**Title of Study:**

# FIND
# FGFR inhibitor in FGFR dysregulated cancer.

A phase II trial to evaluate efficacy and safety of erdafitinib in patients with advanced NSCLC harboring FGFR genetic alterations after relapse of standard therapy

Short Title/Acronym: FIND

Eudra-CT Number: 2018-000399-13

ID of Trial Protocol: Uni-Koeln-3254

**Start of Study – Completion of Study**

First patient enrolled on July 17, 2019, last study visit of last patient September 23, 2022.

## Final Study Report

**Version 1.0 / Date: July 28th, 2023**

**Sponsor of Clinical Trial:**

University of Cologne, Albertus-Magnus-Platz, 50923 Cologne, Germany

Represented by

PD Dr. med. Lucia Nogova, MSc

Lung Cancer Group Cologne

University Hospital Cologne

Kerpener Straße 62, 50937 Cologne, Germany

Phone ++49 (0) 221 478-88028 / Fax ++49 (0) 221 478-3978

**Head of Clinical Trial Team/Principal Investigator:**

PD Dr. med. Lucia Nogova, MSc

**Authors of Final Study Report:**

PD Dr. med. Lucia Nogova, MSc

Lung Cancer Group Cologne

University Hospital Cologne

Kerpener Straße 62, 50937 Cologne

Phone ++49 (0) 221 478-88028 / Fax ++49 (0) 221 478 3978

## Signatures

By their signatures the authors approve the content of the present final report. The clinical trial described herein was conducted in compliance with the principles of the Helsinki Declaration, Good Clinical Practice (GCP), and pursuant to all applicable legislation.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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| **Sponsor / Representative** | PD Dr. med. Lucia Nogova, MSc | Köln, 28.7.2023<br>Place, Date |
| **Principal Investigator** | PD Dr. med. Lucia Nogova, MSc | Köln, 28.7.2023<br>Place, Date |
| **Biometrician** | Prof. Dr. rer. medic. Martin Hellmich | Köln, 28.07.2023<br>Place, Date |
| **Additional authors of the Final Study Report, if applicable** | I. Terjung<br>Inken Terjung, MSc | Köln, 28.07.2023<br>Place, Date |

# 2 Synopsis

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| Full Study Title | A phase II trial to evaluate efficacy and safety of erdafitinib in patients with advanced NSCLC harboring FGFR genetic alterations after relapse of standard therapy.<br><br>*Study title before protocol amendment 1: A phase II trial to evaluate efficacy and safety of erdafitinib in patients with advanced squamous NSCLC (sqNSCLC) harboring FGFR genetic alterations after relapse of standard therapy* |
| Short Title | FIND: FGFR inhibitor in FGFR dysregulated cancer. |
| Study Sponsor | University of Cologne, Germany, represented by the Principal Coordinating Investigator (PCI) |
| PCI | PD Dr. Lucia Nogova, MSc, University Hospital Cologne |
| Study Centers | Lung Cancer Group Cologne (LCGC), Department I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, Germany<br><br>Interdisciplinary Study Center, Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Germany<br><br>Evangelische Lungenklinik, Berlin, Germany<br><br>Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Germany<br><br>Department II of Internal Medicine, Hematology/Oncology, University Hospital Frankfurt, Germany<br><br>Thoracic Oncology, Asklepios Clinic, Gauting, Germany<br><br>National Center for Tumor Diseases/University Cancer Center, Early Clinical Trial Unit, University Hospital Dresden, Dresden, Germany<br><br>Department of Hematology and Oncology, Pius Hospital Oldenburg, Germany<br><br>Hematology/Oncology, Städtisches Klinikum Braunschweig, Germany<br><br>Department V of Internal Medicine, University Hospital of Saarland, Homburg, Germany<br><br>Early Clinical Trial Unit, Interdisciplinary Tumour Center, University Hospital Freiburg, Germany |
| Biostatistics | Institute of Medical Statistics and Computational Biology, University of Cologne |
| Study Drug | Erdafitinib (JNJ-42756493) |
| Study Design | Phase II, genetically preselected, multicenter, multi-cohort, open-label |
| Primary Objective | • To evaluate the efficacy of erdafitinib in non-small cell lung cancer (NSCLC) with fibroblast growth factor receptors (FGFR) genetic alteration |
| Primary Endpoint | • Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 under erdafitinib treatment in NSCLC with genetic alteration in FGFR |

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| Secondary Objectives and Endpoints | • To evaluate the tolerability of erdafitinib (endpoints: assessment of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTC-AE) V5.0)<br>• To evaluate the clinical efficacy of erdafitinib descriptively (endpoints: progression-free survival (PFS), overall survival (OS)) |
| Exploratory Analyses | • To correlate clinical efficacy of erdafitinib with specific hot spot mutations/grouped FGFR alteration status (endpoints: ORR, PFS, OS)<br>• To describe the frequency of mutated and translocated FGFR patients in NSCLC<br>• To identify clear driving mutations from potential passenger mutations<br>• To identify potential mechanisms of resistance to treatment with erdafitinib and passenger mutations in biopsy tumor tissue (formalin-fixed paraffin-embedded (FFPE) and fresh frozen) and circulating tumor DNA (ctDNA) isolated from blood samples |
| Treatment Design | Patients were prescreened for FGFR alterations within the National Network of Genomic Medicine (nNGM) Germany. FGFR mutations in diagnostic biopsies were determined routinely with standardized Next Generation Sequencing (NGS) methods in molecular screening centers of nNGM.<br>NSCLC samples without any activating mutations in FGFR or other therapeutic relevant drivers and without presence of mutations excluded for the purpose of this study (see exclusion criteria) were tested with NGS for FGFR fusion genes.<br>The NGS for the FGFR fusion genes were performed either locally or at the Institute of Pathology in Cologne. In Cologne, the anchored multiplex Polymerase Chain Reaction analysis (Archer) was used for the identification of FGFR fusion genes.<br>Pathologists within the nNGM/NGM informed the treating oncologist through the pathology report about the FGFR alteration and the possibility to treat the patient in the FIND trial. In case the patient was potentially suitable and willing to be treated within the FIND trial, the oncologist refered the patient to one of the participating study centers in the FIND trial.<br>The study center sent via an e-mail the particular FGFR genetic alteration to the FIND molecular board in Cologne (FINDallocation@uk-koeln.de). The FIND molecular board (comprising members of pathology, translational research and medical oncology) determined if the FGFR alteration was likely to be pathogenic. In case of a clinically relevant genetic alteration, the patient was allocated to the appropriate cohort and was allowed to enter study screening.<br>Patients with advanced NSCLC and FGFR alterations, in good clinical condition (Eastern Cooperative Oncology Group (ECOG) performance status score 0-2), with acceptable laboratory results, after standard treatment and consenting for a fresh frozen biopsy were considered eligible for the study.<br>Once the patient had consented study participation and fulfilled all inclusion and no exclusion criteria, a fresh frozen biopsy and blood for ctDNA had to be obtained before the initiation of treatment. In case the archival biopsy of the molecular prescreening was not available at the Sponsor, the archival biopsy was sent to the Sponsor along with fresh screening biopsy. |

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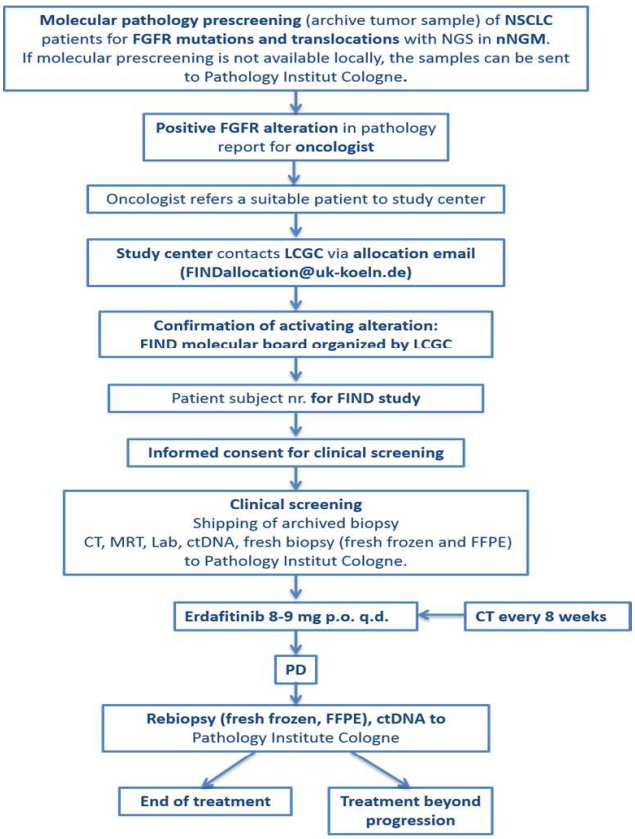
| | The duration of a study cycle was defined as 28 days. Study treatment started at Cycle 1 Day 1 (C1D1) with 8 mg erdafitinib per os daily with the possibility to uptitrate to 9 mg based on phosphate levels on C1D15. CT/MRI-scans for response evaluation according to RECIST 1.1 were conducted every 8 weeks and from C13 every 12 weeks. The patient continued on study drug until disease progression, unacceptable toxicity or investigator's or patient's decision to withdraw the treatment.<br><br>At the time of progression, a fresh frozen rebiopsy of a progressing tumor lesion and blood for ctDNA was obtained to characterize resistance mechanisms to FGFR targeted treatment. Treatment beyond progression was possible, but had to be confirmed by the Sponsor.<br><br>For biopsies (clinical screening and progression), at least two samples were required. One biopsy sample (FFPE-sample) was put into formalin for paraffin embedding and pathological assessment (tumor cell content, quality of samples etc.), immunohistochemistry (IHC) and NGS. The second sample (fresh frozen sample) was stored on dry ice to be used as fresh frozen material for sequencing at the Department of Translational Genomics. Both samples were shipped to the Institute of Pathology, University of Cologne for central registration.<br><br>  <br>**Figure 1: Study flowsheet** |
| Patient Cohorts | • Cohort 1: Activating (high confidence) FGFR translocations (max. 15 patients, cohort for primary objective; Simon's two-stage minimax design))<br>• Cohort 2: Activating (high confidence) hotspot FGFR mutations (max. 15 patients, cohort for primary objective; Simon's two-stage minimax design)<br>• Cohort 3: Activating (low confidence) FGFR alteration (max. 20 patients, cohort not evaluable for primary objective) |
| Number of Patients | **Patient number in cohort 1 and 2** was calculated with respect to response to erdafitinib based on Simon's two-stage minimax design (Simon, 1989): |

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| | The null hypothesis (inefficacious treatment) $H_0$:$p_{new}$≤10% was tested at one-sided significance level $\alpha$=10%. A power of at least 90% (i.e. $\beta$=10%) should have been attained for the alternative hypothesis (efficacious treatment) $H_A$:$p_{new}$≥40%.<br><br>Stage 1: In the first stage, 8 patients were supposed to be treated. If less than 1 partial response (PR) on erdafitinib according to RECIST 1.1 was observed, enrollment would have been stopped and it would have been concluded that the treatment is inefficacious (Machin et al., 2011).<br><br>Stage 2: If at least 1 PR on erdafitinib was observed in the first trial phase (i.e. 1 in 8), another 7 patients would have been enrolled and treated as described above.<br><br>If at least 4 in 15 patients responded, it would have been concluded that the treatment had shown sufficient promise of efficacy for further investigation.<br><br>Not evaluable patients would have been replaced (≤2 expected).<br><br>**In the exploratory cohort 3,** it was planned to include a maximum of 20 NSCLC patients with different FGFR alterations. A sample size of 20 would have been sufficient to yield an exact 95% confidence interval with widths 30% (or 45%) for an assumed ORR of 10% (or 40%, respectively) (Shan et al., 2017). |
| Inclusion Criteria | • Age ≥ 18 years.<br>• Stage IIIB/IV NSCLC patients with activating FGFR alteration after failure on standard treatment, or in the opinion of the investigator no effective standard therapy exists, is appropriate, tolerated, or is considered equivalent to study treatment.<br>• Activating FGFR alteration as approved by FIND Molecular Board.<br>• ECOG performance status score 0, 1, or 2.<br>• Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.<br>• Clinical laboratory values and cardiovascular measurements at screening:<br><br>Hematology<br>Hemoglobin: ≥8 g/dL (≥5 mmol/L) (must be without red blood cell [RBC] transfusion within 7 days prior to the laboratory test; recombinant human erythropoietin use is permitted)<br>Platelets: ≥75×$10^9$/L<br>Absolute Neutrophil Count (ANC): ≥1.5×$10^9$/L (prior growth factor support is permitted more than 7 days prior to the laboratory test)<br>Chemistry<br>AST and ALT: ≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for patients with liver metastases<br>Creatinine clearance: ≥40 mL/min based upon CKD-EPI formula |

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| | Total bilirubin: ≤1.5 × ULN; except in patients with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)<br>**Cardiovascular**<br>Corrected QT interval according to Fridericia (QTcF): ≤480 msec based on the average of triplicate assessments performed approximately 5 minutes apart<br>ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; GFR=glomerular filtration rate; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal<br>• Disease measurable per RECIST 1.1 for cohort 1 and 2.<br>• A woman of childbearing potential who is sexually active must have a negative pregnancy test (β-human chorionic gonadotropin [β-hCG]) at Screening (urine or serum, minimum sensitivity 25 IU/L or equivalent units of β-hCG) within 24 hours prior to the start of erdafitinib.<br>• WOCBP and men who are sexually active with WOCBP must use appropriate method(s) of contraception with a failure rate of less than 1% per year before study entry, during the study and until 5 months after taking the last dose of study drug.<br>Note: Appropriate methods of contraception are:<br>Total abstinence, if it is the appropriate lifestyle, female sterilization or tubal ligation (at least 6 weeks prior to the start of the study treatment), male sterilization (at least 6 months prior to the start of the study treatment) and/or a combination of a hormonal method of contraception with a barrier method or/and an intrauterine device or system are considered as highly effective methods of contraception.<br>• Sexually active men must use a condom to prevent delivery of the drug via seminal fluid.<br>• Women must not be breastfeeding.<br>• Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.<br>• Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 5 months after the last dose of study drug. |
| Exclusion Criteria | • Pathogenic somatic alterations in the following genes: EGFR, BRAF, ALK ROS1 and NTRK (Please note that molecular testing might be reduced in heavy smokers with NSCLC. If discrepancies occur, please contact the Sponsor).<br>• Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 30 days or 5 half-life times (whichever is longer). |

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| | • Treatment with small molecules or chemotherapy within 7 days prior to C1D1.<br>• Treatment with monoclonal antibodies within 28 days prior to C1D1.<br>• Any other ongoing malignancy that would potentially interfere with the interpretation of erdafitinib efficacy.<br>• Symptomatic central nervous system metastases.<br>• Received prior FGFR inhibitor treatment or if the patient has known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients.<br>• Any corneal or retinal abnormality likely to increase the risk of eye toxicity, i.e.:<br>a. History of or current evidence of central serous retinopathy or retinal vascular occlusion<br>b. Active wet, age-related macular degeneration<br>c. Diabetic retinopathy with macular edema (non-proliferative)<br>d. Uncontrolled glaucoma (per local standard of care)<br>e. Corneal pathology such as keratitis, keratoconjunctivitis, keratopathy, corneal abrasion, inflammation or ulceration.<br>• Has persistent phosphate level >ULN during screening (on 2 consecutive assessments at least 1 week apart, within 14 days prior to C1D1) and despite medical management.<br>• Has a history of current uncontrolled cardiovascular disease including:<br>a. unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes tachycardia, cardiac arrest, or known congestive heart failure NYHA Class III-V within the preceding 3 months (Attachment 3 of the study protocol); cerebrovascular accident or transient ischemic attack within the preceding 3 months.<br>b. QTcF prolongation as confirmed by triplicate assessment at screening (QTcF >480 milliseconds).<br>• Pulmonary embolism or other venous thromboembolism within the preceding 2 months.<br>• Known HIV infection, testing is mandatory (a-HIV 1/2).<br>• Patients with acute or chronic Hepatitis B infection (tests should include assessment of HBsAg and HBc IgG antibody. If one parameter is positive, determine HBV-DNA to confirm acute infection. Patients with positive results for HBsAg and/or HBV-DNA are considered positive for acute or chronic infection).<br>• Patients with acute or chronic Hepatitis C infection (determine HCV-RNA. Patients with positive result for HCV-RNA are considered positive for acute or chronic infection). |

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| | • Has not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, Grade 1 neuropathy, Grade 1-2 hearing loss).<br>• Has impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.<br>• Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the patient is expected to participate in the study or within 2 weeks after the last dose of study drug administration. (Note: patients with planned surgical procedures to be conducted under local anesthesia may participate).<br>• Any serious underlying medical condition, such as:<br>a. Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection requiring current systemic treatment.<br>b. Psychiatric conditions (e.g., alcohol or drug abuse), dementia, or altered mental status.<br>• Any other issue that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (i.e., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. |
| Timelines | Inclusion first patient: 07/2019<br>Inclusion last patient: 09/2022<br>Last patient last visit: 09/2022<br>Closure of database: 07/2023 |
| Study Conduct | LCGC Study Center (Clinical Trial Management)<br>Acromion GmbH (Monitoring, Data Management, Project Management, Pharmacovigilance (in collaboration with Scratch GmbH))<br>NGM Cologne and 15 academic centers of nNGM (Tumor Tissue Analysis)<br>Department of Translational Genomics (Sequencing and Data Analysis)<br>Clinigen Clinical Supplies Management (Study Drug Management) |
| Study Results | In the study, 26 patients have been enrolled, of which 4 patients have failed screening. Of the 22 patients on erdafitinib, seven patients have been enrolled in cohort 1, eight patients in cohort 2 and seven patients in cohort 3.<br>In cohort 1, two patients achieved PR. However, one PR remained unconfirmed (uPR). The best response in the cohort 2 was stable disease (SD). No new significant safety findings were observed in the study. The study was terminated prematurely due to slow recruitment and decision of funder. |

# 3 Table of contents

# 4 Acronyms/abbreviations and definitions

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| AE | Adverse event (*cf.* SAE below) |
| AMG | Arzneimittelgesetz (German Medicinal Products Act) |
| AR | Adverse reaction |
| AUC | Area under the concentration curve |
| β-hCG | β-human chorionic gonadotropin |
| C | Cycle of treatment |
| Cmax | Maximum serum concentration |
| CR | Complete response |
| CRO | Clinical research organization |
| CT | Computed tomography |
| CTC-AE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor DNA |
| D | Day of treatment |
| DMSC | Data Monitoring and Safety Committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed paraffin-embedded |
| FGFR | Fibroblast growth factor receptors |
| HIV | Human immunodeficiency virus |
| ICF | Informed consent form |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| LCGC | Lung Cancer Group Cologne |
| MRI | Magnetic resonance imaging |
| NGS | Next Generation Sequencing |
| nNGM | National Network of Genomic Medicine |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PCI | Principal Coordinating Investigator |
| PFS | Progression-free survival |
| PI | Principal Investigator |
| PK | Pharmacokinetics |

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| PR | Partial response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction |
| SD | Stable disease |
| sqNSCLC | Squamous non-small cell lung cancer |
| SUSAR | Suspected unexpected serious adverse reaction |
| uPR | Unconfirmed partial response |

# 5 Ethics

## 5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study and all required documents (study protocol, ICF and any amendments) were submitted to the Central Ethics Committee of the University of Cologne and to local Ethics Committees of the sites, and were approved by the Committees.

For a list of all Ethics Committees consulted, please refer to appendix 17.1.3.

## 5.2 Ethical conduct of the study

This study was conducted in compliance with the Declaration of Helsinki (in its version of 2013) and the AMG (German Medicinal Products Act), esp. its §§ 40-42, in its current versions, as well as the principles of the proper conduction of clinical trials (ICH-GCP).

As provided in the AMG, the study Sponsor took out the insurance for every patient who agreed to participate in this clinical trial.

## 5.3 Patient information and consent

Prior to their inclusion in the study, a registered and study specifically trained investigator discussed the study with every patient informing them in detail about the objectives, risks, and the study procedures. The patient ICF was provided to the patients, and if, after a minimum time of 24 hours for consideration and another discussion of potentially open questions, they agreed to participate, patient and investigator signed the ICF. In the FIND study, patients and investigators signed two ICFs – one for the clinical part of the study and one for the biobanking of the samples (blood and tumor sample). A copy of the signed ICFs was handed out to the patient, the original versions remained at the site.

The sample ICFs including their amendments are provided in appendix 17.1.3.

# 6 Investigators and study administrative structure

The Sponsor of the trial was the University of Cologne, represented by the PCI PD Dr. Lucia Nogova. The trial was carried out as a multicenter study at eleven study sites:

- University Hospital Cologne (LCGC)
  Principal Investigator (PI): PD Dr. Lucia Nogova, deputy: Prof. Dr. Jürgen Wolf
- University Hospital Würzburg
  PI: Dr. Jens Kern, deputy: Dr. Horst Hummel
- Evangelische Lungenklinik Berlin
  PI: Prof. Dr. Christian Grohé, deputy: Dr. Sylke Kurz
- University Hospital Aachen
  PI: Dr. Jens Panse, deputy: Dr. Martin Kirschner
- University Hospital Frankfurt
  PI: Dr. Martin Sebastian, deputy: Dr. Jan Alexander Stratmann
- Asklepios Hospital Munich-Gauting
  PI: Prof. Dr. Niels Reinmuth, deputy: PD Dr. Thomas Duell
- University Hospital Dresden
  PI: Dr. Martin Wermke, deputy: Dr. Tina Thomas/Dr. Katrin Wetzko
- Pius Hospital Oldenburg
  PI: Prof. Dr. Frank Griesinger, deputy: Johannes Hoffmann
- Städtisches Klinikum Braunschweig
  PI: PD Dr. Arne Trummer, deputy: Dr. Miriam Ahlborn
- University Hospital Saarland Homburg

PI: Sven Henschke, deputy: Prof. Dr. Heinrike Wilkens
- University Hospital Freiburg
  PI: Prof. Dr. Waller, deputy: Dr. Justyna Rawluk

Medical treatment and management of the patients were in the hands of the investigators and study nurses at each site. Imaging procedures to be applied during the study included computed tomography (CT) and/or magnetic resonance imaging (MRI) scans at each site. Additionally, ophthalmologists were involved for specific examinations concerning possible eye toxicity of erdafitinib. Paraffin embedded biopsy samples were pathologically assessed (tumor cell content, quality of samples etc.) at the Institute of Pathology and IHC and NGS were performed. Clinigen Clinical Supplies Management was responsible for labelling and logistics of study drug.

The following persons contributed to the planning, implementation and evaluation of the study:

- Investigators at the sites
- Study nurses at the sites
- Data Monitoring and Safety Committee (DMSC) (Prof. Dr. Reck, Prof. Dr. Gautschi, Prof. Dr. Lehmacher)
- Prof. Dr. rer. medic. Martin Hellmich, University of Cologne (biometric planning)
- Julia Frank, M.Sc., and Pierce Heiden, M.Sc., University of Cologne (biometric analysis)
- Acromion GmbH (Clinical research organization (CRO) responsible for Monitoring, Data Management, Project Management and Pharmacovigilance (in collaboration with Scratch GmbH))
- LCGC Study Center (Clinical Trial Management, Sponsor Tasks)

# 7 Introduction

Downstream signaling of FGFR1-4 regulates cell proliferation, migration, differentiation and survival in healthy cells (Turner and Grose, 2010). Genetic alterations (amplifications, point-mutations and translocations) in FGFR1-4 genes cause altered signaling and oncogenic transformation (Helsten et al., 2015; Babina and Turner, 2017). FGFR-alterations with sensitivity to kinase inhibition have been identified in a variety of tumors such as breast-, bladder- and endometrial-cancer, squamous cell lung and head and neck cancer, cholangiocarcinoma and glioblastoma (Jacquemier et al., 1994; Courjal et al., 1997; Cappellen et al., 1999; Freier et al., 2007; Dutt et al., 2008; Turner et al., 2010; Weiss et al., 2010; Göke et al., 2015).

The frequency of somatic FGFR1-3 mutations in lung cancer is about 4% (Helsten et al., 2016). Translocations occur with a similar frequency of about 4% in lung cancer (Wu et al., 2013). Multiple of these FGFR alterations are shown to have oncogenic potential as demonstrated in multiple in vitro, in vivo and first-in-man studies (Liao et al., 2013; Tabernero et al., 2015; Nogova et al., 2017).

Preclinical models in NSCLC cell lines and xenografts showed oncogenic activity of FGFR2/3 mutations with consecutive sensitivity to FGFR inhibitors (Liao et al., 2013). Similarly, FGFR3-TACC translocation exerted kinase activation in squamous non-small cell lung cancer (sqNSCLC) cell lines and other tumor types (Singh et al., 2012; Wu et al., 2013). Furthermore, patient derived FGFR3-fusion lung xenograft model showed responses to FGFR targeted treatment (crownbio.com).

Thus, patients with particular activating hotspot mutations and translocations might benefit from FGFR inhibitor therapy.

A selective pan-FGFR inhibitor, BGJ398, showed in a phase I study clinical responses with differences according to the type of FGFR alterations and histological subtypes (Gettinger et al., 2016; Nogova et al., 2017). The PR rate was 11% (4/36) in patients with FGFR1 amplified sqNSCLC and 38% (3/8) in patients with FGFR3-mutant bladder cancer. No PR was observed in patients with FGFR1/2 amplified (n=25) and FGFR3 mutant (n=1) breast cancer. Patients with FGFR2-translocated (n=2) and FGFR2-mutated cholangiocarcinoma (n=1) showed reduced tumor burden of 20% and 10%, respectively (Nogova et al., 2017). In the published results from phase II trial with BGJ398 in FGFR2 translocated cholangiocarcinoma, the ORR was 14.8% with a median PFS of 5.8 months (Javle et al., 2018).

Another selective FGFR-inhibitor pemigatinib showed activity in FGFR2-altered cholangiocarcinoma (Abou-Alfa, 2020) with an ORR of 36% for patients with FGFR2 rearranged cholangiocarcinoma. Pemigatinib was approved for FGFR2 rearranged cholangiocarcinoma after previous treatment by the Food and Drug Administration (FDA) in 2020 and by EMA in 2021. Additionally, pemigatinib was approved for myeloid und lymphoid neoplasms with FGFR1 rearrangements by FDA in 2022.

## 7.1 Treatment with erdafitinib

Erdafitinib is a potent, oral pan-FGFR tyrosine kinase inhibitor with half maximal inhibitory concentration (IC50) values in the low nanomolar range for all members of the FGFR family (FGFR1 to 4). It has demonstrated potent inhibition of cell proliferation with IC50 values ranging from <1 to <100 nM in FGFR pathway-activated cancer cell lines. Erdafitinib has been shown to have in vivo antitumor activity in various murine xenograft and patient-derived mouse models of FGFR-driven cancers including gastric, bladder, and others.

Pharmacokinetic (PK) properties

In humans, treatment with erdafitinib exhibited dose-related increase in maximum serum concentration (Cmax) and area under the concentration curve (AUC) and time-independent PK within the dose range of 0.5 mg to 12 mg, both after single and multiple daily dosing. Median time to maximum serum concentration observed ranged from 2 to 4 hours (erdafitinib as capsule). Erdafitinib is highly bound to plasma proteins such as α1-acid glycoprotein. In patients, free fractions of erdafitinib in human plasma were small (average ~0.36%). In in-vitro experiments, erdafitinib was shown to be a P-glycoprotein substrate and inhibitor.

Only unchanged erdafitinib was present in plasma with no circulating metabolites. The metabolites, mainly N- and O-dealkylated derivatives (M8 and M6, respectively), formed via CYP2C9 and CYP3A enzymes, are efficiently eliminated after their formation in the excreta (majority excreted in feces). Long terminal phase half-life of erdafitinib (>50 hours) in plasma was observed resulting in approximately 3- to 5-fold accumulation of Cmax and AUC following multiple daily dosing.

Clinical efficacy in erdafitinib trials

In the phase I study (Study 42756493EDI1001), the antitumor effect of erdafitinib was observed both in patients with urothelial cancer with selected FGFR alterations, as well as other solid tumors. The safety profile was acceptable in this study population. A total of 187 patients were enrolled. For response-evaluable patients with relapsed/refractory urothelial cancer who harbored selected FGFR alterations, the objective response rate across all dose levels was 46.2%. At the 9 mg dose level, the response rate was 70.0% for response-evaluable patients with urothelial cancer who harbored selected FGFR alterations. The most frequently reported AEs were hyperphosphatemia (65%), dry mouth

(46%), asthenia (45%), stomatitis (39%), constipation (37%), and decreased appetite (34%). Twenty-two patients (12%) discontinued treatment due to AEs.

Focusing on histologic entities, FGFR alterations, and on ORR, the published interim analysis from the phase I trial showed 5 PRs in FGFR translocated tumors: in 3/8 (37.5%) patients with urothelial carcinoma, 1/3 (33%) patients with glioblastoma and in 1 patient with endometrial cancer (Tabernero et al., 2015).

A global phase II trial (Study 42756493BLC2001) is currently ongoing in patients with relapsed/refractory advanced urothelial cancer with selected FGFR mutations and translocations. As of 15 March 2018, 210 patients have been treated in this study: 33 patients in the 10 mg intermittent dosing regimen, 78 patients in the 6 mg daily regimen, and 99 patients in the 8 mg daily regimen. The ORR, including complete response (CR) and PR, was 40%. The most frequently reported AEs, most of which were Grade 1 or 2 in severity, were hyperphosphatemia (77%), diarrhea (51%), dry mouth (46%), stomatitis (58%) and decreased appetite (38%). Thirteen patients discontinued treatment due to AEs (Loriot et al, 2019).

### 7.2 Rationale for the study objectives

Approximately 80% of all NSCLC patients have no druggable genetic alterations. Treatment benefit from immunotherapy in combination with chemotherapy in advanced NSCLC patients is limited for first line treatment only. Thus, patients without druggable genetic alteration have reduced treatment options with minimal benefit by using chemotherapy alone.

FGFR genetic alterations have been identified in a small subset of patients with NSCLC. Thus, there is a relevant demand to explore therapeutic targeting of the FGFR altered NSCLC. Erdafitinib, a pan FGFR kinase inhibitor has shown clinical activity in FGFR altered solid tumors with favorable benefit-risk ratio with convincing evidence for a potential benefit in FGFR altered NSCLC patients.

Taken together, the current available data indicated a rationale to use erdafitinib in NSCLC - in a patient population without druggable genetic alteration and thus with a high unmet medical need.

Based on currently available clinical data, the safety profile for erdafitinib is anticipated to be manageable. This study will monitor safety closely to ensure resolution of the anticipated erdafitinib toxicities. These considerations strongly support the conduct of this study in an effort to improve the treatment outcomes for eligible patients with NSCLC.

For this study, based on the mechanism of action, potential risks and mitigation strategies were implemented based on experience following administration of erdafitinib.

## 8 Study objectives

The results of the phase I and II trials showed that the inhibition of the FGFR pathways exerted clinical activity in FGFR translocated and mutated solid tumors (Tabernero et al., 2015; Nogova et al., 2017; Javle et al., 2018; Siefker-Radtke et al., 2018). Thus, focusing treatment with FGFR inhibitors on FGFR mutated and translocated solid tumors may increase ORR, PFS and OS in these tumors with otherwise adverse prognosis.

NSCLC is one of the leading cancers worldwide. Targeted treatment with small molecules in NSCLC patients with genetic alterations led to significant longer OS comparing to chemotherapy. FGFR alterations are one of the potential targets with treatment impact for patients with otherwise poor prognosis (Valle et al., 2010; Paz-Ares et al., 2013; Gilbert et al., 2014; Gettinger et al., 2016; Chudasama et al., 2017, Liao et al., 2013).

### 8.1 Primary objective

- To evaluate the efficacy of erdafitinib in NSCLC with FGFR genetic alteration (endpoint: ORR per RECIST 1.1.)

### 8.2 Secondary objectives

- To evaluate the tolerability of erdafitinib (endpoints: assessment of AEs according to CTC-AE V5.0)
- To evaluate the clinical efficacy of erdafitinib descriptively (endpoints: PFS, OS)

### 8.3 Exploratory objectives

- To correlate clinical efficacy of erdafitinib with specific hot spot mutations/grouped FGFR alteration status (endpoints: ORR, PFS, OS)
- To describe the frequency of mutated and translocated FGFR patients in NSCLC
- To identify clear driving mutations from potential passenger mutations
- To identify potential mechanisms of resistance to treatment with erdafitinib and passenger mutations in biopsy tumor tissue (FFPE and fresh frozen) and ctDNA isolated from blood samples

## 9 Investigational plan

### 9.1 Overall study design and plan-description

FIND was a phase II, genetically preselected, multicenter, multi-cohort, open-label study.

NSCLC patients were prescreened within the nNGM for FGFR mutations/translocations. FGFR mutations in diagnostic biopsies were determined routinely with standardized NGS methods in molecular screening centers of nNGM.

NSCLC samples without any activating mutations in FGFR or other therapeutic relevant drivers and without presence of mutations excluded for the purpose of this study (see exclusion criteria) were tested with NGS for FGFR fusion genes.

The NGS for the FGFR fusion genes were performed either locally or in Pathology Institute in Cologne. In Cologne, the anchored multiplex Polymerase Chain Reaction analysis (Archer) was used for the identification of FGFR fusion genes.

Pathologists within the nNGM/NGM informed the treating oncologist through the pathology report about the FGFR alteration and the possibility to treat the patient in the FIND trial. In case the patient was potentially suitable and willing to be treated within the FIND trial, the oncologist referred the patient to one of the participating study centers in the FIND trial.

The study center sent via e-mail the particular FGFR genetic alteration to the FIND molecular board in Cologne (FINDallocation@uk-koeln.de). The FIND molecular board (comprising members of pathology, translational research and medical oncology) determined if the FGFR alteration was likely to be pathogenic. In case of a clinically relevant genetic alteration, the patient was allocated to the appropriate cohort and was allowed to enter study screening.

Patients with advanced NSCLC and FGFR alterations, in good clinical condition (ECOG performance status score 0-2), with acceptable laboratory results, after standard treatment and consenting for a fresh frozen biopsy were considered eligible for the study.

Once the patient had consented study participation and fulfilled all inclusion and no exclusion criteria, a fresh frozen biopsy and blood for ctDNA had to be obtained before the

initiation of treatment. In case the archival biopsy of the molecular prescreening was not available at the sponsor, the archival biopsy was sent to the sponsor along with a fresh screening biopsy.

The duration of study cycle was defined as 28 days. Study treatment started at C1D1 with 8 mg erdafitinib per os daily with the possibility to uptitrate to 9 mg based on phosphate levels on C1D15. CT/MRI-scans for response evaluation according to RECIST 1.1 were conducted every 8 weeks until C11 inclusive and from C13 every 12 weeks. The patient continued on study drug until disease progression, unacceptable toxicity or investigator's or patient's decision to withdraw the treatment.

At the time of progression, a fresh frozen rebiopsy of a progressing tumor lesion and blood for ctDNA was obtained to characterize resistance mechanisms to FGFR targeted treatment. Treatment beyond progression was possible, but had to be confirmed by the Sponsor.

For biopsies (clinical screening and progression), at least two samples were required. One biopsy sample (FFPE sample) was put into formalin for paraffin embedding and pathological assessment (tumor cell content, quality of samples etc.), IHC and NGS. The second sample (fresh frozen sample) was stored on dry ice to be used as fresh frozen material for sequencing at the Department of Translational Genomics. Both samples were shipped to the Institute of Pathology, University of Cologne for central registration.

A study flowsheet is displayed in Figure 1.

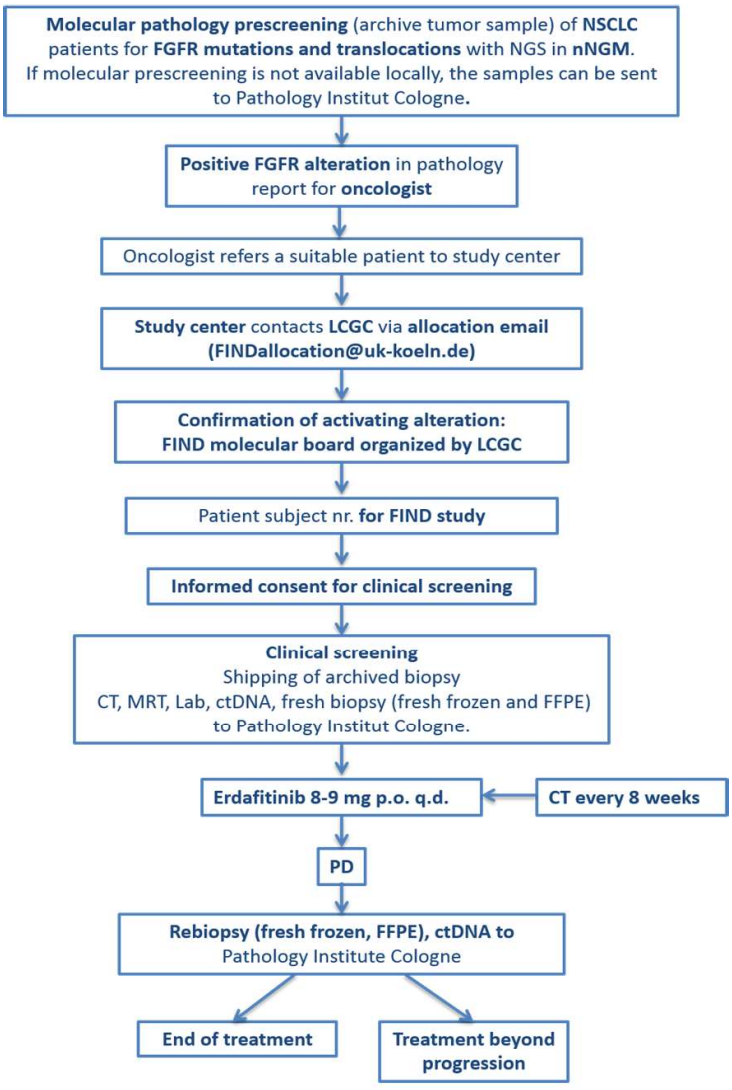


**Figure 1: Study flowsheet**

## 9.2 Discussion of study design, including the choice of control groups

The OS in NSCLC is currently strongly dependent on the presence of actionable genetic alterations or PD-L1 expression level. Briefly, patients having driver alteration or high PD-L1 expression benefit from targeted treatment or immunotherapy, respectively. The ORR is transferred to long term median OS reaching over 50 months in selected groups with genetic alteration (Mok et al., 2020; Shaw et al., 2019). NSCLC patients with high PD-L1 expression benefit from immunotherapy first line with a median OS of about 30 months (Reck et al., 2016; Garassino et al., 2023). This group accounts for approximately 40–45% of all NSCLC patients. Remaining patients are treated with immunochemotherapy or chemotherapy alone reaching a median OS of approximately 20 months (Garassino et al., 2023).

Especially in patients with sqNSCLC, the frequency of druggable genetic alterations is very low, accounting maximal 10% (Wolf et al., 2020; Soria et al., 2018). Thus, patients with sqNSCLC have even less treatment options as adenocarcinoma lung cancer patients.

FGFR genetic alterations are very rare in NSCLC accounting for approximately 2-4% of all NSCLC patients (Helsten et al., 2015). The majority of patients have sqNSCLC (Wang et al., 2014).

The challenge of this genetically preselected clinical trial was to find an effective treatment for advanced NSCLC patients with FGFR alterations. The preclinical data as well as phase II studies in urothelial cancer and cholangiocarcinoma had indicated that targeting FGFR altered tumors with FGFR inhibitor caused responses in about 30-40% of patients with advanced urothelial cancer or cholangiocarcinoma (Loriot et al., 2019, Abou-Alfa et al., 2020).

Thus, the primary objective of the trial was to assess the ORR of lung cancer patients with FGFR genetic alterations treated with erdafitinib.

However, the challenging aspect of the study was the low frequency of FGFR genetic alterations in advanced NSCLC patients. According to available published data, we assumed the frequency of FGFR genetic alterations was maximal 4% in advanced NSCLC. Due to this fact, we proposed a Simon's two-stage design for the study in order to early indicate low/high clinical benefit and avoid inclusion of necessary high patient numbers. This decision was in line with a "proof of concept" study: to stop the recruitment early, if no clinical benefit is seen.

The above reasons led to the decision to not investigate the study treatment in a control arm. In case of a positive trial according to Simon's two-stage design, we would have started a phase II trial with a classical design and statistical power to confirm the clinical benefit. In case of positivity of such a phase II trial, we would have decided to start a control trial.

## 9.3 Selection of study population

Patients were treated only if all inclusion criteria were fulfilled, no exclusion criteria were met and written informed consent has been obtained. No difference in recruitment concerning gender was applied.

### 9.3.1 Inclusion criteria

Each potential patient had to satisfy all of the following criteria to be enrolled in the study:

1. Age $\geq$ 18 years.

2. Stage IIIB/IV NSCLC patients with activating FGFR alteration after the failure on any prior line of standard treatment, or in the opinion of the investigator no effective standard therapy exists, is appropriate, tolerated or is considered equivalent to study treatment.
3. Activating FGFR alteration as approved by FIND Molecular Board.
4. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
5. ECOG performance status score 0, 1, or 2.
6. Clinical laboratory values and cardiovascular measurements at screening:

| Hematology | |
|---|---|
| Hemoglobin | ≥8 g/dL (≥5 mmol/L) (must be without red blood cell [RBC] transfusion within 7 days prior to the laboratory test; recombinant human erythropoietin use is permitted) |
| Platelets | $\geq 75 \times 10^9$/L |
| Absolute Neutrophil Count (ANC) | $\geq 1.5 \times 10^9$/L (prior growth factor support is permitted more than 7 days prior to the laboratory test) |
| **Chemistry** | |
| AST and ALT | ≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for patients with liver metastases |
| Creatinine clearance | ≥40 mL/min based upon CKD-EPI formula |
| Total bilirubin | ≤1.5 × ULN; except in patients with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required) |
| **Cardiovascular** | |
| Corrected QT interval (QTcF) | ≤480 msec based on the average of triplicate assessments performed approximately 5 minutes apart |

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; GFR=glomerular filtration rate; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal

7. Disease measurable per RECIST 1.1 for cohort 1 and 2 or evaluable disease.
8. A woman of childbearing potential who is sexually active must have a negative pregnancy test (β-hCG) at Screening (urine or serum, minimum sensitivity 25 IU/L or equivalent units of β-hCG) within 24 hours prior to the start of erdafitinib.
9. WOCBP and men who are sexually active with WOCBP must use appropriate method(s) of contraception with a failure rate of less than 1% per year before study entry, during the study and until 5 months after taking the last dose of study drug.
   - Appropriate methods of contraception are:
     Total abstinence – if this is a natural lifestyle, female sterilization or tubal ligation (at least 6 weeks prior to the start of the study treatment), male sterilization (at least 6 months prior to the start of the study treatment) and/or a combination of a hormonal method of contraception with a barrier method or/and an intrauterine device or system are considered as highly effective methods of contraception.

Sexually active men must use a condom to prevent delivery of the drug via seminal fluid.

10. Women must not be breastfeeding.

11. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.

12. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 5 months after the last dose of study drug.

### 9.3.2 Exclusion criteria

Any potential patient who meets any of the following criteria was excluded from participating in the study due to safety concerns or lack of suitability for the trial:

1. Pathogenic somatic alterations in the following genes: EGFR, BRAF, ALK, ROS1, and NTRK (Please note that molecular testing might be reduced in heavy smokers with NSCLC. If discrepancies occur, please contact the sponsor).
2. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 30 days or 5 half-life times (whichever is longer) prior to recruitment.
3. Treatment with small molecules or chemotherapy within 7 days prior C1D1.
4. Treatment with monoclonal antibodies within 28 days prior C1D1 if related to the underlying malignancy.
5. Any other history of ongoing malignancy that would potentially interfere with the interpretation of erdafitinib efficacy.
6. Symptomatic central nervous system metastases.
7. Received prior FGFR inhibitor treatment or if the patient has known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients.
8. Any corneal or retinal abnormality likely to increase the risk of eye toxicity, i.e.:
   a. History of or current evidence of central serous retinopathy or retinal vascular occlusion
   b. Active wet, age-related macular degeneration
   c. Diabetic retinopathy with macular edema (non-proliferative)
   d. Uncontrolled glaucoma (per local standard of care)
   e. Corneal pathology such as keratitis, keratoconjunctivitis, keratopathy, corneal abrasion, inflammation or ulceration.
9. Has persistent phosphate level >ULN during screening (on 2 consecutive assessments at least 1 week apart, within 14 days prior to C1D1) and despite medical management.
10. Has a history of or current uncontrolled cardiovascular disease including:
    a. unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes tachycardia, cardiac arrest, or known congestive heart failure NYHA Class III-V within the preceding 3 months (Attachment 3 of the study protoco); cerebrovascular accident or transient ischemic attack within the preceding 3 months.
    b. QTcF prolongation as confirmed by triplicate assessment at screening (QTcF >480 milliseconds).

c. Pulmonary embolism or other venous thromboembolism within the preceding 2 months.

11. Known human immunodeficiency virus (HIV) infection, testing is mandatory (a-HIV 1/2).
12. Patients with acute or chronic Hepatitis B infection (tests should include assessment of HBsAg and HBc IgG antibody. If one parameter is positive, determine HBV-DNA to confirm acute infection. Patients with positive results for HBsAg and/or HBV-DNA are considered positive for acute or chronic infection.
13. Patients with acute or chronic Hepatitis C infection (determine HCV-RNA. Patients with positive result for HCV-RNA are considered positive for acute or chronic infection).
14. Has not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, Grade 1 neuropathy, Grade 1-2 hearing loss).
15. Has impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.
16. Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the patient is expected to participate in the study or within 2 weeks after the last dose of study drug administration. (Note: patients with planned surgical procedures to be conducted under local anesthesia may participate).
17. Any serious underlying medical condition, such as:
    Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection requiring current systemic treatment
    Psychiatric conditions (e.g., alcohol or drug abuse), dementia, or altered mental status.
18. Any other issue that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

### 9.3.3 Removal of patients from therapy or assessment

Patients who did not fulfill one or several inclusion criteria or fulfilled any of the exclusion criteria were not included in the study.

Predefined reasons for discontinuing a patient from the trial were:

- Voluntary discontinuation by the patient, who is at any time free to discontinue his/her participation in the study without prejudice of further treatment
- Safety reasons as judged by the investigator or the Sponsor
- Severe non-compliance or situations which would jeopardize compliance with the protocol as judged by the investigator or Sponsor
- Patient lost to follow-up
- Disease progression (treatment beyond progression may be allowed after discussion with the sponsor)
- Unacceptable toxicity

- Treatment interruption of >28 days due to an adverse drug reaction of study medication or other causes related to study medication. (After discussion with the sponsor, an exception was possible, if the patient has been deriving benefit from treatment, and the investigator could demonstrate that continued treatment with erdafitinib was in the best interest of the patient.)
- Occurrence of other serious disease, which may interfere with study medication or with the primary endpoint of the study
- Death
- Pregnancy

The response-evaluable population is the primary population for the efficacy endpoints ORR, PFS and OS. It includes all eligible patients who received at least one dose of study medication, who have an adequate baseline tumor assessment - at least a CT scan of the thorax, abdomen and pelvis that has been registered no longer than 28 days prior to the start of the trial treatment - and whose NSCLC was FGFR mutated or translocated by NGS testing and proved by the sponsor in study defined molecular board.

The safety analysis population is the primary population for evaluating patient characteristics, treatment administration/compliance, toxicity, AEs and quality of life. It includes all enrolled patients who received at least one dose of study medication.

## 9.4 Investigational products

### 9.4.1 Investigational medicinal products (IMP)

The IMP assessed in the study was erdafitinib (JNJ-42756493). It was supposed to be administered using 8 mg or 9 mg daily (full dose). Erdafitinib was provided as tablets for oral administration. The detailed information on dosing and dose reductions is provided in following 9.4.2 to 9.4.8 sections.

### 9.4.2 Identity of IMP

Erdafitinib (JNJ-42756493) is a potent, oral pan-FGFR tyrosine kinase inhibitor with half maximal inhibitory concentration (IC50) values in the low nanomolar range for all members of the FGFR family (FGFR1 to 4). It has demonstrated potent inhibition of cell proliferation with IC50 values ranging from <1 to <100 nM in FGFR pathway-activated cancer cell lines.

The IMP was supplied as 3 mg, 4 mg and/or 5 mg film-coated tablets for oral use in bottles of 30 tablets each.

It was stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. The storage temperature had to be between 15 and 30 degrees Celsius. A Temperature Log had to be maintained or electronic measurements filed. The initial supply and any resupply had to be ordered manually by the sites by sending a Drug Order Form via email. In case of expiration of IMP, it was quarantined and destroyed after drug accountability check by the Clinical Research Associate.

The batch numbers of the dispensed IMP per patient are listed in appendix 17.1.6.

### 9.4.3 Method of assigning patients to treatment groups

Since the trial was a single arm study, no randomization was required. The allocation of a study subject to one of the cohorts was based on the assessment of the FIND molecular board depending on the FGFR alteration of the patient.

After signing of ICF, the patient received a patient number comprising of the study center number and the consecutive number of enrolled patients in the study center (i.e. 01-01, 01-02, 02-01, etc.). Patients kept their identification numbers through the study.

Because of the heterogeneity of the patient population (pretreatments, molecular pathological findings, etc.), a comparison with a historical or other control group had not been intended from the outset.

### 9.4.4 Selection of doses in the study

The dosing regimen for the study was based on clinical efficacy data from other erdafitinib trials, as described in section 7.1.

### 9.4.5 Selection and timing of dose for each patient

All patients started with erdafitinib 8 mg once daily from D1 to D14. On D15, a blood sample was drawn to determine serum phosphate concentration.

Patients with serum phosphate levels higher than 9 mg/dL (2.88 mmol/l) withheld erdafitinib treatment, with at least weekly assessment of serum phosphate until it returns to less than 7.0 mg/dL (2.24 mmol/l). Patients with serum phosphate levels between 7.0 (2.24 mmol/l) to 9.0 mg/dL (2.88 mmol/l) should have increased the erdafitinib dose to 9 mg once daily, while concurrently initiating treatment with a phosphate binder such as sevelamer or equivalent. Patients with serum phosphate level less than 7.0 mg/dL (2.24 mmol/l) increased the erdafitinib dose to 9 mg once daily without concomitant phosphate binder such as sevelamer or equivalent.

Dosing may have been delayed for 1 day, if phosphate levels could not be determined before start of dose adjustment.

Treatment with erdafitinib should have been discontinued or modified based on toxicity dependent on the toxicity grade. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines were provided in protocol and in medicinal product information as erdafitinib was already approved for urothelial cancer at the time of the study. If erdafitinib had to be withheld for more than 28 days for a drug-related AE that fails to resolve to acceptable level (e.g. ≤ Grade 1 non-hematologic toxicity or back to baseline), treatment with erdafitinib should have been discontinued except when the patient has been deriving benefit from treatment, and the investigator was able to demonstrate that continued treatment with erdafitinib was in the best interest of the patient. In these cases the approval of the PCI was needed.

Dose modification rules are provided in Table 1.

| Category | No up-titration | With up-titration |
|---|---|---|
| | Dose | Dose |
| Starting dose | 8 mg | 8 mg |
| | | |
| Up-titration | None | 9 mg |
| | | |
| 1st dose reduction | 6 mg | 8 mg |
| | | |
| 2nd dose reduction | 5 mg | 6 mg |
| | | |
| 3rd dose reduction | 4 mg | 5 mg |
| | | |
| 4th dose reduction | stop | 4 mg |
| | | |
| 5th dose reduction | | stop |

**Table 1. Erdafitinib Dose Reduction Levels**

The IMP had to be taken with approximately 240 mL (8 ounces) of water. The tablets had to be swallowed intact and patients should not attempt to dissolve them in water. Each dose should have been taken at approximately the same time each day. If a dose was

missed, it could be taken up to 6 hours after the scheduled time; the patient may have returned to the normal schedule the following day. If it has been more than 6 hours since the missed dose, then that dose should have been skipped and the patient should have continued treatment at the scheduled time the next day. Missed doses have not been replaced and the next dose remained unchanged. If vomiting occurred with drug administration, no replacement dose had been taken and any such event that occured up to 4 hours following dose administration had to be recorded on the eCRF.

The bottles with erdafitinib tablets were handed out to the patient by the sites during a study visit. At each consecutive visit, the patient had to return the bottles (also empty or partly used bottles) and new study medication was dispensed to the patient. The residual tablets in the returned bottles were counted by a study nurse in order to calculate the patient's compliance. In case of non-compliance, the patient was asked for reasons. The study nurse had to document the dispense and return of bottles in the IMP Dispensing and Accountability Log and in the Site IMP inventory Log.

### 9.4.6 Blinding

As this was a single-arm open-label study, blinding did not apply.

### 9.4.7 Prior and concomitant treatment

Information on the patient's previous cancer therapies was collected during screening and documented in the appropriate section of the electronic Case Report Form (eCRF). As defined in the inclusion criteria, the patients participating in the study had already received any prior line of standard treatment, except no effective standard therapy existed in the opinion of the investigator. In line with the exclusion criteria described, treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 30 days or 5 half-life times (whichever is longer) prior recruitment was not allowed. Neither treatment with small molecules or chemotherapy within 7 days prior to C1D1 nor treatment with monoclonal antibodies within 28 days prior to C1D1 if related to the underlying malignancy was allowed. It was not permitted that the patient had received prior FGFR inhibitor treatment.

All concomitant medications and therapies (prescriptions or over the counter medications) were to be recorded at the time of screening (within 30 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in in the concomitant medication/therapy section of the eCRF.

No other systemic antineoplastic therapy was allowed in addition to the study regimen. Medications known to increase serum levels of phosphate were also prohibited.

Caution should have been exerted for patients taking anti-coagulant therapies. Frequent monitoring for international normalized ratio was performed at the treating physician's discretion.

Permitted and prohibited medications and precautions for concomitant medications was listed in the study protocol in sections 8.1, 8.2 and 8.3 (see appendix 17.1.1).

The Sponsor had to be notified in advance, or as soon as possible thereafter, of any instances where prohibited medications and treatments were administered or a new unexpected drug-drug interaction had occurred.

### 9.4.8 Treatment compliance

Patients received instructions on compliance with study treatment at the screening visit. The investigator or designated study personnel maintained a log of the amount of study drug dispensed and returned and used this to calculate the patient's compliance. During the course of the study, the investigator or designated study research staff were responsible for providing additional instruction to reeducate any patient who was not compliant with the study drug schedule. In case of discrepancies between the number of

tablets the patient should have taken and the number of missing tablets in the returned bottle, the site personnel was supposed to ask the patient for reasons. These discrepancies were documented in the section "Special Reporting Situations" in the eCRF.

Drug supplies were inventoried and accounted for throughout the study in the study center.

## 9.5 Efficacy and safety variables

### 9.5.1 Efficacy and safety measurements assessed and flow chart

For a detailed time and event schedule of all examinations and assessments, please refer to the study protocol pages 16ff. (see appendix 17.1.1).

The specific efficacy and safety variables were measured as follows:

| Effect variable | Time and method of evaluation | Parameter or variable incl. units | Staff/institute responsible for data acquisition | Staff responsible for interpretation and assessment |
|---|---|---|---|---|
| Adverse events | Structured questioning at each study visit; face-to-face or phone contact at any time between visits, data acquisition using written or electronic sources like e. g. medical reports, lab findings, imaging | Naming the AE (AE term)<br>Degree of severity acc. to the CTCAE<br>Criterion for "seriousness" (SAE)<br>Relatedness with IMP | Study nurses/ investigators at each study site | Investigators at each study site |
| Lab values | Blood collection as described in study protocol | Parameters as in study protocol, normal values and units conforming to standards of each study site | Study nurses/ investigators at each study site<br>Clinical Chemistry at each study site | Investigators at each study site |
| Restaging by CT/MRI | CT/MRI of affected region (screening; every 8 weeks until C11 incl.; from C13 every 12 weeks until progression or discontinuation of treatment) | Measurement and documentation of target and non-target lesions and of any new tumor manifestations acc. to RECIST 1.1 | Radiology departments at each study site | Radiology departments at each study site |
| Descriptive coverage of treatment and survival data | Data coverage from inclusion into study, start of treatment, end of treatment, progression of disease, death | Calculations for "time on treatment", "progression-free survival" und "overall survival" | Study nurses/ investigators at each study site | Investigators at each study site |

Variables for demographics were age at diagnosis, gender, ethnicity, smoking status with pack years, histology, type of FGFR alteration (e.g. FGFR3-TACC3) and number of previous treatment lines.

Variables for baseline characteristics were weight, height, ECOG performance status score, evidence of brain metastases, blood pressure and heart rate.

The primary variable was ORR per RECIST 1.1 under erdafitinib treatment in NSCLC with genetic alteration in FGFR. ORR is defined as percent frequency of patients with complete CR and PR in cohorts 1 and 2, respectively relating to the population of all patients included to cohorts 1 and 2, respectively.

Secondary variables were efficacy and safety/tolerability.

Efficacy was measured by PFS and OS. PFS was defined as the time from registration (signing of ICF) to first documentation of objective disease progression or to death on study due to any cause, whichever occurs first. The time of the progression was determined using the first date when there is documented evidence that the criteria have been met, even in situations where progression is observed after one or more missed visits, treatment discontinuation, or new anti-cancer treatment. PFS was censored on the date of the last evaluable on-study tumor assessment documenting absence of progressive disease for patients who are alive, on study and progression free at the time of the analysis.

OS was defined as the time from registration (signing of ICF) to the date of death to any cause. For patients still alive at the time of analysis (data cut-off), the OS time was censored on the last date the patients were known to be alive.

The variable for safety/tolerability was the assessment of AEs according to CTC-AE V5.0.

For the flow chart of the study, please refer to section 9.1.

### 9.5.2 Appropriateness of measurements

RECIST 1.1 is an accepted methodology by regulatory authorities. RECIST 1.1 was applied by the investigator as the primary measure for assessment of tumor response. Identical methodology of involved or progressed areas (CT scan or MRI) was supposed to be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document the disease status. It must be noted that the study protocol includes standard imaging procedures according to current S3 guidelines: CT-thorax and –abdomen and CT/MRI of all other involved areas every 8 weeks.

Concerning the safety, AEs were assessed for degrees of severity acc. to CTC-AE V5.0. Their seriousness was assessed according to the GCP/ICH definition and a causal relationship compared with the IMP. If the causal connection was found, their classification as "expected" or "unexpected" was accordingly classified. This comprised all clinical AEs and lab results. The terminology used, i.e. AE, serious adverse event (SAE), adverse reaction (AR), serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR) and the criteria applied were those of the ICH/GCP guidelines and are standard procedures.

### 9.5.3 Primary efficacy variable(s)/ endpoint(s)

The primary endpoint of the study was ORR per RECIST 1.1. under erdafitinib treatment. ORR was defined as percent frequency of patients with CR and PR in cohorts 1 and 2, respectively relating to the population of all patients included to cohorts 1 and 2, respectively.

### 9.5.4 Drug concentration measurements

PK assessment of erdafitinib was not performed according to the protocol as these data was provided from previous phase I studies in patients with solid tumors. No new safety data were expected in the population of lung cancer patients.

## 9.6 Data quality assurance

For all studies, in which the University of Cologne assumes the function of the Sponsor, as it is the case in the FIND study, the Rectorate of the University of Cologne has assigned the Dean's Office of the Faculty of Medicine with the quality-assured fulfillment of these Sponsor duties. The executing body is the Sponsor's Quality Assurance Unit (Sponsor-QA) under the technical and official supervision of the Vice Dean's Office for Science. The Office of the Vice Dean for Academic Affairs delegates the performance of the assigned Sponsor duties to the PCI, who becomes the authorized Sponsor in this respect, provided that he/she is appropriately qualified. Qualified third parties may also be involved in the performance of sponsoring duties.

The Sponsor's Quality Assurance Unit has conducted an audit of the CRO acromion GmbH regarding their structure, organization and processes, as well as the underlying quality management system, using the FIND study as example. The objective of the audit was to verify that systems and processes are in place to fulfill the Sponsor's responsibilities in accordance with the applicable regulatory requirements (AMG, GCP-V, ICH-GCP), the study protocol, SOPs, and the agreements with collaborators and sites.

At the sites, as required by the GCP/ICH guidelines, the study physicians and other involved study team members had been registered and trained and were familiar with the content of the study protocol. Formalized training on study procedures and protocol was carried out during the study initiation.

External quality assurance was based on the regular monitoring by the CRO acromion GmbH. These monitoring visits primarily concentrated on reviewing the patients' ICF for correctness, assessed the measures carried out for conformance with the protocol, the handling of AEs, completeness of the eCRF including reconciliation of source data, management of the study medication and overall progress of the study. A detailed list of the individual aspects of the monitoring and the frequency of monitoring visits is included in the Monitoring Manual.

Using the source data (paper or electronic patient records), the study nurses at each site documented the data obtained in the course of the study in standardized eCRFs in the Elecronic Data Capture System "Marvin". Data were signed off by an investigator.

Lab parameters were evaluated at the local lab of each site following their institutional standards. Measurements were documented in the above mentioned eCRFs.

Evaluation of the CT-/MRI-based restagings under clinical aspects during the course of the study was carried out by the radiologists of the sites.

## 9.7 Statistical methods planned in the protocol and determination of sample size

### 9.7.1 Statistical and analytical plans

All patients enrolled were analyzed. Fulfilment of inclusion/exclusion criteria was listed. Patients discontinuing study medication or not completing the study were listed along with the reason for their premature discontinuation. Patients excluded from each analysis population were listed with reasons for exclusion.

Demographic and baseline disease characteristics were tabulated and summarized, as applicable, by mean, standard deviation, median, minimum and maximum or count and percentage.

First diagnosis and the subsequent course of the underlying disease were described using frequency tables. The frequencies of previous cancer therapy and concurrent illnesses,

respectively, were calculated. All prior therapies were listed per patient in chronological order with dates and response. Concomitant medications/therapies were listed per patient.

The distribution of duration and dose intensity (dose per unit time) of study medication was described using median, maximum/minimum and quartiles. Deviations from protocol (change of dose, interruption, reduced duration (<50% per cycle)) were listed with reasons.

ORR per RECIST 1.1 with 95% confidence interval was calculated based on all patients in the response-evaluable population. ORR was defined as the percentage of patients with CR or PR in cohorts 1 and 2, respectively relating to the population of all patients included to cohorts 1 and 2, respectively.

Statistical inference regarding ORR followed the approach proposed by Jung and Koyama (Jung and Kim, 2004), (Koyama and Chen, 2008) (point estimate, p-value, confidence interval). Outcome measures (efficacy and safety) are summarized either by count and percentage or mean, standard deviation and percentiles (0, 25, 50, 75, 100), contingent on distributional characteristics.

In case the interim analysis does not take place, statistical inference is based on the exact Clopper-Pearson 95% confidence interval.
Time-to-event outcomes (PFS, OS) was analyzed by the Kaplan-Meier method. AEs, especially treatment emergent events were summarized by body system, MedDRA preferred term and worst CTCAE V5.0 grade, period of occurrence and relatedness to study medication. Laboratory results assessed as clinically significant or outside the normal range were listed. Changes in ECOG performance status score, weight, ECG, heart rate were described using median, maximum/minimum and quartiles.

An independent DMSC was supposed to monitor the cumulative safety data for evidence of treatment harm and benefit and to pronounce recommendations in the interest of patient's health care to terminate the trial before recruitment of data, e.g. specific complications such as unacceptable high recurrence rate. Also, unfeasibility for successful termination of the study may lead to premature termination. Throughout the study, the DMSC was supposed to especially monitor the incidence rates of SAEs.

### 9.7.2 Determination of sample size

Patient number in the NSCLC cohort 1 and 2 was calculated with respect to response to erdafitinib based on Simon's two-stage minimax design (Simon, 1989):

The null hypothesis (inefficacious treatment) $H_0$:$p_{new}$≤10% was tested at one-sided significance level $\alpha$=10%. A power of at least 90% (i.e. $\beta$=10%) should have been attained for the alternative hypothesis (efficacious treatment) $H_A$:$p_{new}$≥40%.

Stage 1: In the first stage, 8 patients were supposed to be treated. If less than 1 PR on erdafitinib according to RECIST 1.1 was observed, enrollment would have been stopped and it would be concluded that the treatment is inefficacious (Machin et al., 2011).

Stage 2: If at least 1 PR on erdafitinib was observed in the first trial phase (i.e. 1 in 8), another 7 patients would have been enrolled and treated as described above.

If at least 4 in 15 patients responded, it would have been concluded that the treatment had shown sufficient promise of efficacy for further investigation.

Not evaluable patients would have been replaced (≤2 expected).

Patients with NSCLC and FGFR alteration with high evidence on oncogenic transformation according to FIND molecular board have been included to cohort 1 (FGFR translocated NSCLC patients) and cohort 2 (FGFR mutated patients).

Patients with NSCLC and FGFR alterations without enough evidence (inter-mediate/low evidence according to FIND molecular tumor board) for recruitment into cohorts 1 or 2, were treated in cohort 3. In the exploratory cohort 3, it was planned to include a maximum of 20 NSCLC patients with different FGFR alterations. A sample size of 20 would have been sufficient to yield an exact 95% confidence interval with widths 30% (or 45%) for an assumed ORR of 10% (or 40%, respectively) (Shan et al., 2017).

Summarized, planned patient number per cohort was as follows:

Cohort 1: Activating (high confidence) FGFR translocations (max. 15 patients)

Cohort 2: Activating (high confidence) hotspot FGFR mutations (max. 15 patients)

Cohort 3: Activating (low confidence) FGFR alteration (max. 20 patients)

### 9.7.3 Subgroup analysis

A subgroup analysis for all major efficacy and safety variables was planned to be done by sex. However, it was expected to be of descriptive character due to small number of patients.

### 9.7.4 Interim analysis

Two interim analyses were planned within the trial, one after completing stage 1 in cohort 1 and one after completing stage 1 in cohort 2 according to Simon's two-stage minimax design. The decision to proceed with the second stage in each cohort was supposed to be taken independently of the other cohort.

## 9.8 Changes in the conduct of the study or planned analyses

One amendment to the study protocol became necessary during the course of the study. The following describes the content-related changes, the reasons for them and the approval day. Both versions of the study protocol are given in appendix 17.1.1.

***Amendment 1 (*28-01-2020*)***

Amendment 1 comprised the inclusion of patients with adenocarcinoma, changes to molecular exclusion criterion, the approval of erdafitinib for urothelial carcinoma as well as minor redactional clarifications. Also, Special Reporting Situations were added to the protocol.

The reason for adding of adenocarcinoma to inclusion was the fact, that the molecular testing for FGFR on adenocarcinoma was added to standardized protocols on study site centers. According to preclinical and clinical data, there is no expected difference in responses between lung adenocarcinoma and sqNSCLC. As adenocarcinoma patients with FGFR alterations have no other druggable genetic driver, there was a clinical reason to offer the study also to these patients. Other changes in amendment 1 concerned new safety data on erdafitinib and its approval for urothelial cancer.

All statistical methods were used as predefined in the trial protocol. An initially planned interim analysis had to be converted into a final analysis as the study was terminated prematurely in October 2022 due to slow enrolment.

# 10 Study population

## 10.1 Disposition of patients

If an inclusion criterion has not been fulfilled or an exclusion criterion has been identified within the screening phase, i.e. after patients had signed the ICF and thus had been

formally included in the study, these cases were considered as "screening failures", and the patients received no treatment with the study medication.

Four patients had to be considered as screening failures in this study. This concerned the following patients: 0103, 0202, 0702, 0801.

- Patient 0103 showed a deterioration of general condition due to the AE of pneumonia during screening, so that the inclusion criterion ”ECOG performance status score 0, 1, or 2” was not fulfilled.
- Patient 0202 did not have a disease measurable per RECIST 1.1 (not fulfilled inclusion criterion).
- Patient 0702 had a history of or current uncontrolled cardiovascular disease (fulfilled exclusion criterion).
- Patient 0801 withdrew Informed Consent during screening.

A flow chart for enrolled patients is displayed in Figure 2.

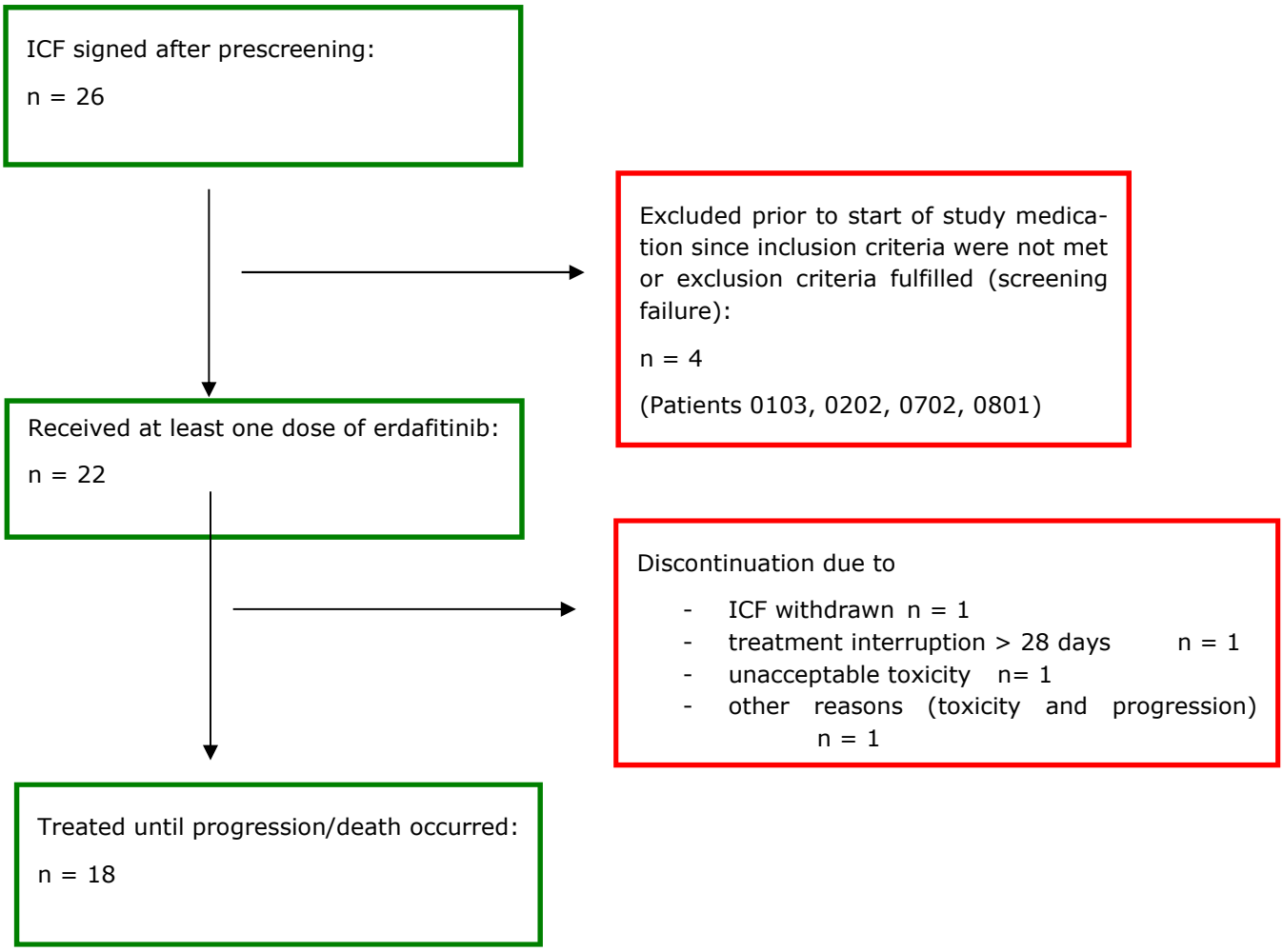


**Figure 2: Flow chart for included patients**

## 10.2 Protocol deviations

Patient 0102 took the double dose of 6mg, i.e. 12 mg totally of erdaftinib for 10 days by mistake. Consequently, drug administration was interrupted for 10 days. The overdose did not result in an AE.

For 10 days, patient 0101 took study medication that was affected by a temperature excursion and assessed as unusable by the responsible GMP department. As soon as the

site became aware of the temperature excursion, patient 0101 had already stopped study treatment. No related SAE occurred during this period.

# 11 Efficacy evaluation

## 11.1 Data sets analyzed

The efficacy of erdafitinib was the primary objective of the study with the primary endpoint ORR per RECIST 1.1 under erdafitinib treatment in NSCLC with genetic alteration in FGFR. To evaluate the clinical efficacy of erdafitinib descriptively with the endpoints PFS and OS was one of the secondary objectives.

The response-evaluable population includes all eligible patients who received at least one dose of study medication, who have an adequate baseline tumor assessment - at least a CT scan of the thorax, abdomen and pelvis that has been registered no longer than 28 days prior to the start of the trial treatment - and whose NSCLC was FGFR mutated or translocated by NGS testing and proved by the sponsor in study defined molecular board.

As the screening failures did not receive any study medication (for the individual reasons please refer to section 10.2), these patients were not included in the response-evaluable population. For one patient (0701), the baseline CT scan was registered longer than 28 days prior to the start of the treatment (35 days). However, this was in agreement with the PCI and this patient was included in the response-evaluable population.

Thus, a data set of seven patients in cohort 1 and eight patients in cohort 2 is analyzed for treatment response.

The details on patient analysis are presented in the Biostatistics Annex in section 16 of this report.

## 11.2 Demographics and other baseline characteristics

The demographic and baseline characteristics are listed in the Biostatistics Annex, sections 1.1.6 (cohort 1), 2.1.6 (cohort 2) and 3.1.6 (cohort 3).

## 11.3 Measurements of treatment compliance

The treatment compliance was measured by appearance at scheduled study visits. The compliance to study medication was assessed by conduction of a drug accountability by an investigator or designated study personnel at each visit. In case of discrepancies, the Sponsor had to be notified about the potential medication error, being defined as a Special Reporting Situation in the study protocol in section 11.1.7.

## 11.4 Efficacy results and tabulations of individual patient data

### 11.4.1 Analysis of efficacy

For the descriptive analysis of efficacy, please see the Biostatistics Annex, sections 1.3 and 1.4 for cohort 1 and 2.3 and 2.4 for cohort 2.

Since this trial was a single-arm phase II study, a comparative evaluation of efficacy against standard therapies or against a similar historic patient population was not feasible or even useful.

### 11.4.2 Statistical/analytical issues

The statistical evaluation of the study was carried out as described under 9.7. The various subitems are given below in as much as these aspects apply to the study.

#### *11.4.2.1 Adjustments for covariates*

The concurrent illnesses are listed in the Biostatistics Annex, sections 1.1.9 (cohort 1), 2.1.9 (cohort 2) and 3.1.9 (cohort 3). The concomitant medications/therapies of the evaluable patients are listed in sections 1.1.10 (cohort 1), 2.1.10 (cohort 2) and 3.1.10 (cohort 3) of the Biostatistics Annex.

As the patient number in the study was too small, no adjustments for covariates were needed and feasible.

#### *11.4.2.2 Handling of dropouts or missing data*

As mentioned, 26 patients consented for the study, 4 of them were screening failures. Thus, 24 patients received at least one dose of erdafitinib.

The available information of the four screening failures is included in the Biostatistics Annex.

#### *11.4.2.3 Interim analyses and data monitoring*

The planned interim analysis at stage one of Simon's two-stage design was simultaneously the final analysis as the recruitment was too slow and the study funder proposed to close the trial.

The trial data including study procedures, safety results and efficacy results were extensively reviewed by the participating DMSC members. They concluded that the trial was conducted in an appropriate way, and no unexpected safety and efficacy results were observed. The DMSC agreed to the closing of the study. For a summary of the DMSC meeting, please refer to appendix 17.4.

#### *11.4.2.4 Multicenter studies*

The study was conducted as a multicenter trial – at the sites as listed in Table 2 below. Due to small patient numbers per site, an analysis per site is not valuable.

| Site | Clinic | Number of enrolled patients (incl. screening failures) |
|---|---|---|
| 01 Cologne | University Hospital Cologne | 10 |
| 02 Würzburg | University Hospital Würzburg | 3 |
| 03 Berlin | Evangelische Lungenklinik Berlin | 3 |
| 04 Aachen | University Hospital Aachen | 1 |
| 05 Frankfurt | University Hospital Frankfurt | 0 |
| 06 Munich-Gauting | Asklepios Hospital Munich-Gauting | 3 |
| 07 Dresden | University Hospital Dresden | 3 |
| 08 Oldenburg | Pius Hospital Oldenburg | 3 |
| 09 Braunschweig | Städtisches Klinikum Braunschweig | 0 |
| 10 Homburg | University Hospital Saarland Homburg | 0 |
| 11 Freiburg | University Hospital Freiburg | 0 |

**Table 2: Listing of sites with number of enrolled patients**

#### *11.4.2.5 Multiple comparisons/multiplicity*

With only one primary dependent variable and one treatment group, adjusting for alpha error was not necessary.

#### *11.4.2.6 Use of an "efficacy subset" of patients*

Statistical analysis concerning the primary endpoint was performed on target population of patients who received at least one study medication dosing. Screening failures were monitored after study exclusion in term of SAE assessment until death, withdrawal of consent, or end of study, whichever occurs first.

Variables for the analysis of PFS and OS were calculated for all patients, who signed the ICF.

#### *11.4.2.7 Active-control studies intended to show equivalence*

This phase II study did not include the testing of active controls due to the small number of patients in each cohort.

#### *11.4.2.8 Examination of subgroups*

The sample size of the study was too small for any subset analysis.

### 11.4.3 Tabulation of individual response data

For individual response data, please see the Biostatistics Annex, sections 1.3 and 1.4.4 (cohort 1) and 2.3 and 2.4.4 (cohort 2).

### 11.4.4 Drug dose, drug concentration, and relationships to response

The doses of erdafitinib ranged from 4 mg to 12 mg daily. However, the dosage of both 4 mg and the overdose of 12 mg were mistakenly applied respectively due to a misunderstanding by the patient.

Actions taken were dose increase for the patient, who had taken 4 mg daily, and drug interruption for the patient who had taken 12 mg per day. The overdose did not result in any AE.

For a detailed listing of duration and dose intensity overall, please refer to the Biostatistics Annex, sections 1.1.11 (cohort 1), 2.1.11 (cohort 2) and 3.1.11 (cohort 3).

No relationship between dose and response was observed.

### 11.4.5 Drug-drug and drug-disease interactions

Study results revealed no apparent interaction between the effects of the investigational product and any concomitant treatment or comorbidity.

### 11.4.6 By-patient displays

For a detailed listing of dose intensity and change of dose per patient, please refer to the Biostatistics Annex, sections 1.1.12 (cohort 1), 2.1.12 (cohort 2) and 3.1.12 (cohort 3).

### 11.4.7 Efficacy conclusions

Section 1.4.4 in the Biostatistics Annex shows the best response for the patients of cohort 1 and section 2.4.4 for cohort 2, which is also summarized in Table 3.

| Best CT response | Cohort 1 (N=7) | Cohort 2 (N=8) |
|---|---|---|
| **CR** | 0 | 0 |
| **PR** | 2 | 0 |
| **SD** | 1 | 4 |
| **PD** | 1 | 1 |
| **Non-CR/Non-PD** | 0 | 0 |
| **Missing** | 3 | 3 |

**Table 3: Best response according to RECIST 1.1**

Of the two achieved PRs in cohort 1, one was confirmed, one remained unconfirmed (uPR). Of the three patients in cohort 1 with missing best CT response, two patients died before first restaging, so a PD is assumed, and one patient was lost to follow-up.

All three patients in cohort 2 with missing best CT response died before first restaging, so a PD is assumed.

**Mortality, OS**

OS is presented in the Biostatistics Annex, sections 1.4.1 and 1.4.3 for cohort 1 and in sections 2.4.1 and 2.4.3 for cohort 2.

**PFS**

PFS is presented in the Biostatistics Annex, sections 1.4.1 and 1.4.2 (cohort 1) and 2.4.1 and 2.4.2 (cohort 2).

# 12 Safety evaluation

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment administration/compliance, toxicity and AEs.

## 12.1 Extent of exposure

In cohort 1, seven patients are valid for safety analysis, eight patients in cohort 2 and seven patients in cohort 3.

For a detailed listing of duration and dose intensity overall and per patient, please refer to the Biostatistics Annex, sections 1.1.11 and 1.1.12 (cohort 1), 2.1.11 and 2.1.12 (cohort 2) and 3.1.11 and 3.1.12 (cohort 3).

## 12.2 Adverse events (AEs)

### 12.2.1 Brief summary of AEs

A brief summary of AEs is displayed in the Biostatistics Annex, sections 1.2.1 (cohort 1), 2.2.1 (cohort 2) and 3.2.1 (cohort 3).

Already at entry into the study, many of the patients had relevant tumor-associated signs and in many cases their physical condition was noticeably reduced.

In cohort 1, from seven patients that received treatment, all developed at least one AE. The most frequent AEs of any grade were of gastrointestinal origin (usually diarrhea, dry mouth and vomiting). In six of seven patients, we registered hyperphosphatemia of any grade as a known side of erdafitinib. Six of seven patients developed general disorders (e.g. deterioration of general conditions, fatigue and mucosal inflammation). Five of seven patients had laboratory findings (e.g. elevated liver values).

In cohort 1, we registered 10 SAEs in six patients. The majority of SAEs (four) was related to the underlying malignant disease. Two additional SAEs have a potential relation to underlying neoplasm. The remaining SAEs all occurred once and revealed no new safety signs.

In cohort 2, all patients developed at least one AE. The most frequent AEs were of gastrointestinal origin, followed by AEs of metabolism and nutrition disorders (hyperphosphatemia, hypercalcemia, decreased appetite and others) and general disorders (e.g. deterioration of general conditions, fatigue and mucosal inflammation). Six of eight patients developed light infections and similarly six of eight patients had respiratory AEs (dyspnea, epistaxis, cough and others) – possible due to the underlying disease.

In cohort 2, we registered 15 SAEs in seven patients. The most frequent SAEs (four) were due to underlying malignant disease, followed by three respiratory SAEs possible due to underlying disease. Two SAEs were due to general conditions and two SAEs due to changes in metabolism (hypercalcemia, hyponatremia and hypokalemia). The remaining SAEs all occurred once and revealed no new safety signals.

In cohort 3, the majority of patients developed gastrointestinal AEs and respiratory and thoracic AEs, potentially due to the underlying disease, followed by patients with changes in metabolism such as decreased appetite, hyperphosphatemia, dehydration and hyperglycemia as well as AEs resulting from lung cancer.

In cohort 3, we registered 13 SAEs in seven patients. The majority of SAEs resulted from underlying malignant disease, followed by SAEs of general disorders as general deterioration, dyspnea, dysphagia and arthralgia.

Concerning the relatedness and no relatedness to study medications, there were no aspects, if comparing to the Investigator's Brochure, medicinal product information or current publications.

We registered no SUSAR during the trial.

### 12.2.2 Display of AEs

For a listing of AEs, please refer to the Biostatistics Annex, sections 1.2.1 (cohort 1), 2.2.1 (cohort 2) and 3.2.1 (cohort 3).

### 12.2.3 Analysis of AEs

The incidence and nature of the AEs documented in the study corresponded to the known side-effect profiles of erdafitinib as referred to in the Investigator's Brochure, medicinal product information and current published data.

In addition to these expected AEs, the AEs that patients frequently developed were directly or indirectly related to the metastatic disease. AEs that were associated with concomitant diseases of the patients other than cancer were very rare.

We registered no SUSARs in the study.

### 12.2.4 Listing AEs by patient

For a listing of AEs by patient, please see the Biostatistics Annex, sections 1.2.3 (cohort 1), 2.2.3 (cohort 2) and 3.2.3 (cohort 3).

For a listing of AEs with CTC grade >=3 by patient, please see the Biostatistics Annex, sections 1.2.4 (cohort 1), 2.2.4 (cohort 2) and 3.2.4 (cohort 3).

## 12.3 Deaths, other SAEs, and further significant undesirable incidents

### 12.3.1 Listing deaths, other SAEs, and further significant undesirable incidents

For a listing of deaths and other SAEs, please refer to the Biostatistics Annex, sections 1.2.5 (cohort 1), 2.2.5 (cohort 2) and 3.2.5 (cohort 3).

A listing of the frequency of SAEs per system organ class is presented in the Biostatistics Annex, sections 1.2.2 (cohort 1), 2.2.2 (cohort 2) and 3.2.2 (cohort 3)

There were no other significant AEs that are needed to be mentioned. Concerning all AEs, please refer to the Biostatistics Annex, sections 1.2.3 (cohort 1), 2.2.3 (cohort 2) and 3.2.3 (cohort 3).

### 12.3.2 Narratives of deaths, other SAEs, and certain other significant AEs

In the cohort 1, seven patients received study medication, five patients died due to PD. One patient was lost to follow-up and one patient had developed PD and was still alive at last follow up.

In the cohort 2, eight patients received study medication, six patients died due to PD and two patients were lost to follow up.

In the cohort 3, seven patients received study medication, six patients died due to PD and one patient withdrew consent early in the study.

There were no other SAEs and no other significant AEs that are needed to be mentioned.

### 12.3.3 Analysis and discussion deaths, other SAEs, and other significant AEs

The majority of the SAEs and all death cases that occurred were related to progression of the metastatic disease. Considering the inclusion criterion "patients with solid tumors after standard therapies", this was expected.

Other SAEs were either consistent with metastatic disease or in line with previous data in the Investigator's Brochure, in medicinal product information or in published data.

## 12.4 Clinical laboratory evaluation

### 12.4.1 Listing of individual laboratory measurements by patient

For a listing of individual laboratory measurements (hematology and serum chemistry), please see the Biostatistics Annex under sections 1.1.13 (cohort 1), 2.1.13 (cohort 2) and 3.1.13 (cohort 3).

### 12.4.2 Evaluation of each laboratory parameter

There were no new aspects on laboratory data and given therapy comparing to the Investigator's Brochure, medicinal product information or published data.

#### *12.4.2.1 Laboratory values over Time*

Please see the Biostatistics Annex, sections 1.1.13 (cohort 1), 2.1.13 (cohort 2) and 3.1.13 (cohort 3) for listings of laboratory values (hematology and serum chemistry) per patient over time.

#### *12.4.2.2 Individual patient changes*

Please see the Biostatistics Annex, sections 1.1.13 (cohort 1), 2.1.13 (cohort 2) and 3.1.13 (cohort 3) as well.

#### *12.4.2.3 Individual clinically significant abnormalities*

There were no new clinical significant changes in patient individual laboratory results, comparing to the Investigator's Brochure, medicinal product information or published data.

### 12.5 Vital signs, physical findings, and other observations related to safety

For vital signs, please refer to the Biostatistics Annex, sections 1.1.6 (cohort 1), 2.1.6 (cohort 2) and 3.1.6 (cohort 3).

Concerning the ophthalmologic examinations, no significant observations related to study medication were observed.

### 12.6 Safety conclusions

All related AEs were in line with the known safety profile of the investigational product. AEs that were indicated as not related were in most cases in line with symptoms caused by the underlying disease.

## 13 Discussion and overall conclusions

This phase II study evaluated the efficacy of erdafitinib in advanced NSCLC patients harboring genetic alterations in FGFR genes. Based on preclinical and early clinical data, we calculated the ORR of at least 40% in patients with advanced NSCLC and FGFR genetic alteration. Regarding the Simon's two-stage design, we would have needed to recruit 8 patients in the first stage. If 1 of 8 patients had responded in each cohort 1 and 2, we would have needed to recruit additional 7 patients. If 4/15 patients responded, we would have included that the treatment showed sufficient promise of effectiveness for further investigation.

The recruitment in the study was slow due to very low frequency (about 2%) of NSCLC patients with FGFR alterations. We recruited seven patients in cohort 1 and eight patients in cohort 2. Two patients in cohort 1 achieved partial response, one response was confirmed. Thus, we reached stage 1 of Simon's two-stage design. In theory, the study should have continued with the stage 2 of Simon's two-stage design for patients with FGFR-fusion. However, due to slow recruitment, we have not received further study funding.

Regarding the safety, we observed the known adverse drug reactions, which were already mentioned in the Investigator's Brochure, medicinal product information and in published data.

In the cohort 1, median PFS and OS were 4.3 and 6.5 months, respectively.

In the cohort 2, median PFS and OS were 3.2 and 5.0 months, respectively.

In summary, the study showed clinical activity of erdafitinib in lung cancer patients with FGFR fusions. The study has not continued with the next stage of Simon's two-stage design as the funding of the study was not warranted due to slow recruitment.

Additional studies are needed to confirm the clinical activity of erdafitinib in lung cancer patients with FGFR fusions.

# 14 Tables, figures and graphs referred to but not included in the text

All tables, figures and graphs are included in the text or in the appendix with reference in the text.

# 15 Reference list


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# 16 Biostatistics Annex

2023-07-28_FIND_analysis

# 17 Further appendices

## 17.1 Study information

### 17.1.1 Protocol and protocol amendments

FIND_Clinical Protocol_V1.2_03Jan2020_Final

FIND_Clinical Protocol_Version 1.1_29Jan2019

### 17.1.2 Sample case report form (unique pages only)

FIND_blankCRF_V1.0_24APR2019

### 17.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - representative written information for patient and sample consent forms

| Leading Ethics Committee: |
|---|
| Ethik-Kommission der Medizinischen Fakultät der Universität zu Köln<br>Kerpener Str. 62<br>50937 Köln |
| **Local Ethics Committees:** |
| Ethik-Kommission der RWTH Aachen<br>Pauwelsstraße 30<br>52074 Aachen |
| Landesamt für Gesundheit und Soziales Berlin<br>Fehrbelliner Platz 1<br>10707 Berlin |
| Ethik-Kommission an der Technischen Universität Dresden<br>Fetscherstraße 74<br>01307 Dresden |
| Ethik-Kommission des Fachbereichs Medizin der Johann Wolfgang Goethe-Universität Frankfurt<br>Theodor-Stern-Kai 7<br>60596 Frankfurt am Main |
| Ethik-Kommission der Albert-Ludwigs-Universität Freiburg<br>Engelberger Straße 21<br>79106 Freiburg |
| Ethik-Kommission bei der Ärztekammer Niedersachsen<br>Karl-Wiechert-Allee 18-22<br>30625 Hannover |
| Ethik-Kommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München<br>Pettenkofer Straße 8A<br>80336 München |
| Medizinische Ethik-Kommission der Carl von Ossietzky Universität Oldenburg<br>Ammerländer Heerstraße 140<br>26129 Oldenburg |
| Ethik-Kommission bei der Ärztekammer des Saarlandes<br>Faktoreistraße 4 |

| |
|---|
| 66111 Saarbrücken |
| Ethik-Kommission bei der Medizinischen Fakultät der Universität Würzburg<br>Versbacher Straße 9<br>97078 Würzburg |

**Sample ICFs including their amendments:**

FIND_PatInfo-Einwilligungserklärung_V1.5_05Aug.2022

FIND_PatInfo-Einwilligungserklärung_V1.4_30Aug2021

FIND_PatInfo-Einwilligungserklärung_V1.3_08Oct2020

FIND_PatInfo_Einwilligungserklärung_Zusatzinformation_V1.0_08Oct2020

FIND_PatInfo-Einwilligungserklärung_V1.2_03Jan2020

FIND_PatInfo-Einwilligungserklärung_Biobank_V1.2_03JAN2020

FIND_PatInfo-Einwilligungserklärung_V1.1_30JAN2019

FIND_PatInfo-Einwilligungserklärung_Biobank_V1.1_30JAN2019

### 17.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

FIND_CV_Nogova_2023-07-14

### 17.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

Please refer to signatures on page 2 of this report.

### 17.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

FIND_Listing of patients receiving test drugs_2023-07-20

### 17.1.7 Randomisation scheme and codes (patient identification and treatment assigned)

Not applicable.

### 17.1.8 Audit certificates

Not available. For description of a conducted audit, see section 9.6.

### 17.1.9 Documentation of statistical methods

SAP_FIND_V1.0_final_signedComplete

### 17.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

Not applicable.

### 17.1.11 Publications based on the study

The publication of the final results is currently being prepared.

### 17.1.12 Important publications referenced in the report

See reference list in section 15.

## 17.2 Patient data listings

### 17.2.1 Discontinued patients

Please refer to listing "Study medication overview, EOT, EOS, FU" in the Biostatistics Annex, sections 1.1.5 (cohort 1), 2.1.5 (cohort 2) and 3.1.5 (cohort 3).

### 17.2.2 Protocol deviations

Drug-related protocol deviations are described in section 10.2.

### 17.2.3 Patients excluded from the efficacy analysis

Not applicable, as all patients defined evaluable for efficacy as specified in the statistical analysis plan were evaluated for efficacy. No patient was excluded.

### 17.2.4 Demographic data

Please refer to the Biostatistics Annex, sections 1.1.6 (cohort 1), 2.1.6 (cohort 2) and 3.1.6 (cohort 3).

### 17.2.5 Compliance and/or drug concentration data (if available)

For distribution of duration and dose intensity per cohort, please refer to the Biostatistics Annex, sections 1.1.11 (cohort 1), 2.1.11 (cohort 2) and 3.1.11 (cohort 3). For a listing of the change of dose per patient, please refer to sections 1.1.12 (cohort 1), 2.1.12 (cohort 2) and 3.1.12 (cohort 3).

For compliance, please refer to "FIND SRS Report_2022Q4_action taken added".

### 17.2.6 Individual efficacy response data

For individual best response please refer to the Biostatistics Annex, sections 1.4.4 (cohort 1) and 2.4.4 (cohort 2).

### 17.2.7 AE listings (each patient)

Please refer to the Biostatistics Annex, sections 1.2.3 (cohort 1), 2.2.3 (cohort 2) and 3.2.3 (cohort 3).

### 17.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities

For a listing of individual laboratory measurements (hematology and serum chemistry) by patient, please see the Biostatistics Annex under sections 1.1.13 (cohort 1), 2.1.13 (cohort 2) and 3.1.13 (cohort 3).

## 17.3 Case Report Forms

Not applicable due to CRFs being electronic.

## 17.4 Data Monitoring and Safety Committee

FIND_DMSC Meeting_Results_DMC_Final