansion cohorts/Phase II part only
Performance score	Lansky for patients ≤ 12 years or Karnofsky for patients older than 12 years at time of informed consent
Cardiac assessment (every 3rd course)	• LVEF echocardiography • 12 lead-ECG as detailed in Section 5.2.4
Patient diary	Check for completion
Compliance check	Check on trial drug compliance
Tumour assessment	Imaging assessment every 8 weeks, tumour markers where indicated
Eligibility for treatment continuation	Confirm eligibility for further treatment
If the patient eligibility for further treatment is confirmed:	
Height measurement	Every 2 courses
Dose assessment	Assess appropriateness of the afatinib dose
Dispense trial drug	New afatinib kit(s) must be dispensed to the patient/parent(s)/legal guardian (recalculate BSA for allocation of dose) for a daily drug intake along this treatment course

6.2.3 End of treatment and follow-up period

End Of Treatment visit

This visit will take place as soon as a decision is made to permanently discontinue trial treatment.

The EOT visit will include the following actions:

Repeated procedures	Physical examination and vital signs; blood sampling for safety lab; update on concomitant therapies and adverse events

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Ophthalmological examination	To exclude keratitis
Pulmonary examination	To exclude ILD
Pregnancy test	To be performed in post-menarchal female patients who are of childbearing potential
Performance score	Lansky for patients ≤ 12 years or Karnofsky for patients older than 12 years at time of informed consent
Cardiac assessment	• LVEF echocardiography • 12 lead-ECG as detailed in Section 5.2.4
Assessment of the tumour disease	Depending on the tumour type, an assessment of the tumour disease has to be reported in the eCRF based on: o imaging findings o tumour markers in blood or urine if indicated o clinical findings o bone marrow if indicated
Patient diary	Check for completion
Compliance check	Check on trial drug compliance
Conclusion of treatment	To confirm permanent treatment discontinuation

Follow-up visit for safety (28-30 days after last afatinib intake)

Safety update	Update on concomitant therapies and adverse events
Conclusion of patient participation	Confirmation of trial discontinuation for the patient

6.2.4 Observational period

The observational period is a post-trial period for data collection on vital status. The site will contact patients/parent(s)/legal guardian or patients' health care providers to collect patients' vital status every 12 weeks. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.

The data should be documented in the patient's chart.

Adverse events/serious AEs should still be reported in this period if they are considered relevant by the investigator.

The whole trial will end when the last patient has completed the 28-30 day FU visit.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a Phase I/II, open-label trial (including a Phase I dose finding and a Phase I MTD expansion cohorts/Phase II part) to explore the safety and possibly early signs of efficacy of afatinib in paediatric patients with neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology.

- The dose finding part will use a rolling 6 design and recruit up to 30 patients who are evaluable for DLT to determine the MTD.
- In the MTD expansion cohorts/Phase II part, a minimum of 5 patients in each of the following cohorts, i.e. HGG, DIPG, EM and a mixed histology agnostic cohort of patients with refractory tumours, will be accrued. All patients must fulfil two of the biomarker screening criteria, i.e. EGFR FISH positive and/or EGFR H-score >150 and/or HER2-DDISH positive and/or HER2 H-score > (see Section 3.3.2). An exploratory cohort will recruit patients with proven genomic, transcriptomic or proteomic alterations which are not defined above. All patients must be evaluable for OR/efficacy. Further safety data will be collected.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. All analyses will be descriptive and exploratory in nature.

7.3 PLANNED ANALYSES

All patients who receive at least one dose of afatinib will be included in the analysis for safety and efficacy and they are defined as treated set.

7.3.1 Primary analyses

Dose finding part:

In order to determine the MTD, the number of patients with DLT deemed to be related to administration of afatinib will be assessed based upon the patients in dose finding part of the trial. (See Table 4.1.4.1:2). The advanced disease of the patients in this trial makes it possible that significant adverse events, including events that would qualify as DLT, will occur, but will not be caused by afatinib. The MTD will be determined as the highest dose at which no more than 1/6 patients experienced DLT considered related to afatinib. (See Table 4.1.4.1:1)

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Pharmacokinetics is a primary endpoint for the dose finding part. For details see Section 7.3.5

MTD expansion cohorts/Phase II part:

OR will be assessed when the last patient enrolled in the MTD expansion cohorts/Phase II part will be evaluable for efficacy.

Each patient will be assigned to one of the following categories based on investigator's assessment according to the institutional response evaluation criteria for the given tumour type, irrespective of protocol violation or missing data:

- CR (complete response)
- PR (partial response)
- SD (stable disease)
- PD (progressive disease)
- Not evaluable (not assessable, insufficient data)

Objective response is defined as CR and PR.

If the International Criteria for Neuroblastoma Response Criteria (INRC) (R14-2418) is used, each patient will be assigned to one of the following categories:

- CR (complete response)
- VGPR (very good partial response)
- PR (partial response)
- MxR (mixed response)
- NoR (no response)
- PD (progressive disease)

The objective response is then defined as CR, VGPR, PR or MxR.

OR will be tabulated and provided with the proportion and the exact 95% confidence interval based on all treated patients in the MTD expansion cohorts/Phase II part.

7.3.2 Secondary analyses

In dose finding part, number of patients with OR will be described per dose level.

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In the MTD expansion cohorts/Phase II part, the PFS and DoR will be secondary endpoints. PFS is defined as the time from the date of first administration of treatment to the date of disease progression, or to the date of death, whichever comes first. The Kaplan-Meier estimates of PFS rate and 95% confidence intervals will be calculated at the time of each planned assessment. DoR is defined only for those patients with a response (CR or PR) as the interval between the date of randomization and the earliest date of disease progression. The Kaplan-Meier estimates of DoR and 95% confidence intervals will be calculated at the time of each planned assessment.

Pharmacokinetics is a secondary endpoint for the MTD expansion cohorts/Phase II part. For details see Section 7.3.5.

7.3.3 Safety analyses

DLTs will be tabulated for each dose cohort in the Phase I dose finding part. The tabulation will be done in two ways: (1) DLTs with onset in the first treatment course; (2) all DLTs regardless of treatment course at onset. The definition of DLT is defined in Table 4.1.4.1:2.

Events that started within the course of treatment, starting after the first administration of the treatment and until 28 days after the last administration of treatment will be considered as having occurred on treatment. In general later events will be attributed to the post-study period and will be presented separately. However post-study events will be examined to determine whether they need to be combined with on-treatment events in an additional table.

Adverse events will be graded according to CTCAE v3.0 and reported according to BI standards. Serious adverse events will be tabulated. In addition, events leading to dose reduction or treatment discontinuation will be examined, but may not be reported as individual tables, depending upon the extent of overlap.

Descriptive statistics will be used to describe changes in laboratory parameters over time. In additional, all abnormalities of potential clinical significance will be reported. In general, potential clinical significance is defined as at least CTCAE Grade 2 and an increase in

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CTCAE classification from baseline. The incidence and intensity of adverse events will be correlated descriptively with pharmacokinetic data if possible.

7.3.4 Interim analyses

No formal interim analysis is planned.

Results of the dose finding part and PK may need to be summarized and documented.

7.3.5 Pharmacokinetic analyses

Extensive plasma sampling:

Pharmacokinetic profiles of afatinib will be taken on Day 1 (after single dose) and Day 8 (at steady state) of Course1. An additional trough sample will be taken on day 15 to confirm steady state exposure to afatinib. If data allow, the following pharmacokinetic parameters will be evaluated:

- area under the plasma concentration-time curve
  - over the dosing interval τ (24 h) and after uniform intervals τ, following the first dose and at steady state (AUC_{0-24} and $AUC_{\tau,ss}$)
  - over the time interval from zero to the time of the last quantifiable drug concentration (AUC_{0-tz} and $AUC_{0-tz,ss}$) within the dosing interval τ
- maximum measured plasma concentration following the first dose and at steady state after uniform intervals τ (C_{max} and $C_{max,ss}$)
- time from dosing to the maximum plasma concentration following the first dose and at steady state after uniform intervals τ (t_{max} and $t_{max,ss}$)
- accumulation ratio ($R_{A,Cmax}$ and $R_{A,AUC}$)
- accumulation (or effective) half-life

Other parameters may be calculated as deemed appropriate.

The derivation of the PK parameters will be performed in line with BI internal procedures (MCS-36-472, current version). The accumulation (or effective) half-life can be calculated according to the formula $t_{1/2}=\tau \cdot \ln 2 / \ln(R_{A,AUC}/(R_{A,AUC}-1)$ (P09-09363).

The following descriptive statistics will be calculated for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

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Sparse plasma sampling:

In the clinical trial report, afatinib plasma concentrations from patients who were not able to undergo extensive sampling, and for whom sparse sampling was performed, will be summarised by time point by descriptive statistics and, if feasible, graphically inspected.

Model based analysis

A model-based analysis over all available PK data (extensive and sparse sampling) will be performed.

Structure of the available population PK model

Based on existing afatinib PK models in adult patients having various solid tumours (studies 1200.1; .2; .3; .4 and 20 (U12-1393) and 1200.28; .32 and .33 (U12-1394)), a model will be developed based on 1200.120 data in paediatric population.

Model development

A non-linear mixed effect modelling approach will be taken to conduct the analysis. The parameters of the model are defined by fixed effects, so called θs and potential random effects (Inter (η) or intra-individual variabilities (κ)). These random effects are normally distributed around zero with a variance ω^2. The combination of the fixed effects and random effects allow the estimation of individual parameters (Pi) as described in the following example equation:

$P_i = \theta * \exp(\eta_i)$

In addition, a residual variability, ε, adjusts the prediction of the model to the observed measurement. This residual variability is normally distributed with a variance σ^2 and can be described according to the following equation:

$Y_{i,j} = IPRED_{i,j} + \varepsilon_{i,j}$

where Yi,j is the j^{th} observation for i^{th} individual, IPREDi,j is the individual prediction of the model for the j^{th} observation of the i^{th} individual, εj,i s the residual variability for the j^{th} observation of the i^{th} individual. In the current situation Y is the plasma concentration of afatinib. If possible First Order Conditional Estimation with Interaction (FOCE / INT) will be used for the complete model development. The data from all dose groups of this study will be used for model development.

Effect on Body weight on clearance and on volume of distribution will be evaluated, and the respective parameters (CL, V) will be scaled based on body weight.

Handling of missing data: Samples marked as no sample available (NOS) or non-valid result (NOR) will not be included in the dataset. Handling of missing PK data will be performed according to BI standards as stated in Section 7.4 (MCS-36-472, current version).

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The objective function value as well as the following criteria will be used to evaluate a model:

- A "successful minimization" statement by the NONMEM program at the end of the estimation step.
- The final parameter estimates have a number of significant digits ≥3.
- Estimates of θ's not close to a boundary.
- Correlation of the uncertainty of the estimates of fixed effect parameters < 0.95 and > -0.95
- No significant trends in the basic goodness-of-fit plots (predictions (PRED), individual predictions (IPRED) vs. dependent variable (DV))
- Residuals (weighted and un-weighted) scatter randomly and uniformly around zero when plotted against PRED, IPRED and TIME.
- Symmetric distributions of individual ηs.

Results

The following outcomes of the modeling based analysis will be reported:

- Structure and parameter estimates of the final PK model including the potential covariate submodel.
- Steady state concentrations for appropriate age range will be simulated. $C_{max,ss}$ and $AUC_{\tau,ss}$ as well as apparent clearance (CL/F) and volume of distribution (Vd/F) will be calculated from these predictions.

Further details will be described in the TSAP.

PK data (plasma and CSF) may additionally be used to evaluate the penetration of afatinib into the brain, applying non-compartmental methods and pharmacokinetic modelling techniques as appropriate.

7.3.6 Pharmacodynamic analyses

No formal pharmacodynamics analysis is planned.

7.3.7 Pharmacogenomic analyses

No pharmacogenomic analyses are planned.

7.3.8 Biomarker Analyses

The prevalence of biomarkers will be determined during the biomarker prevalence study taking place outside of the clinical trial but being informative for the latter.

7.4 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

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- Missing or incomplete AE onset and end dates are imputed according to BI standards (001-MCG-156_RD-01)

- For pharmacokinetics:

  Handling of missing PK data will be performed according to BI standards (MCS-36-472, current version). For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

No randomisation will be performed.

7.6 DETERMINATION OF SAMPLE SIZE

In order to complete the dose finding part, which uses a rolling 6 design (see Table 4.1.4.1:1) an estimated 24 evaluable patients will be needed given the number of dose levels to be tested in this trial. To further account for early drop-out of patients or patients not evaluable for DLT during the first course of treatment, an estimated 30 patients were planned to be recruited to achieve this. 17 patients were needed to determine the MTD (c09990672-01).

Once the MTD is determined, a minimum of 5 patients in each of the four following cohorts, i.e. HGG, DIPG, EM and a mixed histology agnostic cohort of patients with refractory tumours, (see Section 3.3.2) will be accrued into an MTD expansion cohorts/Phase II part (Table 7.6:1) to confirm a safe recommended Phase II dose (RPIID) and to be assessed for response. An exploratory cohort of patients with proven genomic, transcriptomic or proteomic alterations which are not defined in Tables 5.6:1-5.6:4 will also be included. Table 7.6:1 shows the probability of observing more than one responder given the total number of patients assuming the true response rate being 20% and 30% respectively.

Table 7.6:1 Probability of observing more than one responder for different response rates

Sample size per cohort		P(no response)*	P(1 or more response)**	P(2 or more response)***
ORR = 20%	**5**	32.8%	67.2%	26.2%
ORR = 30%	**5**	16.8%	83.2%	47.1%
ORR = 20%	**6**	26.2%	73.8%	34.4%
ORR = 30%	**6**	11.8%	88.3%	60%
ORR = 20%	**10**	10.7%	89.2%	62.4%
ORR = 30%	**10**	2.8%	97.2%	85.1%

*P(no response) = Chances of observing no response given the assumed response rate
**P(1 or more response) = Chances of observing one or more than one response given the assumed response rate
***P(2 or more response) = Chances of observing two or more than one response given the assumed response rate

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Table 7.6:2 summarizes for different prevalences the adjusted number of patients needed to be screened to ensure for a certain number N of biomarker positive patients with a probability of 90%.

Table 7.6:2 Number of patients to be screened to have with 90% probability at least N biomarker positive patients

Number N of biomarker positive patients	Prevalence of biomarker positive patients (%)							
	5	10	15	20	25	30	35	40
20	529	263	174	130	103	85	72	63
30	754	375	249	185	147	122	104	90
40	975	485	322	240	191	158	135	117
50	1193	594	394	294	234	194	166	144
60	1410	702	466	348	277	230	196	171
70	1626	810	538	402	320	266	227	198
80	1840	917	609	455	363	301	257	224
90	2054	1023	680	508	405	336	287	250
100	2266	1130	751	561	447	372	317	277
200	4370	2180	1450	1085	866	720	615	537

Considering that up to 55 patients will be included into this trial and of these up to 38 will be selected by biomarkers as described earlier (See Section 5.6) into the MTD expansion/Phase II part and assuming a biomarker prevalence of 10-15%, between 322 - 485 patients will need to be screened for that biomarker.

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8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The protocol has been written in compliance with the recommendations given by the ICH E 11 Guidance for Industry (Clinical Investigation of Medicinal Products in the Paediatric Population, R10-4556) and Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (R10-4959).

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from patient's parent(s) (both or one based on national regulation) or the legal guardian, as well as an informed assent of the minor patient according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.

If only mother or father (or one legal guardian) has sole legal custody, this needs to be confirmed with signature and date on the informed consent by the person with legal custody. For the process of informed assenting, a separate patient information suitable for the respective age group will be provided to the patients. In the younger age group, children may not be capable of reading a text alone; in this case the parent(s) or legal guardian and/or site personnel need to read out the document.

Both documents (consent and assent) outline the participant’s rights to decline to participate or to withdraw from the study at any time. Consenting/assenting is a dynamic and continuous process that should be maintained during the trial. At each new treatment course the site staff

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should briefly discuss with parents and patients the main aspects of the trial, focusing in particular on any new information that might affect their willingness to continue the participation in the trial. The site staff is recommended to document this process in the medical records.

The patient (where appropriate) and the patient's parent(s) or legal guardian must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient and his/her parent(s) or legal guardian.

The patient (where appropriate) and the patient's parent(s) or legal guardian must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

The trial will be conducted according to the principles of GCP and the company's SOPs.

Sites and investigators are selected for participation in this trial basing on the fact that they have experience in treating patients in the trial indication and/or being member of the respective network group. An investigators' meeting including training sessions and a clinical monitor/CRA meeting will be organised prior to the initiation of the trial to ensure standardization of procedures and techniques across multiple sites and countries. In case an investigator meeting would not be feasible each investigator and his/her staff will be trained during the initiation visit at the latest. Training will be provided to all investigators, coordinators and CRAs to ensure consistency and accuracy of the entered data. Each site will receive an ISF including all information needed to conduct the trial.

Periodic on Site Visits will be performed by the CRAs to ensure trial conduct according to the protocol and documents referred to above. Details for on-site monitoring and the extent of source data verification are described in the trial monitoring manual and respective BI SOPs.

An external DMC will be tasked to assess the safety and quality of the data during the trial. The DMC will also recommend the dose escalation and/or de-escalation steps. The tasks of the DMC are described in detail in the DMC charter which is filed in the sponsor's CTMF. Adverse events and diagnoses will be coded using the MedDRA coding system. Concomitant therapies will be coded using the WHO drug dictionary.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF.

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

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8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Imaging results if performed
- Bone marrow assessment if performed
- ECG recording
- LVEF results
- Conclusion of Patient's Participation in the trial

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

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8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For afatinib this is the current version of the Investigator's Brochure (c01802941). The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for the study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 COMPLETION OF TRIAL

The whole trial will end when the last patient has completed the 28-30 day FU visit.

For EU member states:

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient out) or early termination of the trial.

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10. APPENDICES

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10.2 CLINICAL EVALUATION OF LIVER INJURY

10.2.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-Specified AESIs, are to be further evaluated using the following procedures:

10.2.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert should be confirmed using the initial sample if possible.

If the alert is confirmed on initial sample, or it is not possible to repeat testing using initial sample, the following must be completed:

1) Evaluate the patient within 48 hours and,
2) Perform the following laboratory tests:
3) Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
    1. Haptoglobin
    2. Complete blood count and cell morphology
    3. Reticulocyte count
    4. CK
    5. LDH
    6. Alkaline Phosphatase

The results of these laboratory tests must be reported to BI as soon as possible.
Use clinical judgement when performing all of the required examinations. Use a staggered approach based on clinical judgement to complete all examinations. If needed, a hepatologist should be consulted for advice. To be considered when proceeding: the patient's disease, clinical situation, exposure, suspected co-medications, past viral infections, vaccination status, social circumstances of life. Sparse blood drawing should be used and diagnostic procedures should be refined accordingly.

If the initial alert values (i.e. AST,ALT, and bilirubin) are confirmed on the second sample described as above, then an abdominal ultrasound or clinically appropriate alternate imaging (to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm) must be completed within 48 hours

The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as possible as part of the adverse event reporting process. In the event the aetiology of the abnormal liver tests results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), then the "DILI checklist" must be completed. Details of the "DILI checklist" are provided in the ISF. The following assessments need to be performed in order to complete the "DILI checklist" and results will be reported via the eCRF:

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- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF;
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;
- complete the following laboratory tests as detailed in the DILI checklist provided in the ISF:

  - *Clinical chemistry*
    alkaline phosphatase, cholinesterase (serum)*, albumin, PT or INR, CK, CK-MB, α-1 antitrypsin*, transferrin*, amylase, lipase, glucose, cholesterol, triglycerides

  - *Serology*
    Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM)*, varicella (IgG, IgM)*, parvovirus (IgG, IgM)*
    Consider virus reactivation due to patient's immune-compromised clinical status; consider assessment of viral load by PCR testing instead of serology (especially in transfused patients)

  - *Hormones, tumour-marker*
    Thyroid-stimulating hormone(TSH)*

  - *Haematology*
    Thrombocytes, eosinophils

  - Diagnostics for auto-immune hepatitis, Morbus Wilson and haemochromatosis can be completed at the very end of all assessments. These examinations are not going to change within a short time period but rather proof of a long persisting chronic condition, i.e. Anti-Smooth Muscle antibody (titre), Anti-nuclear antibody (titre), Anti-LKM (liver-kidney microsomes) Antibody, anti-mitochondrial antibody, coeruloplamin*

**If clinically indicated (e.g. immunocompromised patients)*

- **Long term follow-up**

Use clinical judgement when performing examinations for long term follow up and report these via the eCRF. Always use a staggered approach based on clinical judgement to

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complete all examinations and consider consulting a hepatologist for advice. Sparse blood drawing should be used and diagnostic procedures should be refined accordingly.

- Initiate close observation of subjects by repeat testing of ALT, AST, and bilirubin (with fractionation to total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

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10.3 FLOW CHART (PK SAMPLING)

Visit	Time Point [hh:min]	Extensive sampling[a]		Sparse sampling[b]	
		CRF Time /PTM[c]	Event	CRF Time /PTM[c]	Event
1 (Day 1)	Five minutes before study drug administration	-0:05	PK Blood	-0:05	PK Blood
	0:00	0:00	Drug admin.	0:00	Drug admin.
	1:00	1:00	PK Blood	1:00	PK Blood
	2:00	2:00	PK Blood		
	3:00	3:00	PK Blood	3:00	PK Blood
	4:00	4:00	PK Blood		
	5:00	5:00	PK Blood		
	6:00	6:00	PK Blood		
	8:00	8:00	PK Blood		
	24.0	24.0	PK Blood		
2 (Day 8) or 3 (Day 15) or 4 (Day 22)[d]	Five minutes before study drug administration	-0:05	PK Blood	-0:05	PK Blood
	0:00	0:00	Drug admin.	0:00	Drug admin.
	1:00	1:00	PK Blood	1:00	PK Blood
	2:00	2:00	PK Blood		
	3:00	3:00	PK Blood	3:00	PK Blood
	4:00	4:00	PK Blood		
	5:00	5:00	PK Blood		
	6:00	6:00	PK Blood		
	8:00	8:00	PK Blood		
	24.0	24.0	PK Blood		
3 (Day 15) or 4 (Day 22)[d]	Five minutes before study drug administration	-0:05	PK Blood	-0:05	PK Blood
	0:00	0:00	Drug admin.	0:00	Drug admin.

a Whenever possible a full PK profile should be taken after first dose and at steady state. An additional trough sample will be taken on day 15 to confirm steady state exposure to afatinib.

b For paediatric patients who are not able to undergo extensive PK sampling, a limited sampling approach should be applied

c All samples should be taken as close as possible to the given time points

d In case patients' switch from tablet to liquid formulation or vice versa becomes necessary during treatment or if for any other reason (e.g. AE) PK sampling cannot be performed as planned, additional PK profiles may be obtained within treatment course 1 as deemed appropriate by the investigator and after consultation with the sponsor.

In addition, in patients carrying a Rickham- or Ommaya reservoir, or undergoing lumbar puncture for clinical reasons not related to the trial, trough CSF sampling may be performed

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on day 8 or later to investigate CNS exposure to afatinib. This procedure is optional. The trough CSF PK sample always must to be accompanied by a trough plasma PK sample taken at the same time-point

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10.4 P-GLYCOPROTEIN INHIBITORS AND INDUCERS

Examples of P-gp modulators that can be considered as potent inhibitors and/or potent inducers of the P-gp (P-gp is also known as MDR1) are listed below in Table 10.4: 1.

Table 10.4: 1 List of potent inhibitors and inducers of P-glycoprotein (MDR1)

Inhibitors	Inducers
Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporine Diltiazem Dronedarone Erythromycin Felodipine Itraconazole Ketoconazole Lopinavir Nelfinavir Ritonavir Quinidine Ranolazine Saquinavir Tacrolimus Ticagrelor Verapamil	Carbamazepine Phenytoin Rifampicin St John's wort Phenobarbital salt Tipranavir Ritonavir

As the information on potent inhibitors and inducers of P-gp may evolve, it is important for the investigator to assess such status on concomitant therapies. Of note, co-administration of P-gp modulators must be avoided during course 1 of Phase I dose finding.

In addition P-gp modulators should be avoided within 14 days or at least 5 half-lives of the drug (whichever is longer) prior to the first dose of afatinib. For use of strong P-gp inhibitors after course 1 of the dose finding part and during the MTD expansion cohort, staggered dosing must be considered. For use of strong P-gp inducers after course 1 of the dose finding part and during the MTD expansion cohort, afatinib daily dose should be increased based on tolerability and discussion with the sponsor.

In case of questions the sponsor/sponsor representative should be contacted.

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10.5 TUMOUR DIAGNOSIS AND TREATMENT OF PAEDIATRIC TUMOURS

The below table summarizes the different tumour types to be considered in the dose finding part of this trial

Table 10.5:1 Standard methods for diagnosis and treatment of paediatric tumours

Tumour diagnosis	Standard methods for diagnosis	Standard treatment at diagnosis
1. HGG	**Clinical presentation**: variable and nonspecific, depending on the location of the lesion. Frequently symptoms suggestive of increased intracranial pressure are observed e.g. headache, nausea, and vomiting, neurological symptoms: Ataxia, cranial nerve palsies, meningisms, changes in consciousness, visual and verbal disturbances, endocrine disorders, pareses, urine and stool incontinence, mood and personality changes, school difficulties, seizures, obstructive hydrocephalus with severe lethargy. Increased head circumference or bulging fontanel, failure to thrive can occur in infants. **Imaging and other diagnostics** measures include: Neurological exam, ophthalmological exam, cerebral MRI, cerebral CT with contrast to discover calcifications; histopathological diagnosis is made from tumour tissue, sometimes additional IHC exams like glial fibrillary acidic protein (GFAP), synaptophysin or neurofilament protein staining may be needed In case of **recurrent/refractory or metastatic disease** cMRI with and without gadolinium and CSF puncture are indicated	multimodality therapy consisting of surgery, radiotherapy and chemotherapy; chemotherapy: vincristine and carboplatin combinations; lomustine, topotecan, temozolomide, iproplatin, actinomycin D, ifosfamide, cyclophosphomide
2. DIPG	see HGG	no effective therapy; hyperfractionated radiotherapy, pre-irradiation chemotherapy, adjuvant chemotherapy (for standard chemotherapy agents used, please refer to HGG), high dose chemotherapy, concurrent chemo-radiotherapy and radiosensitizers

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Table 10.5:1 Standard methods for diagnosis and treatment of paediatric tumours (cont'd)

3. Lower grade astrocytomas	see HGG	Resection; extent of resection strongly correlates with survival; chemotherapy at recurrence: carboplatin and vincristine, cisplatin, etoposide, lenalidomide, TMZ
4. Neuro-blastoma	**Clinical symptoms** largely depend on the location of the tumour. Nerve palsy, paralyses, renal symptoms and obstructions (tracheal and genitourinary) are frequently observed. Neurological symptoms include the Horner-syndrome, fever, and periorbital ecchymosis may be present. **Laboratory exams** include urine and serum HVA/VMA assessment, NSE, LDH, ferritin, molecular markers (nmyc, chromosome 1p changes) are also included. **Bone marrow biopsies** reveal typical Homer Wright rosettes and material can be used for RT-PCR **Imaging exams** include but are not limited to Xray, CT, MRI and ultrasound; MIBG scans and scan using somatostatin receptor analogues;	chemotherapy combinations of alkylating agents, anthracyclines, topoisomerase inhibitors, platinum compounds and vinca alkaloids (i.e. combination therapies including agents like ifosfamide, cyclophosphamide, dacarbazin, melphalan, adriamycin, etoposide, topotecan, cisplatin, carboplatin, vincristine and vinblastin), radiotherapy, MIBG treatment, high dose chemotherapy with bone marrow rescue, immunotherapy with anti-GD2 antibodies
5. Ependymoma	see HGG As most of the ependymomas (60%-70%) are located in the posterior fossa, typically, there is a relatively short (few weeks to few months) history of the symptoms described above. Supratentorial ependymomas can cause lobar syndromes, mood and personality changes with un-explained school difficulties, headaches, nausea and vomiting, and less commonly seizures. Due to the young age at diagnosis symptoms as described for infants above, occur more frequently.	high frequency of chemotherapy and radiation resistance → surgery with the at most curative intent, mostly chemotherapy combinations of cisplatin or carboplatin and vincristine, also and/or etoposide, cyclophosphamide

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Table 10.5:1 Standard methods for diagnosis and treatment of paediatric tumours (cont'd)

6. Medullo-blastomas and PNETs	see HGG Many patients already demonstrate symptoms of systemic metastases at diagnosis and clinical may be dominated by symptoms of metastases (loss of function, pain); **Histopathology** Homer Wright rosettes or at least two of the below mentioned markers must be present: translocation t(11;22)(q24;q12) (1), t(21;22)(q22;q12) or t(7;22)(p22;q12); NSE, S100 synaptosin, chromogranin, vimentin, cytokeratin, actin und LCA stains are performed Usually patients show elevated levels of LDH and ferritin in their **blood labs**; **Imaging exams** include but are not limited to Xray, Ct, MRI and ultrasound; in case of metastatic disease FDG-PET is used. **Tumour biopsies** are mandated to confirm the initial diagnosis.	surgery, radiation and chemotherapy; combination chemotherapy for medulloblastoma: vincristine, carbo-/cisplatin, cyclophosphamide and/or lomustine, etoposide, TMZ; Chemotherapy for PNETs, like those for neuroblastoma: combinations of agents like alkylating agents (ifosfamide, cyclophosphamide), anthracyclines(adriamycin), etoposide, actinomycin D and vincristine
7. RMS	**Clinical symptoms** largely depend on the location of the tumour **Imaging exams** include but are not limited to Xray, CT, MRI and ultrasound; in case of metastatic disease FDG-PET is used. **Tumour biopsies** are mandated to confirm the initial diagnosis, and should be performed as open surgical intervention to assure that sufficient material is obtained **for histopathology**, IHC and cyto-, and molecular genetical exams. Myogenin, MyoD1, desmin, vimentin, myoglobin, actin, NSE, S-100, MIC2 stains are done. Furthermore e.g. in alveolar RMS - t(2;13)(q35;q14)) exams are done.	Treatment options for high- risk limited; conventional treatment with chemotherapy, surgery and radiotherapy; chemotherapy: dactinomycin, vincristine, alkylating agents (ifosfamide, cyclophosphamide), anthracyclines (doxorubicin and epidoxorubicin), etoposide, and platinum compounds.

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10.6 DATA OF THE RELATIVE BIO-EQUIVALENCE STUDY 1200.35

The statistical evaluation of the relative BA results is summarized in Table 10.6: 1 below.

Table 10.6:1 Summary of results from the relative bioavailability trial 1200.35 20 mg film-coated tablet versus drinking solution

Test	Reference	Parameter	Geometric mean ratio (%)	Lower 90% CI (%)	Upper 90% CI (%)	Intra-individual gCV (%)
20 mg film-coated tablet (FF tablet)	Drinking solution 20 mg per bottle	C_{max} [ng/mL]	85.31	68.75	105.88	42.3
		$AUC_{0-\infty}$ [ng·h/mL]	92.24	76.30	111.51	36.7

Source data: Trial 1200.35 (U09-2233, Table 11.5.2.1.3: 1)

It should be noted that the trial was not intended to show bioequivalence between the formulations (N=22 healthy volunteers were treated in a cross-over design; considering the variability in PK observed in this trial, N=84 healthy volunteers would have been required to have a targeted power of 90% to show bioequivalence assuming a ratio of 0.95 for both formulations).

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10.7 BODY SURFACE AREA CALCULATION

The target dose of Afatinib has been calculated based on BSA derived from the Dubois and Dubois formula.

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

Whereas:

W is the weight is in kilograms

H is the height is in centimetres.

The paediatric dose was calculated as follows:

Dose child = Dose adult x (BSA child / BSA adult) considering BSA = 1.75 m2 for adult

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10.8 EXAMPLE FOR FORMULA APPROPRIATE FOR GFR ESTIMATION IN CHILDREN

Please use the modified Schwartz-formula below or your institutional standard formula appropriate for GFR estimation in paediatric patients. In case GFR measurements are available, these may replace GFR estimation.

$$\mathbf{eGFR = k \times L/Scr}$$

whereas:

eGFR is estimated GFR in millilitres per minute per 1.73m²

L is height in centimeters

Scr is serum creatinine in milligrams per decilitre

k is 0.45 for term infants throughout the first year of life, 0.55 for children and adolescent girls and 0.7 for adolescent boys

Note that the Cockroft-Gault formula is not suitable to estimate GFR in paediatric patients

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		04 May 2015
EudraCT number		2014-002123-10
BI Trial number		1200.120
BI Investigational Product(s)		Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution
Title of protocol		Phase I open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged 2 years to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒ applies to optional CSF PK sampling
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☒ applies to clarification for P-gp modulators
Section to be changed		1. Flow-Chart 2. Abbreviations 3. Section 1.2 4. Section 4.2.3.1 5. Section 5.5 6. Section 7.3.5 7. Appendix 10.3 8. Appendix 10.4
Description of change		1. Add optional CSF PK sampling 2. Add CSF 3. Additional details on handling of strong P-

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Number of global amendment		1
		gp inhibitors/inducers provided 4. Same as change 3 5. Same as change 1 6. Same as change 1 7. Same as change 1 8. Same as change 3
Rationale for change		Changes 1, 2, 5, 6, 7 : To assess afatinib penetration into the CSF Changes 3, 4, 8: Clarification that the use of strong P-gp inhibitors/inducers is prohibited during course 1 of dose finding to assure that MTD definition is not affected by potential co-administration of strong P-gp inhibitors/inducers. Additional details are given on how to use strong P-gp inhibitors/inducers with afatinib if their use cannot be avoided after course 1 of the dose finding part and how to handle them during MTD expansion cohort.

Number of global amendment		2
Date of CTP revision		18 Aug 2016
EudraCT number		2014-002123-10
BI Trial number		1200.120
BI Investigational Product(s)		Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution
Title of protocol		Phase I open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged 2 years to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology
To be implemented only after approval of the IRB/IEC/Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of		☐

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Number of global amendment		2
change with request for approval		
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Flow-Chart, Section 4.1.2, 4.2.1, 5.2.2, 6.2.1 and 6.2.2 2. Section 6.2.1 3. Section 6.2.2 4. Section 1.2, 2.3, 5.2.2.1, 8.4.1 and 9.2
Description of change		1. Clarification on the possible use of a pre-screening informed consent for the collection and testing of tumour tissue sample 2. Clarification on how to manage collection of tumour images during the screening period 3. Alignment of the section with Flow Chart 4. Deletion of IB version reference
Rationale for change		1. Clarification 2. Clarification 3. Clarification - correction of typo and omission 4. Clarification to always refer to the most recent IB version

Number of global amendment		3
Date of CTP revision		02 June 2017
EudraCT number		2014-002123-10
BI Trial number		1200.120
BI Investigational Product(s)		Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution
Title of protocol		Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 years to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology
To be implemented only after approval of the		☒

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Number of global amendment		3
IRB/IEC/Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Synopsis 2. Flow Chart 3. Section 1 (1.1 and 1.2) 4. Section 2 (2.1, 2.2, 2.3) 5. Section 3 (3.1, 3.2, 3.3) 6. Section 4 (4.1.2, 4.1.3, 4.1.4, 4.2.2.3, 4.2.3) 7. Section 5 (5.1, 5.2.1, 5.3.1, 5.4, 5.5.1, 5.5.3, 5.6-5.6.1) 8. Section 6 (6.2.1, 6.2.2, 6.2.3) 9. Section 7 (7.1, 7.3.1, 7.3.2, 7.3.5, 7.6) 10. Section 9 (9.1, 9.2) 11. Section 10 (10.1, 10.3)
Description of change		1. Multiple changes for adaptive Phase I/II design 2. Same as 1 3. Same as 1 and literature update 4. Same as 1 5. Same as 1 6. Same as 1, literature update and update on contraception methods 7. Same as 1 8. Clarification on pre-screening informed consent use/editorial changes 9. Same as 1 10. Addition of literature references 11. Same as 1 and clarification on alternative PK samplings
Rationale for change		Changes 1 to 7, 9, 11: to reflect changes necessary to comply with the Written Request received from FDA

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Number of global amendment		3
		Additional change 6: to follow the contraception guidance per ICH M3 (R2) and HMA CTFG Change 8 and 11: clarifications and correction of typos Additional changes 3, 6 and change10: to consider latest updates from literature

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APPROVAL / SIGNATURE PAGE

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Title: Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor		02 Jun 2017 15:30 CEST
Approval-Therapeutic Area		02 Jun 2017 15:44 CEST
Author-Trial Statistician		02 Jun 2017 15:51 CEST
Approval-Team Member Medicine		03 Jun 2017 01:29 CEST
Author-Clinical Pharmacokineticist		06 Jun 2017 10:17 CEST
Author-Clinical Monitor		06 Jun 2017 10:20 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed