27 June 2024
EMA/336561/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Balversa

International non-proprietary name: erdafitinib

Procedure No. EMEA/H/C/006050/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADC	Antibody-Drug Conjugate
ADME	Absorption, Distribution, Metabolism, Elimination
ADR	Adverse Drug Reactions
AE	Adverse Event
AGP	Alpha-1 Acid Glycoprotein
ALDG	Adaptive Licensing Discussion Group
ASAP	Accelerated Stability Assessment Programme
AUC	Area Under The Curve
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BSC	Best-Supportive Care
CCP	Critical Control Point
CHMP	Committee For Medicinal Products For Human Use
CI	Confidence Interval
CPP	Critical Process Parameter
CPS	Combined Positive Score
CQA	Critical Quality Attribute
CR	Complete Response
CTCAE	Common Terminology Criteria For Adverse Events
CV	Coefficient Of Variation
CYP	Cytochrome
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DOR	Duration Of Response
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapor Sorption
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESI	Elektrospray-Ionisation
ESMO	European Society For Medical Oncology
EU	European Union
FGFR	Fibroblast Growth Factor Receptor
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
HRQoL	Health-Related Quality Of Life
ICH	International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IDMC	Independent Data Monitoring Committee
IPC	In-Process Control
IR	Infrared
ITT	Intent-To-Treat
JP	Japanese Pharmacopoeia
LDPE	Low Density Polyethylene
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary For Regulatory Activities
MS	Mass Spectrometry
mUC	Metastatic Urothelial Carcinoma
MVAC	Methotrexate/Vinblastine/Doxorubicin/Cisplatin
NAS	New Active Substance
NGS	Next Generation Sequencing
NIR	Near Infrared Spectroscopy
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance

NMT	Not More Than
NOAEL	No Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
OOS	Out Of Specification
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PAR	Proven Acceptable Range
PBPK	Physiologically Based Pharmacokinetic Modelling
PCR	Polymerase Chain Reaction
PCTFE	Polychlorotrifluoroethylene
PD-(L)1	Programmed Death-Ligand
PDCO	Paediatric Committee
PFS	Progression-Free Survival
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Polypropylene
PPES	Palmar-Plantar Erythrodysaesthesia Syndrome
PPQ	Process Performance Qualification
PR	Partial Response
PSD	Particle Size Distribution
PT	Preferred Term
PVC	Polyvinyl Chloride
QTPP	Quality Target Product Profile
RECIST	Response Evaluation Criteria In Solid Tumors
RPE	Retinal Pigment Epithelium
RPED	Retinal Pigment Epithelial Dystrophy
RPM	Rotations Per Minute
SAE	Serious Adverse Event
SAR	Structure-Activity Relationships
SD	Stable Disease
SmPC	Summary Of Product Characteristics
SoC	Standard Of Care
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
UC	Urothelial Carcinoma
UHPLC	Ultra-High Performance Liquid Chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet
WHO	World Health Organization
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 8 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Balversa, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2021.

The applicant applied for the following indication.

Balversa is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC), harboring susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations with disease progression during or following at least one line of therapy containing a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor in the locally advanced unresectable or metastatic treatment setting.

1.2. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision *P/0126/2017* on the granting of a product-specific waiver for all paediatric subsets.

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.3.2. New active substance status

The applicant requested that the active substance erdafitinib contained in the above medicinal product be considered as a new active substance, as the applicant claims it is not a constituent of a medicinal product previously authorised within the European Union.

1.4. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
19 November 2015	EMEA/H/SA/3195/1/2015/I	*Dieter Deforce and Helgi Helgason*
9 November 2017	EMEA/H/SA/3195/2/2017/III	*Martin Mengel and Olli Tenhunen*

The scientific advice(s) pertained to the following *quality, non-clinical, and clinical* aspects:

- *Designation of Starting Materials for the synthesis of the Drug Substance*
- Adequacy of the proposed nonclinical pharmacology, ADME, and toxicity studies to support registration.
- Existence of unmet medical need in a proposed target indication.
- The potential of Study BLC2001 with supporting data from EDI1001 to support registration.
- The main elements of the proposed Phase 3 study including studied population, comparators, statistical design, endpoints and its potential to provide confirmatory data following registration.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	8 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 December 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding	28 May 2024

Issues on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Balversa on	27 June 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	27 June 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Claimed therapeutic indication (initially)

Balversa is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC), harboring susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations with disease progression during or following at least one line of therapy containing a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor in the locally advanced unresectable or metastatic treatment setting.

Before taking erdafitinib, the physician must have confirmation of select FGFR3 gene alterations as confirmed with an appropriate diagnostic test.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Urothelial cancer (UC) is the tenth most common malignancy worldwide, with approximately 570,000 new cases per year and causing approximately 210,000 deaths per year worldwide (Globocan 2020). Ninety percent of all UC cases originate in the bladder, while the remaining cases originate in other parts of the urinary tract (Hepp et al, 2020; Miyazaki & Nishiyama, 2017). Smoking tobacco is the strongest risk factor, accounting for approximately 50–65% of new cases each year, and exposure to occupational and environmental toxins accounts for approx. 18% of new cases each year. Schistosomiasis is a common risk factor in certain regions (Africa and Middle East) associated with squamous cell carcinoma of the bladder (EAU Guideline invasive metastatic bladder cancer, 2020).

Bladder cancer is over four times more common in men than in women, with a respective incidence of 9.5/100,000 among men and 2.4/100,000 among women worldwide. Gender differences in the incidence of urothelial bladder cancer are most likely due to different smoking habits and exposition to exogenous carcinogens (International Agency for Research on Cancer. World Health Organization. 2021).

While the majority of new cases can be attributed to preventable risk factors, metastatic urothelial carcinoma (mUC) is incurable and is associated with significant morbidity and a dismal prognosis, with 5-year survival rates less than 10% (Saginala 2020).

2.1.3. Biologic features

Erdafitinib is a pan-FGFR tyrosine kinase inhibitor. The fibroblast growth factor family of receptors (FGFRs) are protein tyrosine kinases and consist of 4 related members (FGFR1, FGFR2, FGFR3, FGFR4) (Parker 2014). Activating mutations and translocations in FGFR genes have been associated with neoplastic progression and tumour vascularisation in multiple cancer types including UC (Dienstmann 2014; Parker 2014). Deregulation of FGFR signalling (e.g., via FGFR mutation and gene fusion) may be involved in bladder cancer pathogenesis (Babina 2017; Dienstman 2014; Touat 2015). Recurrent FGFR mutations and gene fusions are observed in urothelial cancer (Robertson 2017). Approximately 15 to 20% of locally advanced or metastatic UCs are found to harbour FGFR mutations and gene fusions, thus, FGFR inhibition may be particularly appropriate in those patients.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Typically, UC presents with painless haematuria. At initial diagnosis, approx. 75% of cases are non-muscle-invasive bladder cancer (NMIBC) and 25% are muscle invasive or even more advanced (ESMO guideline for bladder cancer, 2014). Urothelial carcinoma is a progressive disease with a part of patients presenting with or progressing to locally advanced or metastatic urothelial carcinoma. Untreated metastatic UC is associated with a median survival time rarely exceeding 3 to 6 months (Bellmunt et al, 2012). Approximately 10%-15% of patients present with metastatic UC at the time of diagnosis. Despite the low frequency of de novo disease, approximately half of the patients with locally advanced UC progress to metastatic disease within two years of cystectomy. Locally advanced or metastatic UC is an incurable disease with poor long-term survival and represents a high unmet medical need. Among patients treated with a cisplatin-containing regimen as the first-line treatment, the median OS is approximately 12 to 14 months and the 5-year mortality rate exceeds 85% (von der Maase et al, 2005).

2.1.5. Management

In urothelial cancer, locally advanced disease may be resectable or unresectable. If the disease is deemed resectable, a multidisciplinary approach ensues, which could involve neoadjuvant systemic therapy + surgery + adjuvant systemic therapy +/- radiation (systemic therapy may include chemotherapy and/or immunotherapy). If the disease is deemed unresectable, it is treated as if metastatic. Metastatic urothelial cancer is incurable and systemic therapy is given with the intent of palliation of cancer-related symptoms, delay in disease progression and prolongation of survival while maintaining quality of life.

Available systemic therapies in the EU can be broadly categorised as platinum-based chemotherapy regimens, other chemotherapy regimens, antibodies targeting programmed death receptor-1 or programmed death-ligand 1 (anti-PD-(L)1), and antibody-drug conjugates (ADCs). Due to the significant toxicities and morbidities, in particular kidney dysfunction and peripheral neuropathy, a relevant proportion of patients do not receive any systemic chemotherapy and the number of patients who are eligible for subsequent therapies decreases with every line of treatment (ESMO; Powles 2022).

Importantly, no therapies for a biomarker-selected population are approved so far.

Recommended treatments according to the European Society for Medical Oncology (ESMO; Powles 2022) at the time of the current submission are shown below.

First-line therapy for advanced or metastatic UC in patients who are fit enough to tolerate cisplatin is cisplatin-containing combination chemotherapy, such as gemcitabine-cisplatin or dose-dense MVAC (methotrexate/vinblastine/ doxorubicin/cisplatin) (Sternberg 2006). For cisplatin-containing treatment combinations overall survival between 12.5 and 15.8 months are reported (Bellmunt 2012, Loehrer 1992). For patients that are ineligible for cisplatin, combination therapy with carboplatin-gemcitabine is an option that is associated with generally inferior outcomes.

Anti-PD-(L)1 agents represent an important therapeutic advantage for patients with mUC:

- in platinum-eligible patients,
    - for the first-line maintenance treatment in patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy avelumab is approved as monotherapy (Powles 2020).

- for use in patients with progressive disease after prior platinum-based chemotherapy pembrolizumab (Bellmunt 2017), atezolizumab (Balar 2017) and nivolumab (Galsky 2020) are approved.

- in cisplatin-ineligible patients,
  - as first-line treatments pembrolizumab and atezolizumab monotherapy are currently approved for PD-L1 positive tumours (https://www.ema.europa.eu/en/medicines/human/EPAR/Keytruda; https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq).

- Furthermore, nivolumab was approved as adjuvant therapy for patients with muscle-invasive UC with PD-L1 expression with high risk of recurrence after radical cystectomy. Thus, future patients may have received nivolumab prior to the first line treatment in the metastatic setting.

- For patients who have previously received both, platinum-based chemotherapy and an anti-PD-(L)1 agent, the antibody-drug conjugate enfortumab vedotin is approved in the EU since 2022. Enfortumab vedotin was investigated in a Phase 3 randomised controlled trial (n=608) comparing enfortumab vedotin with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy, which demonstrated significant OS benefit of approx. 4 months (12.91 months vs 8.94 months; HR 0.704, 95% CI: 0.581, 0.852). Patients with preexisting comorbidities such as neuropathy and diabetes may not be candidates for enfortumab vedotin due to the toxicity profile, including neuropathy, and hyperglycaemia and severe cutaneous skin reactions, (McGregor 2021; Petrylack 2019; Rosenberg 2022).

Single-agent chemotherapy agents, e.g., docetaxel, paclitaxel and vinflunine are typically reserved for patients who have progressed after one or more lines of anti-cancer therapies. These treatments provide limited clinical benefit with ORR ranging from 10% to 20%, median PFS of approximately 2 months, and 30% to 40% 1-year survival rates (Bellmunt 2009; Culine 2006; Lorusso 1998; McCaffrey 1997; Witte 1997).

Vinflunine is approved in the EU based on a RCT in comparison to best supportive care, a significant difference in median PFS (3.0 vs 1.5 months) and a trend in median OS (6.9 vs 4.6 months) was shown (Bellmunt 2009).

Table 1: Treatment Regimens Recommended by the European Society for Medical Oncology (ESMO) for Advanced or Metastatic Urothelial Carcinoma

Treatment Regimens Recommended by the European Society for Medical Oncology (ESMO) for Advanced or Metastatic Urothelial Carcinoma[a]								
ESMO Recommendation	**Product**	**Sample Size**	**Endpoints**					**EU Marketing Authorisation Status**
			OS (mo)	**PFS (mo)**	**ORR**	**CR**	**DOR (mo)**	
Patients fit enough to tolerate cisplatin-based combination chemotherapy								
First-line SoC	Gemcitabine-cisplatin[a,b]	Gemcitabine +cisplatin N=203	13.8	7.4	49.4 %	12.2 %	9.6	Generics approved in EU member states via MRP
First-line alternative	Dose-dense MVAC[c]	ddMVAC N=126	12.5	10	39%	13%	Not reported	Generics approved in EU member states via MRP
First-line alternative	MVAC with granulocyte colony-stimulating factor[d]	MVAC +GCSF N=134	15.1	9.5	72%	25%	Not reported	Generics approved in EU member states via MRP

Treatment Regimens Recommended by the European Society for Medical Oncology (ESMO) for Advanced or Metastatic Urothelial Carcinoma[a]								
First-line alternative	gemcitabine, cisplatin and paclitaxel[e]	G+C+P N=312	15.8	8.3	55.5 %	13.5 %	Not reported	Generics approved in EU member states via MRP
SoC maintenance treatment	BAVENCIO (avelumab)[g]	Avelumab+BSC N=350	21.4	3.7	9.7%	6%	Not reported	Post approval variation 21 Jan 2021[h]
Second-line	KEYTRUDA (pembrolizumab)[i]	Pembrolizumab N=270	10.1	2.1	21%	9%	29.7	Post approval variation 24 Aug 2017*[j]
Second-line	TECENTRIQ (atezolizumab)[k]	Atezolizumab N=467	11.1	2.1	13.4 %	3%	21.7	Initial MAA approval** 20 Sep 2017[l]
Second line, less preferred	OPDIVO (nivolumab)[m]	N=270	8.6	2.0	20%	3%	10.4	Post approval variation 02 June 2017[n]
Second line, less preferred	IMFINZI (durvalumab)[o]	N=61	Not reported	Not reported	31.0 %	Not reported	Not reached	Not approved for this indication[p]
ESMO Recommendation	**Product**	**Sample Size**	**Endpoints**					**EU Marketing Authorisation Status**
			OS (mo)	**PFS (mo)**	**ORR**	**CR**	**DOR (mo)**	
Second-line in patients where anti-PD-(L)1 therapy is not possible	JAVLOR (vinflunine)[q]	Vinflunine + BSC N=253	6.9	3.0	8.6%	0%	7.4	Initial MAA approval 21 Sep 2009[r]
Second-line in patients where anti-PD-(L)1 therapy is not possible	TAXOTERE (docetaxel)[s]	N=30	Not reported	Not reported	Not reported	Not reported	4	Not approved for this indication[t]
Third-line after platinum and an anti PD-(L)1 agent[u,v] (includes chemotherapy followed by maintenance avelumab)	PADCEV (enfortumab vedotin)	enfortumab vedotin N=301	12.9	5.6	40.6 %	4.9%	7.4	Initial MAA approval 13 April 2022[x]
Patients not eligible for cisplatin-based combination chemotherapy								
First-line SoC	carboplatin and gemcitabine[f]	gemcitabine/carboplatin N=119 methotrexate/ carboplatin/ vinblastine N=119	9.3 8.1	5.8 4.2	41.2 % 30.3 %	3.4% 3.4%	Not reported	Not applicable, used per treatment guidelines
SoC maintenance treatment	BAVENCIO (avelumab)[g]	Avelumab+BSC N=350	21.4	3.7	9.7%	6%	Not reported	Post approval variation 21 Jan 21[h]
First line in patients whose tumors express 22C3	KEYTRUDA (pembrolizumab)[y]	Pembrolizumab N=370	11.3	2.2	28.6 %	8.9%	30.1	Post approval variation 24 Aug 2017*[j]
First line in patients whose tumors express SP142	TECENTRIQ (atezolizumab)[y]	Atezolizumab N=119	15.9	2.7	22.7 %	9%	Not reached	Initial MAA approval** 20 September 2017[l]

Treatment Regimens Recommended by the European Society for Medical Oncology (ESMO) for Advanced or Metastatic Urothelial Carcinoma[a]								
Second line following anti-PD-(L)1 therapy	PADCEV (enfortumab vedotin)[w]	N=89	16.1	6.7	51%	22%	13.8	Not approved in this indication[x]

Key: BSC=best supportive care; CR=complete response; ddMVAC=dose-dense methotrexate+vinblastine+doxorubicin+cisplatin; DOR=duration of response; EU=European Union; G+C+P= gemcitabine+cisplatin+paclitaxel; GCSF= granulocyte colony-stimulating factor; ITT=intent-to-treat [analysis]; MAA=marketing authorisation application; mUC=metastatic urothelial carcinoma; MVAC=methotrexate+vinblastine+doxorubicin+cisplatin; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SoC=standard of care; UC=urothelial carcinoma; US=United States

* Approval as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥10 was initially granted on 24 Aug 2017; the indication was later restricted to exclude patients whose tumours express PD-L1 with a CPS <10, based on review of interim analysis data from KEYNOTE-361.

** On 2 July 2018, the indication was restricted to include "and whose tumours have a PD-L1 expression ≥5%," based on the review of interim analysis data by the IDMC from study IMvigor211.

*** According to the ESMO guideline, treatment with vinflunine, docetaxel, and paclitaxel can be considered for platinum-refractory disease, although vinflunine is the only EMA-approved agent. Combinations with taxanes may be considered as an option in selected patients[a]

Sources:

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There is an unmet need for more effective therapies for patients with advanced urothelial cancer having received one or two lines of treatment.

2.2. About the product

Erdafitinib is a pan-FGFR tyrosine kinase inhibitor.

Erdafitinib belongs to the pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors. ATC code: L01EN01

The claimed indication was Balversa is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations with disease progression during or following at

least one line of therapy containing a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor in the locally advanced unresectable or metastatic treatment setting.

The finally approved indication is Balversa as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting (see SmPC section 5.1).

The recommended starting dose of Balversa is 8 mg orally once daily. This dose should be maintained and serum phosphate level should be assessed between 14 and 21 days after initiating treatment. Up-titrate the dose to 9 mg once daily if the serum phosphate level is <9.0 mg/dL, and there is no drug-related toxicity. After day 21 the dose should not be up-titrated regardless of serum phosphate level. Treatment should continue until disease progression or unacceptable toxicity occurs.

2.3. Type of application and aspects on development

Several clinical pharmacology and PK studies have been performed in healthy volunteers and patients with advanced or refractory solid tumours or lymphoma. The clinical pharmacology profile and population pharmacokinetic (PK) and population pharmacokinetic/pharmacodynamic (PK-PD) analyses of erdafitinib, are summarised in this dossier based on data from the completed Phase 1 studies in healthy volunteers, Phase 1 studies in subjects with advanced or refractory solid tumours or lymphoma, the Phase 2 studies in subjects with urothelial carcinoma (BLC2001 and BLC2002), subjects with advanced solid tumours and FGFR alterations (CAN2002), Asian subjects with NSCLC or other selected solid tumours (LUC2001), and the Phase 3 study in subjects with advanced or metastatic UC (BLC3001). The clinical development programme in support of the proposed indication concerns the following clinical studies:

- one phase 3 study BLC3001 with 2 cohorts in patients with advanced urothelial carcinoma:
  - BLC3001 Cohort 1 - in patients who had received 1 or 2 prior treatment including therapy with an anti-PD-(L)1-containing therapy, erdafitinib versus chemotherapy, ie, vinflunine or docetaxel;
  - BLC3001 Cohort 2 - in patients who had received 1 prior treatment, and no prior anti-PD-(L)1-containing therapy, erdafitinib versus pembrolizumab.
- Data sets from 2 phase 2 studies in patients with advanced urothelial carcinoma,
  - BLC2001 - in patients who may or may not have received prior therapy; erdafitinib monotherapy.
  - BLC2002 – cohort of erdafitinib monotherapy within multi-arm phase 1b/2 study, no prior therapy.

The study considered to be key to the proposed indication is study BLC3001 cohort 1, a phase 3 randomised, open-label study comparing erdafitinib versus chemotherapy, ie, vinflunine or docetaxel in "FGFR positive" (for details please refer to biomarker / CDx section below) urothelial carcinoma. Data from cohort 2 are included to support the overall activity of erdafitinib in urothelial carcinoma.

Specific CHMP guidelines relevant for the current application:

- Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95 Rev.5, 22 September 2017.
- Points to consider on application with 1. Meta-analyses; 2. One pivotal study. CPMP/EWP/2330/99, 31 May 2001

CHMP scientific advice in relation to this MAA on quality aspects was obtained in November 2015 (ref. EMEA/H/SA/3195/1/2015/I). CHMP scientific advice in relation to this MAA on nonclinical and clinical aspects was obtained in November 2017 (ref. EMEA/H/SA/3195/2/2017/III).

Paediatric investigation plan

No paediatric investigation plan (PIP) was submitted. A product specific waiver *P/0126/2017* was granted for ureter and bladder carcinoma. The PDCO had agreed that FGFR3 mutations have not been observed in paediatric samples of urothelial cancer.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 3 mg, 4 mg or 5 mg of erdafitinib as active substance.

Other ingredients are:

Balversa 3 mg film-coated tablets
Tablet core
Croscarmellose sodium
Magnesium stearate (E572)
Mannitol (E421)
Meglumine
Microcrystalline cellulose (E460)

Film-coating (Opadry amb II)
Glycerol monocaprylocaprate Type I
Polyvinyl alcohol-partially hydrolysed
Sodium lauryl sulfate
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

Balversa 4 mg film-coated tablets
Tablet core
Croscarmellose sodium
Magnesium stearate (E572)
Mannitol (E421)
Meglumine
Microcrystalline cellulose (E460)

Film-coating (Opadry amb II)
Glycerol monocaprylocaprate Type I
Polyvinyl alcohol-partially hydrolysed
Sodium lauryl sulfate
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

Balversa 5 mg film-coated tablets
Tablet core
Croscarmellose sodium
Magnesium stearate (E572)
Mannitol (E421)
Meglumine
Microcrystalline cellulose (E460)

Film-coating (Opadry amb II)
Glycerol monocaprylocaprate Type I
Polyvinyl alcohol-partially hydrolysed
Sodium lauryl sulfate
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

The product is available in a high-density polyethylene (HDPE) bottle with a child-resistant polypropylene (PP) closure and induction seal liner, or in a polyvinyl chloride-polychlorotrifluoroethylene (PVC-PCTFE) blister with aluminium push-through foil, as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of erdafitinib is N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine corresponding to the molecular formula $C_{25}H_{30}N_6O_2$. It has a relative molecular mass of 446.56 g/mol and the following structure:

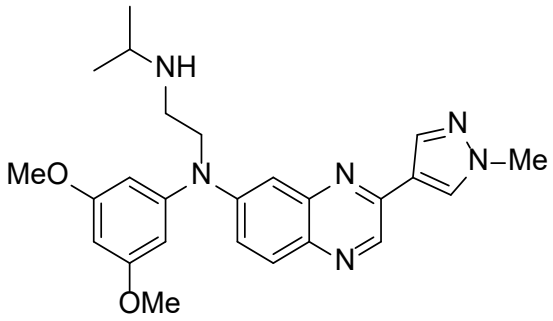


Figure 1: Active substance structure

The chemical structure of erdafitinib was elucidated by a combination of elemental analysis, high resolution mass spectrometry (MS), infrared (IR) spectroscopy, ultraviolet (UV) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetry (TGA), IR and dynamic vapor sorption (DVS) analysis. Physico-chemical characterisation included appearance, melting point, solubility, permeability, dissociation constant (pKa), partition/distribution (log P/log D) coefficients, specific optical rotation, polymorphism, hygroscopicity, and particle size distribution (PSD).

The active substance is a non-hygroscopic crystalline yellow powder, slightly soluble to practically insoluble or insoluble in aqueous media over a wide range of pH values. However, based on *in-vitro* permeability and solubility data in combination with human clinical data, it was concluded that erdafitinib qualifies as BCS 1 (Biopharmaceutics Classification System Class 1) compound at the highest proposed clinical dose of 9 mg per intake, despite the fact that erdafitinib is not considered as highly soluble from a chemical point of view. The molecule has a non-chiral molecular structure. Polymorphism has not been observed for erdafitinib. The particle size distribution of the active substance is controlled by the final crystallisation step, which assures consistency in the particle size of each active substance batch.

The applicant requested erdafitinib to be considered as a new active substance (NAS). During the assessment, a major objection was raised concerning the applicant's justification of erdafitinib NAS claim, requesting additional information about database searches performed by the applicant for structurally related substances in relation to the therapeutic moiety of the claimed NAS. The applicant has adequately addressed this issue and, therefore, erdafitinib is to be qualified as a new active substance in itself as it was concluded that it is not a constituent of a medicinal product previously authorised within the European Union.

2.4.2.2. Manufacture, characterisation and process controls

Satisfactory GMP documentation has been provided for all sites involved in manufacturing and testing of the active substance. The synthesis flow scheme for erdafitinib is depicted in the dossier.

The process description for erdafitinib is adequately described, covering all synthesis steps from the firstly used starting materials to the final active substance. The proposed starting materials have been defined in accordance with ICH Q11 and the related Q&A document. The proposed manufacturers are stated for each starting material and the routes of synthesis are indicated. The specifications are considered suitable and ensure the consistent and satisfactory quality of the starting materials. The analytical procedures are described, and validation data of chromatographic methods are presented. Information on structure elucidation has also been provided. Control of other raw materials includes the reagents and solvents of each process step.

During the assessment, a major objection was raised due to insufficient information presented in the dossier with regards to the quality and control of the isolated intermediates. The applicant provided in response the requested information on specifications, analytical procedures, method validations and analytical data for the isolated intermediates. This additional information was assessed as acceptable and the major objection was considered resolved.

An additional major objection was raised during the assessment due to insufficient description of reaction conditions (i.e. quantities or input materials, drying times and temperatures, vacuum and distillation conditions, pH), as well as for the insufficiently justified control strategy. In its response, the applicant provided an updated process flow chart and narrative manufacturing descriptions, based on the quantities of materials used in the process to produce a batch of the typical commercial size. The maximum commercial batch size is stated. Reaction parameters, such as reaction and stirring temperatures and times, distilled amounts, distillation conditions, drying temperatures and drying times are indicated at all reaction stages. The proposed control strategy is considered acceptable with this additional data. Batch analysis data from commercial scale batches demonstrate the consistent quality of the active substance. The major objection is considered resolved.

Process validation on three erdafitinib batches has been conducted.

The characterisation of the active substance and its impurities are in accordance with the EU "Guideline on chemistry of active substances". Descriptions of actual and potential impurities as well as their origin, fate and carryover to the final active substance have been provided and assigned to the respective synthesis steps. The specified and unspecified impurities comprise starting materials, intermediates, reagents, solvents, impurities observed in starting materials, reaction by-products and degradation products. These impurities are controlled in the respective starting materials or the final active substance, respectively, or justification for omission of control has been provided, also backed by spiking/purging experiments and batch analysis. Data on structure elucidation (NMR and MS) have been provided for several unspecified impurities and the single specified impurity.

Residual solvents (including potential contaminants) are controlled according to ICH Q3C guideline.

A risk assessment for the potential presence of elemental impurities was conducted in accordance with the ICH Q3D guideline. Based on the risk assessment and following confirmatory testing using a validated inductively coupled plasma mass spectrometry (ICP-MS) method, it is concluded that testing for each elemental impurity in the active substance specification is not necessary.

Erdafitinib (itself not genotoxic) is indicated for the treatment of patients with unresectable or metastatic urothelial carcinoma, to which ICH S9 applies. As such, potential genotoxic impurities may be controlled according to the limits for non-mutagenic impurities in ICH Q3A. A discussion of genotoxic impurities, including residual class 1 solvents, was nonetheless provided.,. The applicant initially proposed that no additional testing in the active substance is required for these impurities. However, the control and fate of one of these impurities was not sufficiently justified by the applicant and a major objection was raised questioning the control strategy for this impurity. Upon provision of additional comprehensive process-specific data, the major objection was considered resolved. Batch results showed that none of these genotoxic impurities was observed at relevant levels. The depletion of these impurities was demonstrated by the results of spiking studies. In conclusion, routine testing at the active substance level for the impurities identified as potentially mutagenic is not required.

Information on nitrosamines has been provided. There are no nitrosating agents, recovered solvents, reagents or catalysts used in any erdafitinib manufacturing process steps. Nevertheless, a theoretical assessment for the possibility of nitrosamine formation at the level of an intermediate was presented upon request. Based on this data, the presence of nitrosamines at levels of concern in the active substance can be excluded.

The active substance synthesis route has been essentially unchanged during development and has been used to manufacture all batches used in non-clinical and clinical studies, as well as for process qualification and stability testing. Manufacturing process optimisations have been implemented from the initial Synthesis Method A to the proposed commercial Synthesis Method B, leading to a higher purity of the isolated active substance. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of development is considered to be comparable to that produced by the proposed commercial process.

Erdafitinib active substance is packaged in double low-density polyethylene (LDPE) bags with safe seal closure (crimp system), then stored in a HDPE drum. For the primary packaging material, compliance with the Commission Regulation EU/10/2011 has been confirmed, and a specification is provided along with analytical methods, an IR reference spectrum and certificates of analysis.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (IR), assay (ultra-high performance liquid chromatography - UHPLC), impurities (UHPLC), residual solvents (gas chromatography - GC) and residue on ignition (Ph. Eur.), the latter being added to the specification following a request raised during evaluation.

The proposed active substance specification includes relevant testing parameters. The specification was established taking into account applicable ICH and EU guidelines and compendial considerations, as well as manufacturing capability, batch analysis data and stability results. Sufficient justification has been provided for the acceptance criteria for the tested parameters.

During assessment, the proposed limit for total impurities has been tightened upon request to align with batch analysis and stability data.

Furthermore, acceptable justifications based on physico-chemical properties of erdafitinib, process characteristics and/or development data are provided for omission from specifications of certain tests.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for a sufficient number of active substance batches were provided. All batches manufactured by the commercial process meet the acceptance criteria of the active substance specification. Overall, the batch analysis results show that the manufacturing process can produce active substance with consistent quality.

2.4.2.4. Stability

Stability data were provided from primary stability erdafitinib batches (manufactured at commercial scale, using the commercial synthesis method, at the synthesis development site and at the commercial site for at least the final manufacturing step) and from process performance qualification (PPQ) erdafitinib batches (manufactured at commercial scale, using the commercial synthesis method, at the commercial site). All active substance batches used in stability studies were stored in the intended commercial package. Results for up to 60 months under long-term conditions (25°C / 60% RH) and intermediate conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were included in the dossier. Photostability testing following the ICH Q1B guideline and testing under stress conditions (thermal, hydrolytic, oxidative and photochemical conditions, and in the presence of formaldehyde) was also conducted.

The primary stability programme is completed. The PPQ stability programme is ongoing and there are currently 48-month stability data available. The applicant presented a post-approval commitment to report to the agency any confirmed out-of-specification result or significant negative trend, which is endorsed.

The parameters tested are the same as for release, with the exception of several quality attributes which are not expected to change throughout shelf-life. The analytical methods used were the same as for release and were demonstrated to be stability indicating.

Available stability data indicate that erdafitinib active substance remains stable during storage under the different storage conditions, when stored in the proposed container closure system. The test results for all batches, storage conditions and time points comply with the proposed specifications and no significant stability related changes have been observed for any tested parameter.

In conclusion, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container, without any special temperature storage conditions.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as film-coated tablets containing 3 mg, 4 mg or 5 mg of erdafitinib as active substance, described as follows:

- The 3 mg tablet is a yellow, round biconvex, film-coated tablet of 7.6 mm in diameter, debossed with "3" on one side and "EF" on the other side. This tablet has been assigned the formulation number JNJ-42756493-AAA-G023 and may be abbreviated as G023.

- The 4 mg tablet is an orange, round biconvex, film-coated tablet of 8.1 mm in diameter, debossed with "4" on one side and "EF" on the other side. This tablet has been assigned the formulation number JNJ-42756493-AAA-G024 and may be abbreviated as G024.
- The 5 mg tablet is a brown, round biconvex, film-coated tablet of 8.6 mm in diameter, debossed with "5" on one side and "EF" on the other side. This tablet has been assigned the formulation number JNJ-42756493-AAA-G025 and may be abbreviated as G025.

The composition for each strength of erdafitinib finished product is presented in the dossier. The qualitative composition of different strengths is the same, except for the small differences in the film coatings. The quantitative composition of different strengths is proportional. The choice of pharmaceutical form/strengths adequately addresses the proposed dosing regimen.

No novel excipients and no excipients of human or animal origin are used in the manufacture of erdafitinib tablets. The chosen excipients of the immediate release film-coated tablets are described in Ph. Eur., except the Opadry Yellow, Opadry Orange and Opadry Brown coating mixtures, which consists of pharmacopeial ingredients and for which adequate specifications are set. Representative certificates of analysis have been provided for all excipients. The function and rationale for selection of each excipient at the proposed level have been adequately discussed and justified. The compatibility between the active substance and excipients has been demonstrated based on the stability results. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

No overages are used for the manufacture of the finished product, apart from the overage of coating material to compensate for losses during the film coating step.

The development of the finished product has been described in sufficient detail, starting from oral solution to hard capsules to film-coated tablets. The oral solution was used for Phase 1 studies. A degradation product was observed during development studies and the finished product was changed to a capsule formulation (that was also used in Phase 1 studies) with meglumine used as stabiliser. Finally, film-coated tablets were developed containing 1% meglumine and 2% erdafitinib. Three relative bioavailability studies were performed to support bridging of early formulations to the final commercial formulation. The commercial formulation is the same as the one used in the pivotal Phase 3 clinical study, as well as in clinical pharmacology (Phase 1) and selected Phase 2 studies, with the only difference being the debossing of the tablets which is not expected to impact product quality and performance. Similarity of the commercial formulation and formulation used in clinical phase 3 study has been sufficiently demonstrated by comparative dissolution profiles.

Based on the Quality Target Product Profile (QTPP) established for the finished product which describes a film-coated tablet for oral administration. The development of the manufacturing process is described in sufficient detail. An overview of the finished product critical quality attributes (CQAs) identified, together with a justification for their criticality designation, has also been included in the dossier. Optimisation of various process parameters has been discussed for each manufacturing step and comprehensive control strategy for critical process parameters (CPPs) is set in place.

The development and selection of the dissolution method has been described in sufficient detail and its discriminatory power was adequately demonstrated.

The primary packaging is either a HDPE bottle with a child-resistant PP closure and induction seal liner or a PVC-PCTFE blister with aluminium push-through foil. The materials comply with Ph. Eur. and EC requirements. The provided description and details on specifications and dimensions for the proposed container closure systems are considered sufficient. The choice of the container closure systems has been validated by stability data and both formats are adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The erdafitinib finished product is manufactured, filled, packaged, and tested in accordance with GMP.

A flow diagram supplemented by a narrative description of the manufacturing process and selected CPPs and in-process controls (IPCs), is provided in the dossier. Agreed. The manufacturing process has been described in sufficient detail. In-process controls during the finished product manufacture have been established based on the manufacturing process development studies and are considered adequate for this type of pharmaceutical form. Critical IPCs have been defined and justified.

The batch formula is provided for the proposed batch size) and is in accordance with the declared composition of the finished product.

The manufacturing process has been validated on three consecutive commercial scale consecutive batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification of the active substance (UHPLC, UV), identification of meglumine (near infrared, NIR – tested only at release), active substance assay (UHPLC), meglumine assay (NIR at release and UHPLC during shelf-life), related substances (HPLC), uniformity of dosage units/content uniformity (UHPLC/Ph. Eur.), dissolution (UHPLC/Ph. Eur.) and microbial purity (Ph. Eur.).

The release and shelf-life specifications presented for the finished product cover relevant parameters for solid oral dosage forms. The applicant provided a comprehensive justification for each specified parameter.

During the assessment, a major objection was raised, requesting tightening of the specification limit for dissolution in line with dissolution data for the proposed commercial formulation used in clinical trials. The applicant agreed to tighten the limit and the major objection was considered resolved.

Specified impurities have been included in the finished product specification and sufficient characterisation, mutagenicity assessment and toxicological qualification information for these impurities were provided. At the request of CHMP, the limits for one specified impurity and the limit for total impurities were tightened and a limit for meglumine was added to the shelf-life specifications. Overall, the limits for impurities at finished product level are in line with ICH Q3B guideline and considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D guideline. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The control strategy for residual solvents at the finished product level is justified, in line with ICH Q3C(R8) guideline

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). A risk has been identified for potential formation of nitrosamine impurities of erdafitinib and meglumine (both contain

secondary amines) with residual nitrite in the excipients. Erdafitinib is intended for advanced cancer therapy within the scope of ICH S9, therefore nitrosamines can be controlled to ICH Q3B levels. Nevertheless, nitrite spiking studies have been performed using a validated UHPLC-MS procedures and results demonstrated that nitrosamines are not formed in the finished product. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities at relevant levels in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results provided confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data were provided from primary stability batches and PPQ batches of each strength of finished product, manufactured at commercial scale at the commercial site, stored for up to 48 months under long term conditions (25°C / 60% RH) and under intermediate conditions (30°C / 75% RH) for the finished product packaged in HDPE bottles, for up to 36 months under long term conditions (25°C / 60% RH) and under intermediate conditions (30°C / 75% RH) for the finished product packaged in PVC-PCTFE blisters and for up to 6 months under accelerated conditions (40°C / 75% RH) for both packaging configurations, according to the ICH guidelines.

The primary stability programme is completed, while the PPQ stability programme is ongoing. The applicant presented a post-approval commitment to report to the agency any confirmed out-of-specification (OOS) result or significant negative trend, which is endorsed.

A bracketing approach is applied for stability studies. Only 3 mg and 5 mg batches have been tested for the full stability programme, whereas the only test performed on stability for the 4 mg strength was the appearance of the tablet. This approach is considered acceptable. Furthermore, 2-month in-use stability studies for the finished product packaged in HDPE bottles were performed at the beginning and end of shelf-life using the 3 mg strength as it is considered worst case due to the lowest active substance concentration. This is acceptable.

In addition, finished product batches were subjected to forced degradation studies, including exposure to light in line with ICH Q1B.

Stability testing was conducted according to the proposed commercial release specifications and methods, except for the assay of meglumine as described in product specification section of this report. The analytical methods used in the stability studies were demonstrated to be stability indicating.

In general, in both primary stability and PPQ stability programs, results met the specification limits under all storage conditions for all strengths of finished product when packaged in HDPE bottles or PVC-PCTFE blisters.

A slight increase within specification limits in specified degradation products has been observed for the primary stability batches stored under intermediate conditions, when packaged in HDPE bottles or PVC-PCTFE blisters. However, no stability related changes were observed for the PPQ batches. A slight decrease within specification limits in assay of meglumine was observed during storage under all tested conditions for the finished product packaged in HDPE bottles or PVC-PCTFE blisters. This decrease is

expected as meglumine acts as a formaldehyde scavenger. In addition, a slight decrease within specification limits in dissolution upon storage at intermediate and accelerated conditions was observed and was sufficiently explained by the applicant. An OOS result for dissolution at the 30-month time point was observed for one 5 mg PPQ batch when stored at 30°C/75% RH and packaged in HDPE bottles or PVC-PCTFE blisters. However, it is expected that finished product stored as indicated within the EU will be of adequate quality at the end of shelf-life in both packaging formats.

In conclusion, the observed physical and chemical changes were small and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

Based on available stability data, the proposed shelf-life of 48 months for the finished product packaged in HDPE bottles and of 36 months for the finished product packaged in PVC-PCTFE blisters, without any special storage conditions (as stated in the SmPC (section 6.3)) is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During assessment, five major objections were raised on quality grounds concerning: (1) incomplete justification of the erdafitinib new active substance claim, (2) missing critical information from the dossier with regards to the quality and control of isolated intermediates, (3) inappropriate description of reaction conditions and insufficient justification for the process control strategy applied for the active substance synthesis, (4) incomplete justification for the proposed control strategy for one genotoxic impurity at the active substance level and (5) tightening of specification limit for dissolution of the finished product. The major objections, as well as all the other concerns raised throughout the procedure, have been satisfactorily resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Erdafitinib is an orally active small molecule inhibitor of all four isoforms of FGFR kinase with potent activity *in vitro* and anti-tumour activity *in vivo* in FGFR pathway-dependent xenograft tumour models bearing FGFR activating alterations.

Erdafitinib is proposed for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma, harbouring susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations with disease progression during or following at least one line of therapy containing a programmed death-1 receptor (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor in the locally advanced unresectable or metastatic treatment setting.

The non-clinical programme has been designed according to ICH (International Council for Harmonisation) S9 guideline on non-clinical evaluation of anticancer pharmaceuticals in line with the proposed indication (advanced cancer).

The nonclinical primary pharmacodynamic profile of erdafitinib was characterised in several *in vitro* and in vivo models.

Secondary pharmacodynamic studies were performed *in vitro* to assess the potential of erdafitinib to inhibit off-target receptors, ion channels, or neurotransmitter transporters.

Erdafitinib was investigated in a battery of safety pharmacology studies to evaluate potential effects in the cardiovascular and respiratory systems. The disposition of erdafitinib including absorption, distribution, metabolism, and excretion was evaluated in nonclinical species (rat, dog) and was compared with pharmacokinetic information obtained in humans, where applicable. Toxicokinetic (TK) assessments were included in all safety/toxicology and investigative toxicology studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro pharmacology

Erdafitinib activity was evaluated against a panel of 387 kinases (KinomeScan) using a site-directed ATP-independent competition binding assay. Erdafitinib binds to all four isoforms of FGFR with IC_{50} around 1 nM. Six other kinases had IC_{50} values in low nanomolar range as shown in parentheses: RET (2.05 nM), PDGFRB (3.56 nM), CSF-1R (3.94 nM), FLT4 (4 nM), VEGFR2 (5.88 nM), and KIT (6.95 nM).

To confirm the *in vitro* activity in a cellular context, the BaF3-engineered model system was studied. In cellular assays, erdafitinib inhibited growth of FGFR1-overexpressing BaF3 cells in the absence of IL-3 with an IC_{50} of 19 nM. The inhibitory effect was reduced around 480-fold in the presence of IL-3. The IC_{50} values for FGFR3- and FGFR4-overexpressing BaF3 cells in the absence of IL-3 were 11.3 nM and 24.4 nM, respectively. In contrast, growth inhibition of VEGFR2-dependent cells required the IC_{50} of 1,190 nM demonstrating lower erdafitinib potency against this kinase in a cellular context as compared to the biochemical assay.

To demonstrate the ability of erdafitinib to inhibit the proliferation of non-engineered cell lines, the compound was tested against a panel of 21 human tumour cell lines with different tissue origins and driver alterations. The evaluation showed that eight of them had IC_{50} values of less than 10 nM.

Among these 8 cell lines were representatives of lung, gastric, colorectal and bladder cancer (RT-112 and RT-4) cell lines, the latter exhibiting IC_{50} values of 1.13 nM and 4.8 nM, respectively. A study in another panel of 82 cell lines of 17 tumour entities and in broader panels of 271 breast and lung cancer cell lines revealed an association of nanomolar GI_{50} activity with FGFR overexpression.

Erdafitinib inhibited FGFR autophosphorylation in four cell lines featuring activation of each FGFR isoform, namely in SNU-16 gastric cancer (FGFR2) and MDA-MB-453 breast cancer (FGFR4) cells at the concentrations of 10 nM and higher, in the KMS-11 multiple myeloma (FGFR3) cell line from 30 nM onwards and in NCI-H1581 lung cancer (FGFR1) cells from 100 nM. In the latter cell line, the phosphorylation of FGFR substrate 2 alpha (FRS2α), a direct downstream target of FGFR, and the endogenous phosphorylation of ERK1/2 was also inhibited. Sustained inhibition of FGFR phosphorylation for at least 8 hrs was also demonstrated following a 1-h incubation of FGFR2-amplified Kato III gastric cancer cells with erdafitinib. This extended pEGFR inhibition was associated with lysosomal accumulation of the compound.

In vivo pharmacology

Anti-tumour activity of erdafitinib were evaluated in xenograft models implanted in CD-1 mice.

In RT-112 (cell line derived from a human urinary bladder transitional cell carcinoma) bladder cancer xenografts in CD-1 mice, erdafitinib significantly dose-dependently reduced tumour growth and significantly decreased the final tumour weight by 85% (p=0.0001) at the oral dose of 25 mg/kg QD. In BALB-c nude mice with RT-112 bladder cancer xenografts, erdafitinib led to significant tumour growth inhibition of 101.3% (p<0.0001) at 12.5 mg/kg BID administered orally. A good PK/PD correlation was observed in BALB/c mice as peak plasma and tumour concentrations of erdafitinib were associated with the maximum pERK inhibition (around 40%). Cmax of erdafitinib at the efficacious dose of 12.5 mg/kg BID was 28.5 ng/ml, which is far below the average plasma concentration observed for the minimum dose in patients (4 mg QD: total Cmax 675 ng/ml). However, in the RT112-VM tumour model with FGFR3-V555M mutation tumour growth inhibition did not exceed 36.9% (p = 0.0595).

Beside bladder cancer, good anti-tumour activity was demonstrated in several gastric cancer models (e.g. KatoIII and SNU-16). Tumour regression was observed from doses of 6.25 mg/kg BID (Cmax = 91.3 ng/ml) or 20 mg/kg QD. A correlation between plasma levels of erdafitinib and inhibition of FGFR phosphorylation was observed in SNU-16 xenografts.

Overall, efficacy was low in breast and lung cancer models and modest in liver cancer xenografts. In a small number of lung cancer PDX models with FGFR alterations, erdafitinib efficacy was better in models with higher FGFR fusion expression levels.

Erdafitinib exhibited tumour growth inhibition in hepatocellular carcinoma xenografts with FGF19 amplification or FGF19 overexpression but not in the case of simultaneous HGF overexpression, and not in cholangiocarcinoma PDX models with FGF19 gene amplification.

2.5.2.2. Secondary pharmacodynamic studies

In vitro receptor binding assays were done in a panel of 51 targets (receptors, ion channels, neurotransmitter transporters) demonstrated 55.6-85.5% inhibition of 10 targets at 10 µM and 55% inhibition of 5-HT_{1B} at 1 µM.

2.5.2.3. Safety pharmacology programme

In vitro studies

In HEK293 cells transfected with the hKvLQT1/hminK genes, erdafitinib inhibited I_{Ks} current with the IC_{50} value of 25.3 µM. This is far above the unbound clinical plasma Cmax of 11.5 nM. . In hERG-transfected HEK293 cells, I_{Kr} current was inhibited with IC_{50} of 408 nM, which is 35.5-fold higher than the expected clinical plasma levels of erdafitinib. However, low recovery of locally applied drug concentrations was observed in the hERG assay. The corrected IC_{50} value could not be determined since the recovery was only measured at one test item concentration (10 µM).

In vivo studies

The potential electrophysiological effects of erdafitinib were assessed at concentrations from 10 nM to 10 µM in isolated, arterially perfused rabbit ventricular wedge preparations. Relative to vehicle (n = 6), erdafitinib (n = 6) at 10 and 100 nM did not significantly or physiologically relevantly change the QT interval and TdP score. At 1 and 10 µM, erdafitinib significantly prolonged the QT interval (+10% and +29%, respectively) and increased TdP score (+2.0 and +3.5, respectively). Erdafitinib significantly and dose-dependently increased the Tpeak to Tend interval at ≥100 nM.

In guinea pigs, erdafitinib dose-dependently increased the duration of the QT and QTcB intervals starting from 2.5 mg/kg IV (Cmax = 1740 ng/ml corresponding to unbound Cmax = 184 ng/ml). These erdafitinib levels are 35.8 times higher than clinical unbound Cmax of 11.5 nM. The duration of the PQ interval increased at ≥20 mg/kg, and QRS duration significantly increased after administration of 40 mg/kg. Profound ECG changes were observed starting at 20 mg/kg. In the isolated, spontaneously beating right atrium of the guinea pig, erdafitinib slightly to moderately decreased the rate of contraction at 3 and 10 µM (it should be noted that the actual organ exposure was below 66% threshold). The compound dose-dependently increased the force of contraction relative to controls.

In artificially ventilated anesthetised dogs, an increase in the duration of the QT interval and in the action potential duration (APD) at 90% of repolarisation at the endocardium of the right ventricle were seen at ≥0.32 mg/kg (unbound Cmax = 59.2 ng/ml). At ≥0.63 mg/kg (unbound Cmax = 112 ng/ml), a decrease in pulmonary artery blood pressure and left ventricular end-diastolic pressure, increases in the duration of the PQ interval and in the duration of QTcB and QTcF intervals were noted, with no morphologic changes of the ECG. At ≥1.25 mg/kg, a dose-dependent decrease was noted in left ventricular dp/dtmin. At ≥2.5 mg/kg, an increase in heart rate and a concomitant decrease in RR interval duration were observed. At 10 mg/kg, erdafitinib induced a tendency to increase aortic blood pressure (systolic and diastolic), the time constant of relaxation (tau) and pressure rate product. Cardiovascular effects in this study were observed at the lowest dose applied, with the exposure being only 11.5-fold the expected clinical exposure based on Cmax, u.

In vivo GLP studies

Erdafitinib was administered orally to male beagle dogs (n = 4/dose) at escalating doses of 1, 2.5 and 5 mg/kg body weight. A vehicle solution containing 20% w/v hydroxypropyl-β-cyclodextrin was also administered. Toxicologically relevant changes in respiratory rate and oxygen saturation rate were absent at every dose tested. A single oral administration of erdafitinib to conscious male Beagle dogs up to 2.5 mg/kg (Cmax = 90.2 ng/ml, Cmax,u = 12.4 ng/ml) did not induce any relevant changes in cardiovascular and ECG parameters. After dosing at 5 mg/kg (Cmax = 265 ng/ml, Cmax,u = 36.3 ng/ml), a decrease in heart rate and a prolongation of the QT interval were seen in one dog. When corrected for heart rate, minimal increases in QTcB (14.2% and 12.5%) and QTcF (13.0% and 10.6%) were observed in the same dog. The Cmax in this dog was 228 ng/ml (unbound Cmax = 31.2 ng/ml based on 13.7% of unbound erdafitinib in dog plasma) and was lower than the average. The safety margin in this GLP study was only 2.4.

Erdafitinib did not cause any respiratory changes in conscious dogs at oral doses up to 5 mg/kg (total plasma exposure of 265 ng/ml; unbound concentration of 36.3 ng/ml). This represents a safety margin of ca. 7 relative to the unbound Cmax for a 9 mg QD clinical dose.

No dedicated safety pharmacology study was performed to evaluate CNS effects of erdafitinib. CNS endpoints were included in the toxicology studies and the effects are described in Toxicology section.

2.5.2.4. Pharmacodynamic drug interactions

No studies on pharmacodynamics drug interactions were conducted. This is acceptable as erdafitinib is not intended to be used in combination therapies.

2.5.3. Pharmacokinetics

The disposition of erdafitinib including absorption, distribution, metabolism, and excretion was evaluated in rats and dogs and was compared with pharmacokinetic information obtained in humans, where applicable.

2.6. Methods of analysis

Table 2. Overview of the validated bioanalytical methods

Study nr.	Analyte	Matrix	Range	Method	GLP status
BA10077	erdafitinib	dog plasma	0.2 – 100 ng/ml	LC-MS/MS	no formal GLP
BA10081	erdafitinib	dog Li-heparin plasma	0.2 – 100 ng/ml	LC-MS/MS	no formal GLP
BA10981	erdafitinib	rat plasma	0.4 – 400 ng/ml	LC-MS/MS	no formal GLP
BA10076	erdafitinib	rat plasma	0.4 – 400 ng/ml	LC-MS/MS	no formal GLP

Absorption

Following IV administration, the volume of distribution for erdafitinib in mice, rats and dogs was moderate and exceeded total body water, indicating distribution outside plasma. Plasma clearance was high, exceeding hepatic blood flow in rats and dogs and nearing hepatic blood flow in mice. After oral dosing, the T_{max} was rapid in mice and moderate in rats and dogs. The T1/2 was short in rodents and dose-dependent in dogs. Oral bioavailability was low in rodents (12% in mice; ca. 1.8% in rats) and complete in dogs (>100%).

Systemic exposure (C_{max} and AUC) to erdafitinib generally increased more than dose proportionally in all 3 species, with accumulation ranging from 1.2x to 4.6x for C_{max} and from 1.3x to 6.9x for AUC compared to single-dose exposures.

Distribution

Erdafitinib was found to be a moderate-to-high permeability compound.

Binding of ^{3}H-erdafitinib to plasma proteins from Swiss CD1 mouse (pool of males and pool of females), Sprague Dawley rat (pool male and female), NMRI/Nu mouse (pool of males), nude rat RNU (pool of males), Beagle dog (pool of male and female) and human (males) was investigated by means of equilibrium dialysis.

Plasma protein binding of erdafitinib was species-specific. The free fraction ranged from 5.9 to 11.3% in mice, between 2.2 and 7.2% in rats and was 10.6% in guinea pigs and 13.7% in dogs. In human plasma, erdafitinib was highly protein-bound with a concentration-dependent free fraction of 0.55 to 0.74%. Among plasma proteins, strong association with α1-acid glycoprotein was observed.

Binding to microsomal proteins was the weakest in the rat with free fractions of 94.6 - 98.0% and stronger in the dog (fu between 76.4 and 77%). In human, binding to microsomal proteins was concentration-dependent and an unbound fraction ranged from 24.8 to 86.1%.

Blood-to-plasma partitioning was also species-specific. Blood-to-plasma ratio in human (0.6) was the lowest, followed by the nude RNU rat (0.8), mouse and Sprague Dawley rat (around 1), and Beagle dog (1.61).

In Sprague Dawley rats, highest erdafitinib concentrations were found in lungs and in the liver. No brain accumulation was observed. In pigmented rats following administration of [^{14}C]-erdafitinib, high radioactivity levels were detected in the small intestine wall, the liver and the kidney outer medulla. After 72 h post-dose, radioactivity was still present in the lens of the eye and uveal tract/ciliary body, kidney (cortex and medulla), liver, spleen, exorbital lacrimal gland, intra-orbital lacrimal gland, , non-pigmented and pigmented skin and the gastrointestinal tract walls. No apparent association of erdafitinib with melanin was noted.

Metabolism

Intrinsic clearance, Km and Vmax of ^{3}H-erdafitinib were determined in rat, dog and human liver and intestinal microsomes and in human and dog hepatocytes.

Metabolic rate of erdafitinib decreased in the order rat > mouse > dog > human. The metabolism was saturated in animal species at 3 µM, but not in humans. In human and rat hepatocytes, most important *in vitro* metabolic pathways were O-demethylation (M6) followed by glucuronidation (M2or oxidation (M9). In rat hepatocytes, in addition to a few unidentified more hydrophilic secondary metabolites, other metabolites resulted from addition of one oxygen (M5) and a combination of addition of one oxygen and glucuronidation (M3). In dog hepatocytes, metabolites M2, M6 and M9 were detected.

^{3}H-erdafitinib was orally administered to male rats at 4 and 60 mg/kg and male dogs at 0.25 and 1 mg/kg. For both species, metabolic profiles in plasma were qualitatively comparable between both doses. In rat plasma, M2 was by far the major circulating entity at 4 mg/kg whereas at 60 mg/kg the parent drug and M2 were observed, which is in line with saturation kinetics. In dog plasma, parent drug and metabolites M2, M4 and M11 (addition of one oxygen) were the major circulating entities. Minor entities detected in plasma were M1 (rat only), M3, M4 (rat only), M5, M6, M7, M8 (N-dealkylation) and M9 (rat only). In rat faeces, the main components were the unchanged drug (4.56% of the dose), and metabolites M6 (O-demethylation, 9.55% of the dose), M5 (addition of one oxygen, 1.68% of the dose), M4 and M7 (loss of 2 hydrogens, 6.64% and 5.01% of the dose, respectively). The glucuronide of M6 (M2), prominent in plasma, was absent in faeces probably due to deconjugation to its aglycon M6 in the gut microflora. In dog faeces, unchanged erdafitinib (1.39% and 5.37% of the low and high dose, respectively), M4 and M7 and numerous minor metabolites were seen. M4 and M7 are likely artefacts formed from M6.

In rat urine, M2 was by far the most important entity (0.97% of the dose) following 4 mg/kg. At 60 mg/kg, M2 represented 1.09% of the dose while its aglycon M6 was also important (0.9% of the dose). Minor metabolites in rat urine resulted from a combination of oxidation and glucuronidation (M3) and a combination of O-demethylation and loss of two hydrogens followed by addition of one oxygen (M9). In dog urine, only metabolite M2 (0.74% of the low dose and 1.09% of the high dose) and unchanged erdafitinib (0.24% of the low dose and 0.36% of the high dose) were detected.

In the pooled faeces extracts from the bile duct-cannulated rats administered oral ^{14}C-erdafitinib at 4 mg/kg, M6 and the parent drug were the main entities representing 16.3% and 21.5% of the administered dose. M20 (aglycon of M13) represented 1.94% of the dose. These entities could be attributed to intestinal secretion. The main metabolites in rat bile were M2 (formed by O-demethylation of erdafitinib (M6) and subsequent glucuronidation, 14.2 % of the dose), M15 (addition of one oxygen to M6 on the phenyl (M26) and subsequent glucuronidation, 9.24 % of the dose) and M13 (further O-demethylation of M6 (M20) and subsequent glucuronidation, 4.08% of the dose).

In plasma of mice, only parent erdafitinib was found after oral dosing. After IV administration, M6 and M8 (N-depropylation) were detected beside the unchanged drug. In mouse faeces, M20 (36% of the oral dose and 25% of the IV dose), M6 and M9 (-CH2, -2H,+O) were observed. In urine, M13 (2x O-demethylation and glucuronidation, 1.4% of the oral dose and 4.5% of the IV dose), M20 (2x O-demethylation), M2 (O-demethylation and glucuronidation) and M6 (O-demethylation) were detected.

Erdafitinib metabolism in human liver microsomes was low. Therefore, human hepatocytes were considered a more suitable system to investigate the involvement of CYP enzymes. The formation of M6 was inhibited by ketoconazole by 22% and by sulphaphenazole by 90.6% indicating that CYP2C9 is mainly involved in M6 metabolic pathway with a minor contribution of CYP3A4. The formation of M8 is largely mediated by CYP3A4 as it was inhibited by ketoconazole by 73%. These results were further confirmed by metabolic profiling in CYP-specific supersomes and suggest that mainly CYP2C9 and CYP3A4 are responsible for erdafitinib biotransformation in human.

Unchanged erdafitinib was by far the major drug-related material in human plasma. Thus, no metabolites represented more than 10% of the total drug-related material. In human faeces, parent drug (14.1 – 20.8% of the dose) and M6 formed by O-demethylation (23.8 – 24.2% of the dose) were the major entities. The main component in urine was unchanged compound (11.3% of the dose) followed by M6 (2.05%). No human-specific metabolites were found.

Excretion

Erdafitinib was predominantly excreted via faeces in animals (through biliary route) and humans. Faecal elimination represented 66.4-69.9% of the total radioactivity in human healthy volunteers, 38-74% in mice, 75.2-75.8% in dogs, and 87.6-95.1% in intact rats. In bile duct-cannulated rats, 12% of the dose was excreted in faeces and 47.9% via bile. The contribution of the renal elimination was 17.8-19.2% of the total radioactivity in humans, 2-12% in mice, 5.44-6.30% in dogs, 2.32-2.73% in intact rats, and 30.6% in bile duct-cannulated rats.

2.7. Pharmacokinetic drug interactions

Potential interactions with metabolic enzymes

Erdafitinib was found not to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations. The compound was demonstrated to be an irreversible inhibitor of CYP3A. Erdafitinib does not induce CYP1A2 and CYP2B6. Its effect on CYP3A4 is less clear. In one of three donors, erdafitinib induced CYP3A4 more than 2-fold at $15\times C_{max,u}$ and above, albeit a clear

concentration dependency was missing. The applicant investigated the impact of erdafitinib on the PK of CYP3A4 substrate midazolam (see clinical part).

The effect on UGT enzymes was not investigated.

Erdafitinib is a P-gp substrate. Due to saturation of the P-gp-mediated transport above 0.3 μM, DDI at intestinal level can be excluded as 0.1×dose/250ml = 8.06 μM. Erdafitinib is not a substrate of BCRP, OATP1B1 and OATP1B3.

Erdafitinib is an *in vitro* inhibitor of P-gp, MATE1, MATE2-K, OCT1, OCT2.

2.7.1. Toxicology

2.7.1.1. Single dose toxicity

Single dose toxicity studies with erdafitinib were not performed.

2.7.1.2. Repeat dose toxicity

Repeat-dose oral toxicity was evaluated in albino Swiss mice dosed for up to 2 weeks, in Sprague-Dawley rats and Beagle dogs dosed for up to 3 months.

Rats and dogs were selected as relevant species for the pivotal 1- and 3-month repeat-dose toxicology studies since erdafitinib was shown to be pharmacologically active in both animal species.

3-Month Oral Toxicity Study in Rats (TOX10846)

Table 3: 3-Month oral toxicity study in rats

Study ID	Species/ Sex/Number/ Group	Dose/Route/ (Vehicle/Formulation)	NOAEL	Major findings
10846	Rats (Sprague Dawley) 0, 4, 8, 16 + 32 mg/kg: 10M + 10F TK for all doses 3M + 3F	0, 4, 8 mg/kg q.d. PO 16, 32 mg/kg 7 days on/off PO	Males: 4 mg/kg q.d. Females: < 4 mg/kg q.d.	**0 mg/kg** No noteworthy findings **4 mg/kg q.d.** 1 **F** died – gavage-related **M:** FGF23↑ , D3↓, , DPD↑ , PTH↓ **F:** FGF23↑ **8 mg/kg q.d.** **M:** FGF23↑ , D3↓ , DPD↑ , PTH↓, Ca↑ **F:** FGF23↑, D3↓ , DPD↑ , PTH↓, Ca↑, sternum deformation (2 females), broken nail (1 animal), reticulocytes+platelets↓, chondroid dysplasia (sternum, stifle), atrophic changes of harderian gland, increased number of hair follicles in skin, mineralisation of kidney **M+F**: diffuse cornea atrophy of the eyes Diffuse atrophy of exorbital lacrimal gland **16 mg/kg 7 days on/off** **M:** AST↑, ALT↑, AST↑, GGT↑, FGF23↑, limping, deformed tail (2/10), **F:** AST↑, ALT↑, FGF23↑, PTH↓, limping, deformed sternum (2/10) **32 mg/kg 7 days on/off** 2 M died – gavage-related 1 M died – treatment-related **M:** FGF23↑, D3↓, PTH↓, cycle tail deformation (7/10), sternum deformation (5/10), limping (10/10) **F:** FGF23↑, D3↓, PTH↓, cycle tail deformation (1/10), sternum deformation (9/10), limping (7/10), necrosis of ovarian corpora lutea, acute inflammation of the cervix **16+32 mg/kg** **M+F:** deformities + discoloration of bones and incisors, chondroid dysplasia, mineralisation of kidney, atrophy of tongue epithelium and oral mucosa

M: males, F: females, P phosphate, FGF23: fibroblast growth factor-23, PTH: parathyroid hormone, D3: 1,25 (OH)2 vitamin D3, Ca: calcium, ALP: alkaline phosphatase, WBC: white blood cells, DPD: Deoxypyridinoline, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltranferase

Mortalities were reported at 8 mg/kg/day (daily dosing) and 32 mg/kg/day (intermittent dosing, 7 days on/7 days off). The cause of death at 8 mg/kg/day was not determined, and the deaths at 32 mg/kg/day were attributed to soft tissue mineralisation of the heart and aorta, which were proposed to have contributed to the rats' poor condition.

The predominant microscopic findings included atrophy of gland structures, chondroid dysplasia in multiple bones and larynx+trachea, soft tissue mineralisation of multiple organs, atrophy, decreased

cellularity, degeneration of ontoblasts, degeneration/inflammation and increase in hair follicles/reduced size. Test-article-related effects on female reproduction organs were reported at 32 mg/kg/day.

Table 4: Mean toxicokinetic data of erdafitinib in 3-month oral toxicity study in rats.

Dose (mg/kg)	Study Day	C_{max} (ng/mL)		AUC_{0-24h} (ng·h/mL)	
		M	F	M	F
4 (q.d.)	6	2.64	6.43	10.1[1]	29.6[2]
	90	6.98	13.4	26.3[2]	45.2
8 (q.d.)	6	6.40	31.9	29.6[1]	94.3[2]
	90	26.2[2]	59.7	99.8[2]	231[2]
16 (7 days on/7 days off)	6	28.0	257	105[1]	936
	90	88.5	462	327[2]	1780
32 (7 days on/7 days off)	6	524	886	5580[1]	4170
	90	360[2]	929	1910[2]	10000[2]

n=3 unless otherwise stated [a]. AUC values from individual animals were excluded when calculated with more than 25% extrapolation.
Day 6 and Day 90 is at the end of the first and last 7-day dosing period for the intermittently dosed groups.
F = female; M = male

3-Month Oral Toxicity Study in Dogs (TOX10849)

The purpose of this study was to determine and assess the potential toxicity of JNJ-42756493-AAA, when administered once daily by the oral route (via gavage) to beagle dogs, for a period of three months. Additionally, one group was included which was dosed daily every other week to investigate the effects of intermittent dosing.

The toxicokinetic parameters of JNJ-42756493-AAA were also studied.

Table 5: 3-Month oral toxicity study in dogs.

Study ID	Species/ Sex/Number/ Group	Dose/Route/ (Vehicle/Formulation)	NOAEL	Major findings
10849	Dogs (Beagle) 0, 0.5, 0.75, 1.5 + 4M + 4F TK for all doses 4M + 4F	0, 0.5, 0.75 mg/kg q.d. PO 1.5 mg/kg 7 days on/off PO	< 0.5 mg/kg q.d.	**0 mg/kg** No noteworthy findings **0.5 mg/kg q.d.** **M:** FGF23↑, ocular discharge **F:** FGF23↑, reticulocytes↓., WBC ↓, thyroid weight↓, chondroid dysplasia of distal femur **M+F**: epithelial atrophy of tongue, parotid salivary gland + lacrimal glands, rough haircoat, piloerection, longer nails **0.75 mg/kg q.d.** **M:** FGF23↑ **F:** FGF23↑, hunched posture, stiffness of the hindlegs, reticulocytes↓, thyroid weight↓, follicle of thyroid gland **M+F**: rough haircoat, piloerection, longer nails, abnormal red skin, P↑, PTH↓, D3↓ Urine: DPD↑, ocular changes, irregular surface/mineralisation of heart + aorta, chondroid dysplasia of sternum + femur, epithelial atrophy of tongue, parotid salivary gland + lacrimal glands **1.5 mg/kg 7 days on/off** **M:** haemorrhagic faeces (1) **F:** follicle of thyroid gland, increased hair follicles of skin ear M+F: rough haircoat, piloerection, longer nails, abnormal red skin, reticulocytes↓., WBC ↓, ALP↑, FGF23↑, PTH↓, abnormal dentin, atrophy of tongue + oral mucosa Urine: DPD↑, ocular changes, irregular surface/mineralisation of heart + aorta, chondroid dysplasia of sternum + femur, epithelial atrophy of parotid salivary gland + lacrimal glands, abnormal dentin

M: males, F: females, P phosphate, FGF23: fibroblast growth factor-23, PTH: parathyroid hormone, D3: 1,25 (OH)2 vitamin D3, Ca: calcium, ALP: alkaline phosphatase, WBC: white blood cells, DPD: Deoxypyridinoline, AST: aspartate aminotransferase, ALT: alanine aminotransferase

At the dose of 0.5 mg/kg/day, ocular changes consisted of bilateral watery or purulent ocular discharge, periocular alopecia, blepharospasm, diffuse corneal opacification and low tear production.

The predominant target organs were aorta (vascular/degeneration), heart (mineralisation/degeneration), bone femur and sternum (chondroid dysplasia), skin (increased hair follicles) and epithelial atrophy in the tongue, oral mucosa, parotid salivary glands, eye, teeth and lacrimal glands.

Table 6: Mean toxicokinetic data of erdafitinib in 3-month oral toxicity study in dogs. (from Module 2.6.6)

Dose (mg/kg)	Study Day	C_{max} (ng/mL)		AUC_{0-24h} (ng·h/mL)	
		M	F	M	F
0.5 (q.d.)	6	18.5	8.45	108	40.2
	90	21.6	15.9	172	92
0.75 (q.d.)	6	27.2	20.7	218	146
	90	38.9	26.1	394	213
1.5 (7 days on/7 days off)	6	117	71.0	1130	682
	90	113	98.1	1300	969

n=4; F = female; M = male

Systemic exposure to JNJ-42756493 increased in a greater than proportional manner across the dose range on Day 6 and Day 90 in both sexes. Because of the high inter-animal variability, a sex-related difference could not be determined

2.7.1.3. Genotoxicity

In vitro, erdafitinib was negative for an increase in reverse mutations in Ames tests in bacteria and for chromosomal aberrations, polyploidy and endoreduplication in a micronucleus test in TK6 cells, respectively. Erdafitinib did also not increase the formation of micronuclei in PCEs of rat bone marrow *in vivo* at MoE of > 90 x based on C_{max} (unbound).

2.7.1.4. Carcinogenicity

Not conducted.

2.7.1.5. Reproductive and developmental toxicity

The reproductive and developmental toxicity of erdafitinib was investigated in a non-GLP pilot study and a GLP pivotal embryo-foetal toxicity study in Sprague-Dawley rats. In accordance with ICHS9 and ICHS5 (R3) guidelines no studies on fertility and early development and on pre- and postnatal development have been performed. Furthermore, due to the embryolethal and teratogenic effects in rats, investigation in a second species was not necessary.

Effects on epididymides and testes were observed in a non pivotal 2-week rat study at exposure levels >10-fold those reached in humans.

Table 7: Pivotal embryo-foetal developmental study in Sprague-Dawley rats with erdafitinib.

Study ID / GLP /TK	**Number Female/ group**	**Route & dose (mg/kg/day)**	**Dosing period**	**Endpoints**	
TOX12329 / GLP: yes/ TK: yes	Main: 22 TK: 6	Oral (gavage) Ctrl: 0 (vehicle) LD: 1 MD: 4 HD: 8	GD6 to GD17	*Maternal animals:* Mortality, clinical signs, food consumption and body weight *Post-mortem evaluation:* macroscopic abnormalities, pregnancy status, the numbers of corpora lutea of pregnancy, implantations, early and late resorptions, and live and dead foetuses. *Live foetuses:*	F0 F1

				Body weight, sex External, visceral and skeletal abnormalities	

Major findings

≥ 1 mg/kg q.d
Maternal observations:
↓ FC during GD 18-20
↓ BWG during GD 15-20
Litter data:
↓ No Corpora lutea, no implantations, no live foetuses,
≥ 4 mg/kg q.d
Foetal observations:
↓ Foetal BW
↑ Foetal anomalies (% F/L):
Visceral: subclavian artery, retroesophageal (0.8/4.5)
8 mg/kg q.d
Maternal observations:
↓ BWG during GD 12-15
↑ Corrected BWG
Litter data:
↑ early, late and total resorptions
↑ mean % post-implantation loss
Foetal observations:
↑ Foetal anomalies (% F/L):
Visceral:
Gross external: ectrodactyly (7.6/25.0)
Visceral: aortic arch, retroesophageal (11.7/42,9); aortic arch, interrupted (5/21.4); subclavian artery, retroesophageal (8.3/28.6)
Skeletal: paw, multiple abnormalities associated with ectodactyly (9.9/25.0); thoracic vertebrae, multiple abnormalities (8.5/25.0); limb, multiple abnormalities: absent, bent or misshapen long bones (7.0/18.8)

Toxicokinetics

	1 mg/kg	**4 mg/kg**	**8 mg/kg**
$AUC_{0\text{-last}}$ (ng·h/mL)			
Day 6	NC	14.4	47.1
Day 17	NC	24.1	105
Cmax (ng/mL)			
Day 6	0.68	4.93	12.7
Day 17	0.73	10.0	38.8
Proof of foetal exposure (D17) (ng/mL)			
Dams/foetuses +1 hour	0.827/<LLOQ	10.5/<LLOQ	32.2/1.34
Dams/foetuses +2 hours	0.436/<LLOQ	5,17/0.545	38.2/2.63

NOAEL (mg/kg &AUC)

F0 Females: 8 mg/kg q.d.
F1 Litters:1mg/kg q.d.

Relative Exposure Multiples

Steady-state Exposure in Human Subjects and at Relevant Doses in Toxicology Studies	**Maternal AUC (ng·h/mL)**		**Unbound (Free) Exposure Multiples at Relevant. Clinical Doses**	
	Total	**Unbound[c]**	**4 mg q.d.**	**9 mg q.d.**
4 mg q.d. human exposure - minimum clinical dose (Day 21))	13516[a]	37.8[a]	NA	NA
9 mg q.d. human exposure - maximum clinical dose (Day 21)	39587[b]	98.7[b]	NA	NA
Rat Embryo-foetal Development Study				
1 mg/kg q.d. (GD 17)	NC[d]	NC[d]	NC[d]	NC[d]
4 mg/kg q.d. (GD 17)	24.1	1.74	<0.1x	<0.1x

8 mg/kg q.d. (GD 17)	105	7.56	0.2x	0.1x

[a] Mean steady-state plasma AUC after 21 days of daily erdafitinib administration at the minimum clinical dose of 4 mg q.d. in Part 1 of Study EDI1001 in Patients (5 subjects)
[b] Mean steady-state plasma AUC after 21 days of daily erdafitinib administration at the maximum recommended clinical dose of 9 mg q.d. in Part 2 of Study EDI1001 in Patients (Mod5.3.3.2/EDI1001/Tab16; 6 subjects)
[c] Mean unbound fraction of erdafitinib is 7.2% in rat plasma, respectively.
[d] (due to the limited plasma concentrations available, no AUC evaluation was possible)

NA=not applicable; NC= not calculated; TK=toxicokinetics; GD=gestation day; BWG=body weight gain; BW=body weight; LD=low dose; MD=mid dose; HD=high dose; FC=food consumption; Ca=calcium; F=foetus; L=litter; q.d.=once daily

2.7.1.6. Toxicokinetic data

Table 8: Nonclinical exposure multiples in animals and humans

Steady-state Exposure in Human Subjects and at Relevant Doses in Toxicology Studies	AUC (ng·h/mL)		Unbound (Free) Exposure Multiples at Relevant Clinical Doses	
	Total	Unbound [c]	4 mg q.d.	9 mg q.d.
4 mg q.d. human exposure - minimum clinical dose (Day 21)	13,516 [a]	37.8 [a]	-	-
9 mg q.d. human exposure - maximum clinical dose (Day 21)	39,587 [b]	98.7 [b]	-	-
Rat 3-Month Repeat-Dose Toxicity Study				
8 mg/kg q.d. (highest daily dose) – males (Day 90)	99.8	7.19	0.2x	0.1x
8 mg/kg q.d. (highest daily dose) – females (Day 90)	231	16.6	0.4x	0.2x
Dog 3-Month Repeat-Dose Toxicity Study				
0.75 mg/kg q.d. (highest daily dose) – males (Day 90)	394	54.0	1.4x	0.5x
0.75 mg/kg q.d. (highest daily dose) – females (Day 90)	213	29.2	0.8x	0.3x
Rat Embryo-fetal Development Study				
4 mg/kg q.d. (teratogenicity level) (Gestation Day 17)	24.1	1.74	<0.1x	<0.1x

[a] Mean steady-state plasma AUC after 21 days of daily erdafitinib administration at the minimum clinical dose of 4 mg q.d. in Part 1 of Study EDI1001 in Patients (Mod5.3.3.2/EDI1001/Tab16)
[b] Mean steady-state plasma AUC after 21 days of daily erdafitinib administration at the maximum recommended clinical dose of 9 mg q.d. in Part 2 of Study EDI1001 in Patients (Mod5.3.3.2/EDI1001/Tab16)
[c] Mean unbound fraction of erdafitinib is 7.2% and 13.7% in rat and dog plasma, respectively.
- = not applicable

2.7.1.7. Local Tolerance

Skin sensitisation – Local Lymph Node Assay in the Mouse (TOX10363)

Assessment of erdafitinib's skin sensitisation potential has been performed using the local lymph node assay (LLNA).

CBA/Ca mice (4 females/group) received control or erdafitinib at concentrations of 2.5%, 5%, or 10% (in dimethylformamide). The mice were treated by daily application of 25 µL of the appropriate concentration or control to the dorsal surface of both ears for 3 consecutive days. The proliferative response of the lymph node cells from the draining auricular lymph nodes was assessed 5 days following the initial application, by measurement of the incorporation of 3H-methyl thymidine.

The stimulation indices obtained for 2.5, 5 and 10% were 2.7, 4.1 and 7.7, respectively, relative to concurrent vehicle-treated controls. As a stimulation index of 3 or more was recorded for 2 of the concentrations tested, erdafitinib was considered to have the potential to cause skin sensitisation. The concentration of erdafitinib, which would result in a stimulation index of 3 relative to concurrent vehicle-treated controls, was calculated to be 3.5%.

2.7.1.8. Other toxicity studies

Other Toxicology Studies included phototoxicity, skin sensitivity, eye and vascular irritation tests.

Phototoxicity

Erdafitinib absorbs light in the range of 200 - 450 nM with molar extinction coefficients substantially higher than the 1000 l mol^{-1} cm^{-1} threshold for photoreactive compounds of the ICH S10 guideline. The phototoxic potential of erdafitinib was determined in two independent *in vitro* non-GLP 3T3 NRU phototoxicity tests using Balb/c 3T3 mouse fibroblasts. Both experiments revealed Photo-irritation factors (PIF) > 5 (152.5 and 290.07) and thus, erdafitinib was phototoxic *in vitro*. In a subsequent *in vivo* phototoxicity study in male pigmented rats the highest concentration used in the *in vivo* phototoxicity study was in the range of clinical unbound Cmax (8.352 ng/ml) at the MRHD of 9 mg/d while exposure ratio based on AUC were below 1 (0.4 x). The phototoxicity in the eye was not assessed. A constellation of dermatologic adverse events has been observed in clinical trials with erdafitinib. These skin disorders are class effects of FGFR tyrosine kinase inhibitors (erdafitinib, pemigatinib, infigratib, futibatinib) and target related rather than phototoxicities. Toxic events of the skin (including palmar-plantar erythrodysaesthesia syndrome, dry skin, rash, erythema, skin ulcer, xeroderma, rash maculo-papular, skin exfoliation, skin fissures, skin lesion, hyperkeratosis, skin atrophy) occurred in > 50 % in the clinic with erdafitinib.

Skin sensitivity, eye and vascular irritation tests

Erdafitinib caused skin sensitisation in the murine local lymph node assay at concentrations of 3.5%. Erdafitinib did not induce any vascular irritation in the HET-CAM assay. In an *in vitro* Bovine Corneal Opacity-Permeability Eye Irritation assay, erdafitinib induced a severe increase in corneal opacity that was associated with microscopic changes in the corneal epithelium and stroma. As such, erdafitinib scored positive as an eye irritant.

Impurities

Two impurities, (process impurity and degradation product) and (degradation product) were observed at or above the reporting threshold of 0.05 % (ICH Q3A/B). JNJ-42541707 with maximal batch levels of 0.07 % (0.06 %) was toxicologically qualified in the 3-month oral repeat dose toxicity study in rats (TOX10846) up to 32 mg/kg/d whereas JNJ-55002818 was qualified in an independent qualification study of 1-month duration in the rat (TOX10565) spiked with and without 4 % of the degradation product.

For impurity the highest dose used in the study was 32 mg/kg/d corresponding to a toxicologically qualified impurity limit of 2.06% in humans at a maximal dose of 9 mg daily.

For impurity the study results exhibited no differences in relation to clinical signs, clinical chemistry and haematology measurements and histopathology findings. All changes observed were small, and/or fell within the range of the historical control data or vehicle values. Additionally, the toxicity profile was consistent with that observed in the 1 and 3-month toxicity studies at equal dose levels. The toxicologically qualified impurity dose at NOAEL in rat was 0.16 mg/kg/d corresponding to a toxicologically qualified impurity limit of 88.9 % in humans.

A risk assessment and classification of all impurities concerning the mutagenic potential was evaluated according to ICH M7 by means of analysis by database and literature searches for carcinogenicity and mutagenicity data and in silico assessment by SAR prediction methodologies (DEREK and SARAH) and LEADCCOPE. In case of a suspected structural alert, an AMES test has been conducted.

2.7.2. Ecotoxicity/environmental risk assessment

The applicant provided a Phase I ERA including the $PEC_{SURFACEWATER}$ calculation.

Using a default Fpen of 0.01, the $PEC_{SURFACEWATER}$ was calculated to be 0.045 µg/L. Thus, the PEC does meet the Phase I PEC Trigger. Additionally, for Fpen, a refinement based on prevalence was used in Phase I. Based on estimates from the International Agency for Research on Cancer (IARC), the prevalence of urothelial carcinoma in Europe ranges from 8.9 (Moldova) to 45.2 (Greece) in 100000.

Therefore,

$F_{PEN\text{-}REFINED} = P_{REGION} = 0.000452$

The Phase I $PEC_{SURFACEWATER}$ is recalculated as:

$PEC_{SURFACE\ WATER}$ = (9mg/day x 0.000452 x 1000 µg/mg)/(200 L/day x 10)

$PEC_{SURFACE\ WATER}$ = 0.002 µg/L

The recalculated Phase I $PEC_{SURFACEWATER}$ based on the $F_{PEN\text{-}refined}$ is < the action limit of 0.01 µg/L.

For the PBT screening the applicant cited the study from Janssen Report (study no.: DS-TEC-110422).

Summary of main study results

Substance (INN/Invented Name): Erdafitinib			
CAS-number (if available): 1346242-81-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		log Kow = 3.96 log Dow (pH 1) = -1.03 log Dow (pH 4) = -0.05 log Dow (pH 7) = 1.77 log Dow (pH 9) = 3.55 log Dow (pH 12) = 3.96	Potential PBT, N Validity check pending
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.002	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.7.3. Discussion on non-clinical aspects

Erdafitinib has a high binding affinity in low nanomolar range (below or around the unbound Cmax of 11.5 nM at the recommended clinical dose (9 mg once daily)) for all four isoforms of FGFR and six other kinases (RET, PDGFRB, CSF-1R, FLT4, VEGFR2 and KIT). For FGFR kinases, potent binding of erdafitinib translated into inhibition of FGFR phosphorylation and of downstream signalling and into cell growth inhibition in FGFR-dependent BaF3 cells and non-engineered lung, gastric, colorectal and bladder cancer cell lines. Erdafitinib potency against VEGFR2, FLT4, PDGFRB, RET and KIT was lower in a cellular context as compared to the biochemical assay.

The antiproliferative selectivity of erdafitinib was tested on a large panel of human cancer cell lines of diverse tissue origin. Results highlighted the functional selectivity of erdafitinib for FGFR altered pathway. Erdafitinib inhibited the proliferation of a panel of selected cancer cell lines harbouring FGFR

alterations, including the RT-112 cell line that was derived from a human urinary bladder transitional cell carcinoma (alterations of FGFR3) with IC_{50} of 1.3 nM. JNJ-42756493 has lysosomotropic properties *in vitro* and this lysosomal accumulation of JNJ-42756493 contributes to extended target inhibition.

Erdafitinib-induced tumour regression in RT-112 mouse bladder cancer xenograft model (featuring FGFR3 alterations) demonstrating a good PK/PD correlation as erdafitinib plasma levels corresponded to pERK inhibition. Pharmacological activity of erdafitinib in bladder cancer models was observed at clinically relevant concentrations supporting the proposed indication. However, in the RT112-VM tumour model with FGFR3-V555M mutation erdafitinib activity was acceptable.

No clinically relevant off-target activity of erdafitinib was observed in *in vitro* receptor binding assays.

Erdafitinib inhibited I_{Ks} current with the IC_{50} value of 25.3 µM, which is far above the unbound clinical plasma Cmax of 11.5 nM. In hERG-transfected HEK293 cells, I_{Kr} current was inhibited with IC_{50} of 408 nM, which is 35.5-fold higher than the expected clinical plasma concentrations of erdafitinib. However, low recovery of drug concentrations was reported in this assay. Low drug recovery was observed in the assay but the corrected IC_{50} value was not determined.

In guinea pigs, intravenous erdafitinib increased the duration of the QT and QTcB intervals in a dose-dependent fashion from 2.5 mg/kg onwards (unbound Cmax = 184 ng/ml, 35.8 times higher than clinical unbound Cmax). In artificially ventilated anesthetised dogs, an increase in the duration of the QT interval and in the action potential duration (APD) at 90% of repolarisation at the endocardium of the right ventricle were observed starting at 0.32 mg/kg (unbound Cmax = 59.2 ng/ml, 11.5-fold the expected clinical exposure based on Cmax,u).

In a dedicated GLP safety pharmacology study in dogs, 5 mg/kg oral erdafitinib decreased heart rate and prolonged QT interval in one animal. The NOAEL was 2.5 mg/kg with Cmax of 12.4 ng/ml representing 2.4-fold of the expected clinical exposure which is not considered acceptable as a safety margins. As this effect appears in the clinical exposure range it is included in the RMP part II module SII and the SmPC section 5.3.

Erdafitinib had no effect on respiratory parameters in dogs when administered up to 5 mg/kg corresponding to ca.7-fold clinical exposure based on Cmax.

The bioanalytical methods for determination of erdafitinib in rat and dog plasma were successfully developed and validated. Mouse studies were conducted as non-GLP and non-pivotal.

Plasma protein binding and blood-to-plasma partitioning of erdafitinib was species-specific. An unbound fraction in human was 0.55-0.74%. Among plasma proteins, erdafitinib was strongly bound to α1-acid glycoprotein. In rats, highest erdafitinib concentrations were found in lungs and in the liver. No brain accumulation was detected. No apparent association of erdafitinib with melanin was observed.

Metabolic rate of erdafitinib decreased in the order rat > mouse > dog > human. The main metabolic pathways of erdafitinib were Phase I reactions (O-demethylation and oxidation) followed by glucuronidation. A good correlation between *in vitro* and *in vivo* metabolism was observed. No human-specific metabolites were detected. In humans, CYP2C9 and CYP3A4 are mainly responsible for erdafitinib biotransformation. Erdafitinib was predominantly excreted through faeces in animals (via biliary route) and humans.

Erdafitinib is not an inhibitor of the most major CYP enzymes but the compound irreversibly inhibits CYP3A. Erdafitinib is a P-gp substrate and inhibits OCT2 and P-gp to a clinically relevant extent and is reported in section 4.5 of the SmPC.

Repeat-dose toxicology studies were performed in rats and dogs. In the pivotal 1-month (data not shown) and 3-month dog toxicology studies, no mortality was observed during the treatment window

or in the recovery period. This is in contrast to the rat pivotal studies where mortality occurred during the 3-month study but not during the 1-month (data not shown) study. Every other day (QOD) administration was not better tolerated than daily administration (QD).

The predominant microscopic findings reported in rats included atrophy of gland structures (mammary gland), soft tissue mineralisation of multiple organs (kidneys, lung, stomach, tongue, duodenum), decreased cellularity (bone marrow femur), chondroid dysplasia (larynx, trachea), degeneration of odontoblasts (teeth) and degeneration/inflammation heart.

Neurobehavioural endpoints as safety parameters were included in the 1-month rat study using a modified Irwin's method (see PD part above). Erdafitinib showed minimal neurofunctional aberrations (impaired wire manoeuvre and flaccid body tone), which were considered a potential direct effect of treatment, from a maximum plasma concentration (Cmax) of 12.1 ng/mL (unbound concentration of 0.871 ng/mL) which is below the clinical steady-state Cmax (total or unbound) for a 9 mg once daily dose. No effects on the CNS were observed with the other FGFR inhibitors (Pemazyre, Febseltiq, Lytgobi). A possible hypothesis could be the acutely drug induced imbalance of inorganic phosphorus, of which an acute increase could lead to rapid but transient muscle weakness (lower muscle strength). Although these findings were observed in the clinical range at the recommended clinical dose, these are minimal and transient. Thus, it is concluded that the risk of a translational effect on locomotion in human is considered minimal and that no evidence exists that point out similar locomotor effects occurring in humans.

The toxicity profile determined in rats and dogs is consistent between the two species and with other FGFR inhibitors. Toxicities observed with erdafitinib are considered related to the inhibition of FGF/FGFR pathways in different tissues. FGFR inhibitors, via FGF23 pathways, are known to induce hyperphosphataemia *in vivo*. In animal studies, hyperphosphataemia resulted in histological findings of soft tissues mineralisation mainly in aorta, heart and/or stomach. The animal-to-human exposure ratios at the lowest dose levels where hyperphosphataemia in combination with soft tissues mineralisation occurred at below the clinical exposure range in dogs and at clinical exposure range in rats. In general, there were dose-related increases in serum phosphate levels across the dose groups, and soft tissues mineralisation was observed at higher serum phosphate levels.

In investigative studies, more pronounced histopathological changes were seen in rats which received the low phosphate and Vitamin D3 deficient diet when compared to those receiving a normal diet. The administration of a phosphorus-scavenger diet (sevelamer 3%) significantly reduced all vascular and mineralisation lesions when compared with animals that received a low phosphorus diet, although higher exposures were noted in the P-scavenger groups. This result might be an important issue in the clinical setting and clinical recommendations for hyperphosphataemia are made in the SmPC section 4.2.

FGFR signalling has been implicated in lens induction, lens cell proliferation and survival, lens fibre differentiation and lens regeneration. Therefore, the findings in the eye can be attributed to the direct effect of erdafitinib on the ocular system.

Relative exposure multiples were calculated using unbound concentrations because of the large species differences in unbound fraction. The animal-to-human exposure ratios at the highest daily dose of 8 mg/kg and 0.75 mg/kg tested in the 3-month rat and dog study, respectively, are low (<1). Thus, interpretation of the observed adverse effects is difficult since the exposure multiples following repeat dose administration of erdafitinib are much lower than the AUC in humans at the intended clinical dose of 8 or 9 mg.

Findings of the repeat-dose toxicology studies are reflected under section 5.3 of the SmPC.

Erdafitinib was evaluated in a standard GLP genotoxicity battery (AMES, *in vitro* micronucleus on TK6 cells and rat micronucleus after oral administration for 2 days). All studies performed met the criteria requested in the related recommendations and allow the conclusion that erdafitinib had no genotoxicity properties. This is reflected in section 5.3 of the SmPC.

In accordance with ICH S9 guideline, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer. No preneoplastic lesions and/or tissue-specific proliferative effects occurred in the general toxicity studies. This is reflected in section 5.3 of the SmPC.

Erdafitinib was phototoxic *in vitro* and not phototoxic *in vivo* at or below clinical exposures. Skin toxicity events were observed in the clinic and occurred in > 50% of erdafitinib subjects. These findings were similarly observed with other agents of that pharmacological class of active ingredients (FGFR tyrosine kinase inhibitors) and were target related rather than photoactivated drug induced cytotoxicity. To avoid potential phototoxicity recommendation for sun exposure protection when in treatment with erdafitinib is included in the SmPC (see SmPC section 4.4.).

A risk assessment and classification of all impurities concerning the mutagenic potential was evaluated according to ICH M7 by means of analysis by database and literature searches for carcinogenicity and mutagenicity data and in silico assessment by SAR prediction methodologies (DEREK and SARAH) and Leadscope. A following review of human expert knowledge confirmed the final conclusion on mutagenicity (review not presented). The classification of the potential genotoxic impurities according to ICH M7 was agreed.

Reproductive and developmental toxicity

The reproductive and developmental toxicity of erdafitinib has been sufficiently investigated in embryo-foetal developmental studies in rats according to the guidelines ICH S9 and ICH S5 (R3).

Dedicated animal fertility studies have not been conducted with erdafitinib. Erdafitinib showed effects on female reproductive organs in rats in 3-months study (necrosis of the corpora lutea) at exposure approximating the AUC in patients at the maximum recommended dose of 9 mg q.d. (see SmPC 5.3). Ovarian corpora lutea necrosis can potentially impact fertility. However, these studies may have a low sensitivity to detect any effect on human fertility since exposure levels attained in treated animals were not significantly higher than those measured in patients. Effects on epididymides and testes were observed in a non pivotal 2-week rat study at exposure levels >10-fold those reached in humans.

Literature supports a role for FGFR signalling in multiple aspects of regulation and maintenance of the male and female reproductive systems. Given the involvement of FGF/FGFR signalling in reproductive physiology, potential for impairment of fertility in male and female patients through inhibition of FGFR signalling by a small molecule pan-FGFR tyrosine kinase inhibitor cannot be excluded. This is adequately reflected in section 4.6 of the SmPC.

Erdafitinib was clearly embryolethal and teratogenic in rats at exposures far below the human exposure at the maximum recommended dose of 9 mg q.d. Based on the mechanism of action of erdafitinib (FGFR tyrosine kinase inhibitor), the effects on embryo-foetal development seen in rats are expected. These effects should be regarded as relevant for humans and erdafitinib should be classified as a suspected human teratogen.

Adequate recommendations for use during pregnancy in line with the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (EMEA/CHMP/203927/2005) are included in section 4.4 and 4.6 of the SmPC.

Environmental risk assessment

Erdafitinib PECsurfacewater value is below the action limit of 0.01 µg/L and a Phase II ERA is considered not necessary. Erdafitinib is potentially not a PBT substance. However, the data presented are preliminary and a conclusion cannot be made until the study report is submitted. The applicant is requested to submit a study report on an experimentally derived logKow as post-authorisation measure by Q1 2025 (REC).

2.7.4. Conclusion on the non-clinical aspects

Anti-tumour activity of erdafitinib achieved through FGFR inhibition was demonstrated *in vitro* and *in vivo*. Beside FGFR, erdafitinib targets other kinases at clinically relevant concentrations in biochemical assays but the activity in the cellular context is lower. Cardiovascular and respiratory effects of erdafitinib were characterised in a series of safety pharmacology studies including toxicokinetic assessment.

The pharmacokinetics and DDI potential of erdafitinib were thoroughly investigated.

The toxicity profile of erdafitinib in rats and dogs is overlapping and most of the findings could be attributed to the pharmacological activity of erdafitinib as an irreversible inhibitor of FGFR. Effects included increased inorganic phosphorus and calcium in plasma, ectopic mineralisation in various organs and tissues as well as lesions in bone/cartilage. The findings occurred at exposures lower than the human exposure at the intended clinical dose of 8 mg. Most effects were reversible with the exception of chondroid dysplasia in rats and dogs and ectopic mineralisation. Erdafitinib exerts no genotoxic potential. However, a phototoxic risk for erdafitinib at clinical exposures cannot be ruled out. Erdafitinib is teratogenic and causes foetal harm when administered to pregnant women. Further, erdafitinib scored positive as an eye irritant.

Overall, the toxicology programme of erdafitinib is adequate.

As the ERA is concerned, the applicant will submit a study report on an experimentally derived logKow as post-authorisation measure by Q1 2025 (REC).

2.8. Clinical aspects

2.8.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 9: Overview of Studies Contributing Information to the Summary of Clinical Pharmacology Studies

Study ID	Objective(s)	Participants	Dose	Route	Formulation	Included in Pop PK	Pivotal[a]
42756493EDI1001 (EDI1001)	Single and multiple dose PK	Participants with advanced or refractory solid tumors or lymphoma	0.5, 2, 4, 6, 9, 12 mg once daily 10, 12 mg, intermittent (7 days on/7 days off)	Oral	Part 1 Once daily: oral solution or capsule Intermittent doses: capsule Part 2 Once daily: capsule Part 3: Once daily: capsule Part 4: Intermittent doses: capsule	X	
42756493EDI1005 (EDI1005)	Absorption, metabolism, excretion	Healthy male participants	12 mg	Oral	Single oral solution containing 12 mg unlabeled erdafitinib admixed with ^{14}C-erdafitinib	X	
42756493EDI1007 (EDI1007)	Drug interaction Erdafitinib alone Erdafitinib + fluconazole Erdafitinib + itraconazole	Healthy participants	4 mg	Oral	Tablet		
42756493EDI1008 (EDI1008)	Single dose PK Hepatic Impairment	Participants who either have hepatic impairment or normal hepatic function who qualify for the healthy control group	6 mg (2×3 mg), single dose	Oral (fasting condition)	3, 4, and 5 mg tablets	X	

Study ID	Objective(s)	Participants	Dose	Route	Formulation	Included in Pop PK	Pivotal[a]
42756493NAP1001 (NAP1001)	Drug interaction Erdafitinib alone Erdafitinib + carbamazepine	Healthy participants	12 mg (3×4 mg)	Oran (standardized breakfast)	4 mg tablets	X	
42756493BLC2001 (BLC2001) Main Study	Efficacy and PK	Participants who had histologic demonstration for metastatic or surgically unresectable urothelial cancer, that harbor target FGFR3 gene mutations or FGFR gene fusions	6, 8 mg once daily 10 mg intermittent (7 days on/7 days off)	Oral	Regimen 1 Intermittent: tablet Regimens 2 and 3 Once daily: tablet	X	X
42756493BLC2001 (BLC2001) DDI Substudy	Drug interaction Midozalam alone Erdafitinib + Midozalam Metformin alone Erdafitinib + Metformin	Participants with advanced solid tumors, including those with metastatic or surgically unresectable urothelial cancer, that harbor target FGFR gene mutations or FGFR gene fusions	8 mg with the possibility of uptitration	Oral	Tablet	X	
42756493GAC1001 (GAC1001)	Single and multiple dose PK	Japanese participants with advanced or refractory solid malignancies or lymphoma	2, 4, 6 mg once daily 10, 12 mg, intermittent (7 days on/7 days off)	Oral	Part 1 Once daily: capsule Part 1 Intermittent doses: capsule	X	

Study ID	Objective(s)	Participants	Dose	Route	Formulation	Included in Pop PK	Pivotal[a]
42756493HCC1001 (HCC1001)	Single and multiple dose PK	Asian participants with advanced HCC	Intermittent dosing: 8, 10, or 12 mg; Continuous dosing: 8 mg	Oral	3, 4, and 5 mg tablets	X	
42756493LUC2001 (LUC2001)	PK and PD	Asian participants with NSCLC or selected solid tumors (urothelial cancer, gastric cancer, esophageal cancer, and cholangiocarcinoma)	8 mg (with option to uptitrate to 9 mg)	Oral	3, 4, and 5 mg tablets	X	
42756493BLC2002 (BLC2002)	PK and PD	Participants with metastatic or locally advanced urothelial cancer	6 or 8 mg (with/without option to uptitrate to 9 mg depending on cohort)	Oral	3, 4, and 5 mg tablets	X	
42756493CAN2002 (CAN2002)	PK and PD	Participants with advanced solid tumors and FGFR gene alterations	Adults and Adolescents (15 to <18 years): 8 mg (with possible uptitration to 9 mg) Adolescents (12 to <15 years): 5 mg (with possible uptitration to 6 mg or further to 8 mg)	Oral	3, 4, and 5 mg tablets	X	
42756493BLC3001 (BLC3001)	Efficacy and PK	Participants with advanced urothelial cancer and selected FGFR gene aberrations	8 mg	Oral	3, 4, and 5 mg tablets	X	

[a] PK and/or PK-PD results described in proposed label.

2.8.2. Clinical pharmacology

Erdafitinib (referred to as JNJ-42756493 during early development) is an oral pan-FGFR tyrosine kinase inhibitor (FGFR 1, 2, 3 and 4).

Erdafitinib has been studied in healthy subjects and in subjects with cancer with oral doses ranging from 0.5 mg to 12 mg once daily [QD].

Based on the currently proposed SmPC, the recommended starting dose of erdafitinib is 8 mg orally once daily. This dose should be maintained and serum phosphate level should be assessed between 14 and 21 days after initiating treatment. The dose is then to be up-titrated to 9 mg once daily if the serum phosphate level is <9.0 mg/dL, and there is no drug-related toxicity.

The basic PKs of erdafitinib have been characterised using non-compartmental analysis in the Phase I ADME study (EDI1005) in healthy subjects, and in the Phase I FTIH study (EDI1001) of single and multiple doses of erdafitinib in patients with advanced or refractory solid tumors or lymphoma.

The potential effect of intrinsic and extrinsic factors on erdafitinib PK has been quantitatively assessed in the hepatic impairment study (EDI1008), Japanese safety/PK study (GAC1001), "Asian" safety/PK study (HCC1001), formulation/food studies (EDI1002, EDI1003, EDI1004, EDI1006),

fluconazole/itraconazole DDI study (EDI1007), carbamazepine DDI study (NAP1001), midazolam/metformin DDI study (BLC2001), and using population PK analysis.

2.8.2.1. Pharmacokinetics

Absorption

Bioavailability

Healthy Subjects

EDI1005 (ADME)

Study title	An Open-Label Phase 1 Study to Determine the Absorption, Metabolism, and Routes of Excretion Following Oral Administration of (^{14}C) Radiolabeled Erdafitinib to Healthy Male Subjects
Study design	This was a Phase 1, single-centre, open-label, 1-treatment study in 8 healthy adult male participants. All participants received a single oral dose of 12 mg unlabelled erdafitinib, given as a solution (0.5 mg/mL) admixed with ^{14}C-erdafitinib under fasting conditions. Plasma samples for determination of erdafitinib concentrations and measurement of total radioactivity were collected at pre-dose and over 312 hours after administration. Faeces and urine samples were collected for measurement of total radioactivity and erdafitinib (urine). Participants remained at the study site for 14 days after dose administration and possibly longer (up to 28 days), until at least 85% of the total radioactivity was recovered or no more than 1% of the radioactivity was excreted in urine and faeces every 24 hours over 2 consecutive days.
Study objectives	(PK) The primary objective was to investigate the absorption, metabolism, and excretion of erdafitinib in healthy male adult participants after administration of a single oral dose of 12 mg of un-labelled erdafitinib admixed with ^{14}C-erdafitinib.
Study period	24 March 2016 to 06 August 2016
No. of subjects	Of 8 subjects dosed, 6 (75%) subjects completed the study and 2 (25%) subjects exited the study prior to completion. However, as all 8 subjects provided the required PK assessments, they were included in the safety and PK analyses
Treatment	The JNJ-42756493 supplied for this study was a 0.5 mg/mL JNJ-42756493-AAA oral aqueous solution, admixed with ^{14}C JNJ-42756493. Study drug was provided as drink vials containing liquid formulation for oral self-administration.

Results

Table 10: Summary of Plasma PK Results of Erdafitinib and Total Radioactivity After Single Oral Administration of 12 mg Erdafitinib Admixed With ^{14}C JNJ-42756493

PK Parameters[a]	Total JNJ-42756493	Total Radioactivity
N	8	8
C_{max}, ng (eq.)/mL	525±128	508±163
t_{max}, h	2.50 (2.00 – 3.00)	2.00 (2.00 – 4.00)
AUC_{last}, ng (eq.).h/mL	30430±7156	30388±7335
AUC_{∞}, ng (eq.).h/mL	31913±7545	31806±7854
$t_{1/2term}$, h	66.3±15.8	65.3±13.1
CL/F, L/h	0.395±0.0929	-
V_d/F, L	37.5±10.6	-
MRT, h	90.6±20.6	-

a mean±SD, tmax: median [range]

Erdafitinib was highly bound to plasma proteins. The unbound fraction of erdafitinib was low and averaged 0.37 (±0.09) %, with individual values ranging between 0.22% and 0.49%.

An inverse relationship was observed between the fraction unbound and α1-acid glycoprotein.

The unbound exposure parameters Cmax and AUC∞ corrected for the unbound fraction averaged 1.90 (±0.541) ng/mL and 116 (±33.2) ng.h/mL, respectively.

Table 11: Estimation of the Percentage Oral Absorption

	Absorbed Erdafitinib	Reported Data from Study EDI1005
Urine	18.7%	
Total radioactivity excreted in urine (unchanged drug and metabolites)		18.7%
Feces	65.2%	
Total radioactivity recovered in feces (unchanged drug and metabolites)		68.7%
Unchanged drug recovered in feces during the first 3 days (conservative estimate)		3.5%
Total urine and feces	83.9%	
Recovery of radioactivity in urine and feces samples		87.4%
Estimated % absorption	96.0%	

Subjects with advanced or refractory solid tumours or lymphoma

EDI1001 (FTIH)

Study title: A Phase 1 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Erdafitinib, a pan-FGFR Tyrosine Kinase Inhibitor, in Subjects With Advanced or Refractory Solid Tumors or Lymphoma.

Study design: The study consisted of 4 parts:

- Part 1 was the dose escalation phase, designed to determine the RP2D. Part 1 started with a standard 3+3 design and investigated continuous doses of 0.5, 2, 4, 6, 9, and 12 mg erdafitinib taken once daily in cycles of 21 days and intermittent

doses of 10 and 12 mg (7 days on/7 days off) in cycles of 28 days. The 0.5-, 2-, and 4-mg doses were administered as an oral solution. The 6 mg cohort acted as a bridging cohort; the first 5 participants were treated with the oral solution and the next 4 participants with the capsule formulation. The 9, 10, and 12 mg doses were administered as capsules. The 9 mg continuous dose was identified as the first RP2D and the 10 mg intermittent dose (7 days on/7 days off) as the second RP2D.

- Part 2 was a tumour biopsy cohort to evaluate the PD effect of erdafitinib in tumors and to confirm FGFR pathway inhibition at or below the first RP2D (9 mg continuous dose). Erdafitinib 6 and 9 mg once daily were administered as capsules in Part 2.
- Part 3 was the first dose expansion phase at the first RP2D (9 mg continuous dose) and consisted of 3 disease-specific cohorts (squamous NSCLC, small cell lung cancer, and breast cancer) and 1 mixed-disease solid tumour cohort. Erdafitinib was administered as capsules in Part 3.
- Part 4 was the second dose expansion phase at the second RP2D (10 mg intermittent dose, 7 days on/7 days off) and consisted of an NSCLC cohort and a cross-histology cohort with selected tumour types. Erdafitinib was administered as capsules in Part 4.

Blood samples for analysis of erdafitinib concentration in plasma were collected at the following times:

- Part 1: Cycle 1 Day 1 at predose, 0.5, 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours postdose. Cycle 1 Day 8 (for continuous dose cohorts) or Day 7 (for intermittent dose cohorts) and Cycle 2 Day 1 at predose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose. Cycles 3 and 4 at predose.
- Part 2: Cycle 1 Day 1 and Cycle 2 Day 1 (for continuous dose cohorts) at predose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose. Cycles 3 and 4 on Day 1 (predose).
- Parts 3 and 4: sparse samples were collected in Cycle 1 on Day 1 and Day 7 or Day 8, and in Cycles 2, 3, and 4 on Day 1 (predose).

Selected samples were used to determine erdafitinib free concentrations. Serum and plasma were collected in Part 1 to assess changes in the following markers of FGFR inhibition pre- and postdose: FGF-23, PTH, vitamin D, and calcium, in addition to monitoring serum phosphate levels.

Cardiac monitoring included 24-hour Holter monitoring and echocardiograms in Part 1 and triplicate 12-lead ECGs at multiple timepoints in all parts of the study [*see PD Part below*].

Study objectives: To determine the safe and biologically active Phase 2 doses (RP2Ds) for erdafitinib in the Part 1 dose escalation phase and to evaluate the feasibility of treating a molecularly defined subset of participants with different solid tumors at the RP2Ds (Parts 3 and 4). Secondary objectives were to evaluate the PK, PD (biomarkers in blood, in skin, and in the tumour), and predictive biomarkers for erdafitinib.

Study period: DATE STUDY INITIATED: 19 June 2012

DATE OF CLINICAL CUT-OFF: 03 January 2017

Treatment: In Part 1, study drug was provided as either a liquid formulation or as capsules for oral administration. In Parts 2, 3, and 4, study drug was supplied as capsules packaged in blister packs.

Results

Single-dose PK parameters of erdafitinib in patients with advanced or refractory solid tumors or lymphoma are presented in the table below:

Table 12: Summary of Single Dose Plasma PK Parameters of Erdafitinib on Cycle 1 Day 1 for the Continuous and Intermittent Dose Cohorts

Dose (mg)	N	Mean (SD)			
		t_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	AUC_{0-72} (ng.h/mL)
Continuous Doses					
Part 1					
0.5	3	1.00 (0.50-6.00)	24.4 (8.11)	393 (93.4)	873 (203)
2	4	2.50 (1.00-4.07)	108 (51.5)	1757 (678)	4394 (1964)[b]
4	7	1.75 (0.95-6.17)	182 (77.1)	3226 (1508)	6743 (3318)[c]
6	9	2.07 (0.52-24.00)	248 (103)	4239 (2138)	8361 (3250)[d]
9	9	2.07 (2.00-6.00)	431 (177)	7410 (3213)	17564 (9364)[e]
12	7	1.22 (0.50-2.00)	745 (246)	12374 (4400)	30175 (13807)
Part 2					
9	10	3.44 (2.03-8.00)	578 (234)	10069 (2559)[d]	-
Intermittent Doses					
Part 1					
10	14	2.57 (1.00-6.00)	566 (168)	10058 (3136)[f]	-
12	13	2.08 (1.00-4.00)	912 (473)	14209 (5421)	-

As tabulated above, after a single dose (Cycle 1 Day 1) in the 76 participants with serial PK sampling, tmax values ranged between 1.00 and 3.44 hours post-dose across the different cohorts.

Fraction of erdafitinib unbound to plasma proteins ranged on average between 0.250% and 0.506% at corresponding AGP concentrations of 131 and 86.4 mg/dL. The unbound fraction was inversely related to AGP concentrations.

The tmax was not dose-dependent across the 0.5 to 12 mg dose range.

After Cmax, the plasma concentration-time profile declined with a long t1/2.

Cmax and AUCs increased with increasing dose without consistent or significant deviations from the dose-proportionality across the range of dose levels.

Multiple-dose plasma PK parameters obtained on Cycle 2 Day 1 for continuous doses and on Cycle 1 Day 7 for intermittent doses are summarised in the table below:

Table 13: Summary of Multiple Dose Plasma PK Parameters of Erdafitinib on Cycle 2 Day 1 for the Continuous and on Cycle 1 Day 7 for the Intermittent Dose Cohorts

Dose (mg)	N	Mean (SD)					
		t_{max}[a] (h)	C_{max} (ng/mL)	AUC_T (ng.h/mL)	C_{min} (ng/mL)	Accumulation Ratio C_{max}	Accumulation Ratio AUC
Continuous Doses (Cycle 2 Day 1)							
Part 1							
0.5	3	2.27 (1.00-4.07)	65.6 (22.3)	1084 (5.22)[b]	44.9 (13.9)	2.74 (0.58)	3.19 (0.181)[b]
2	4	2.58 (1.92-4.00)	377 (247)	9283 (5090)[c]	263 (201)	3.43 (1.30)	4.96 (1.16)[c]
4	5	4.00 (2.25-7.00)	675 (267)	13516 (8619)[b]	429 (178)	3.18 (0.78)	3.08 (0.50)[b]
6	8	2.55 (2.00-8.02)	818 (352)	13789 (7060)[d]	552 (344)	3.46 (1.21)	4.16 (1.87)[d]
9	1	3.00	494	-	290	4.15	-
12	3	2.00 (1.00-8.25)	3057 (1622)	64085 (43539)	2317 (1527)	3.94 (1.10)	4.55 (1.22)
Part 2							
9	6	2.65 (2.00-23.75)	2018 (744)	39587 (17575)[e]	1247 (766)	3.61 (0.843)	3.74 (0.304)[c]
Intermittent Doses (Cycle 1 Day 7)							
Part 1							
10	13	3.00 (0.92-24.00)	1792 (624)	35880 (12798)	1185 (534)	3.24 (0.684)	3.60 (0.792)[f]
12	10	2.25 (1.00-6.00)	2132 (1032)	41339 (20781)	1311 (784)	2.66 (0.649)	3.16 (0.668)

A Median (range); b N=2; c N=3; d N=6; e N=5; f N=11.

Cmax and AUC increased with the dose without showing relevant or consistent deviations from dose proportionality.

In the intermittent dose cohorts (Cycle 1 Day 7), the mean systemic exposure increased between the 10 and 12 mg dose levels, as expected based on the previously observed dose-proportionality of the PK. Although steady state was not fully achieved after 7 days of administration, the accumulation ratios for AUC_T were 3.60 and 3.16 for the 10 and 12 mg intermittent doses, respectively (see table above). Cycle 2 Day 1 concentrations were higher than the Cycle 1 Day 1 concentrations, albeit lower than Cycle 1 Day 7, and pre- dose samples had measurable drug concentrations due to incomplete washout after 7 days off erdafitinib.

Supplementary PK analysis

Beside other analysis, Individual dose normalised PK parameters pooled over dose levels were presented per dose regimen (daily and intermittent dosing) and for both dosing regimens combined, including descriptive statistics were provided.

Table 14: Individual Dose Normalised PK Parameters, Including Descriptive Statistics (C2D1) - Pooled for All Dose Levels

Pooled results of study 42756493EDI1001

Dose normalized to 8 mg

	Dose normalized PK parameters of erdafitinib - Daily dosing								
Subject	eGFR [mL/min/1.73 m^2]	C2D1 C_{min} [ng/mL]	C2D1 C_{max} [ng/mL]	C2D1 AUC_{24h} [ng.h/mL]	C2D1 Unbound C_{min} [ng/mL]	C2D1 Unbound C_{max} [ng/mL]	C2D1 Unbound AUC_{24h} [ng.h/mL]	C2D1 CL/F [L/h]	C2D1 CL_{free}/F [L/h]
n	50	30	30	21	30	30	21	21	21
Mean	99.3	936	1399	29268	2.69	4.17	81.5	0.362	112
SD	25.7	607	711	17519	1.16	1.66	28.2	0.186	45.6
Min	58	215	439	9995	0.687	1.90	34.8	0.105	59.1
Median	97	755	1240	23068	2.69	3.70	78.8	0.347	101
Max	150	2680	3260	75889	5.53	8.23	135	0.800	230
%CV	25.9	64.9	50.8	59.9	43.1	39.9	34.5	51.4	40.8
Geometric Mean	96.1	774	1238	25220	2.43	3.88	76.7	0.317	104

Pharmacokinetic results from the main efficacy and safety studies BLC2001 (Phase II) and BLC3001 (pivotal Phase III) are summarised below:

BLC2001 (Phase II)

Table 15: Summary of Single and Multiple Dose Plasma Concentrations of Erdafitinib on Cycle 1 Day 1 and Cycle 1 Day 21 for the Continuous and Intermittent Dose Cohorts

Parameter (Unit)	Mean (SD)		
	6 mg Continuous (Regimen 2)	8 mg Continuous (Regimen 3)	10 mg Intermittent (Regimen 1)
Cycle 1 Day 1			
N	74	92	32
C_{2h}	311.0 (134.8)	373.0 (168.1)	529.5 (224.9)
C_{4h}	290.0 (117.9)	365.3 (155.6)[a]	504.0 (189.6)
Cycle 1 Day 21[b]			
N	59	45	25
Predose (steady-state trough)	1039.1 (585.7)	1097.5 (542.0)	1312.6 (782.5)
C_{2h}	1255.1 (640.0)	1371.4 (586.6)	1686.5 (872.3)[c]
C_{4h}	1257.4 (663.2)[d]	1329.9 (550.1)[e]	1753.4 (917.8)[f]

a N=91; b Cycle 1 Day 21 data presented only include those participants who received the same dose on Day 21 as the starting dose (ie, participants who had no dose increases or reductions); c N=23; d N=60; e N=46; f N=24.

BLC3001 (pivotal Phase III study)

Erdafitinib PK parameters for Cohort 1 are summarised in the table below:

Table 16: Summary of Erdafitinib Observed Plasma Concentrations (ng/mL) Over Time; Cohort 1 PK Analysis Set

	Plasma Concentrations of Erdafitinib (ng/mL)					
	8 mg without uptitration			8 mg uptitrated to 9 mg		
	Cycle 1 Day 14 Postdose	Cycle 2 Day 1 Predose	Cycle 2 Day 1 2-4 Hour Postdose	Cycle 1 Day 14 Postdose	Cycle 2 Day 1 Predose	Cycle 2 Day 1 2-4 Hour Postdose
N	20	24	21	89	93	84
Mean	1458	986	1112	1225	1414	1605
Median	1120	917	1020	1180	1330	1445
SD	1272	669	714	530	660	705
Min	102	12.3	23.9	381	315	449
Max	5290	2570	3090	2960	3590	3870
%CV	87.2	67.9	64.2	43.2	46.7	43.9
Geometric Mean	1054	706	815	1115	1266	1460
%Geometric CV	109	149	141	47.2	51.8	46.6

Concentrations below quantification limit (<1 ng/mL) are considered as 0.

Erdafitinib PK parameters for Cohort 2 are summarised in the table below:

Table 17: Summary of Erdafitinib Observed Plasma Concentrations (ng/mL) Over Time; Cohort 2 PK Analysis Set

	Plasma Concentrations of Erdafitinib (ng/mL)					
	8 mg without uptitration			8 mg uptitrated to 9 mg		
	Cycle 1 Day 14 Postdose	Cycle 2 Day 1 Predose	Cycle 2 Day 1 2-4 Hour Postdose	Cycle 1 Day 14 Postdose	Cycle 2 Day 1 Predose	Cycle 2 Day 1 2-4 Hour Postdose
N	22	21	22	127	127	113
Mean	1466	1179	1360	1190	1229	1402
Median	1420	1240	1505	1000	1050	1160
SD	969	771	754	772	818	829
Min	25.9	22.5	123	259	34.0	143
Max	3000	2550	2700	4640	5290	5100
%CV	66.1	65.4	55.4	64.8	66.6	59.1
Geometric Mean	927	761	1047	1007	991	1205
%Geometric CV	216	205	109	62.2	83.3	60.8

Concentrations below quantification limit (<1 ng/mL) are considered as 0.

BCS-class

Erdafitinib is a BCS Class I compound with high solubility, moderate to high permeability, and gastrointestinal stability.

Bioequivalence

A total of 4 biopharmaceutic studies (EDI1002, EDI1003, EDI1004, EDI1006), in addition to a formulation bridging cohort in the first-in-human study (EDI1001), were conducted to support biopharmaceutical properties of erdafitinib and the development of the final formulation.

The mean PK parameters of erdafitinib from all relative bioavailability studies conducted in healthy participants are presented in the table below:

Table 18: PK Parameters Across Studies EDI1002, EDI1003, EDI1004, and EDI1006

Study ID	Dose (mg)	Formulation	N	Median (Range)	Mean (SD)			
				t_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{∞} (ng.h/mL)	$t_{1/2}$ (h)
Single-dose studies assessing the impact of formulation changes								
EDI1002	10	Tablet; G018; fasted	8	3.50 (1.00-4.01)	357 (107)	19900 (6251)	25300 (7474)	53.8 (7.02)
	10	Solution; G004; fasted	8	2.10 (1.01-2.75)	373 (141)	20100 (6537)	24700 (7124)	52.2 (3.46)
EDI1003	10	Tablet; G018; fasted	12	3.00 (2.00-8.00)	357 (113)	21900 (7680)	25400 (8890)	49.1 (5.29)
	10	Capsule; G014; fasted	12	3.00 (2.00-6.00)	372 (110)	23000 (7620)	26400 (8850)	49.7 (6.76)
EDI1004	10	Tablet; G018 (17 micron); fasted	11	2.00 (1.50-4.00)	433 (143)	21845 (7780)	25206 (9717)	50.7 (8.1)
	10	Tablet; G025 (78 micron); fasted	12	2.51 (1.50-8.00)	389 (93.7)	20788 (6089)	23788 (7285)	46.0 (4.9)
	10	Tablet; G025 (119 micron); fasted	11	2.99 (1.00-8.00)	411 (109)	22227 (6707)	26171 (8460)	50.2 (3.3)
Single-dose study assessing the effect of concomitant food intake								
EDI1006	9	Tablet; G025 and G024; fasted	16	2.52 (2.00-5.98)	354 (101)	21067 (5415)	21649 (5729)	69.5 (23.1)
	9	Tablet; G025 and G024; fed	16	3.98 (2.00-6.00)	304 (80.0)	19752 (5374)	20262 (5581)	63.3 (15.5)

AUC=area under the concentration-time curve; CI=confidence interval; C_{max}=maximum concentration; CV=coefficient of variation; GMR=geometric mean ratio; ID=identity; N=number of participants; PK=pharmacokinetics; $t_{1/2}$=half-life.
The 10-mg dose comprised 2×5-mg tablets and the 9-mg dose comprised 1×5-mg tablet + 1×4-mg tablet.
Source: Appendix 6

AUC=area under the concentration-time curve; CI=confidence interval; Cmax=maximum concentration; CV=coefficient of variation; GMR=geometric mean ratio;
ID=identity; N=number of participants; PK=pharmacokinetics; t1/2=half-life.
The 10-mg dose comprised 2×5-mg tablets and the 9-mg dose comprised 1×5-mg tablet + 1×4-mg tablet.

Influence of food

EDI1006

Study title — Randomized, Open-Label, 2-Way Crossover Study to Determine the Effect of Food on the Pharmacokinetics of Erdafitinib in Healthy Participants

Study design — This was a Phase 1, randomised, open-label, single-centre, 2-way crossover study in 16 healthy participants.

On Day 1 of Period 1, participants were randomised to 1 of 2 treatment sequences, AB or BA. The following treatments were administered on Day 1 of each period (separated by at least 28 days):

Treatment A, fasted (reference): a single dose of 9 mg erdafitinib (1×4-mg tablet and 1×5-mg tablet) under fasted conditions (≥10 hours).

Treatment B, fed (test): following an overnight fast (≥10 hours), a high-fat and high-calorie breakfast was provided and had to be consumed within 30 minutes. A single dose of 9 mg erdafitinib (1×4-mg tablet and 1×5-mg tablet) was administered 30 minutes after the start of the breakfast.

Serial blood samples were collected over 336 hours after each dose of erdafitinib for determination of plasma concentrations.

Blood samples to assess Plasma Protein Binding (PBB) were collected predose and 2 hours postdose for each treatment.

Study objectives — (PK) The primary objective was to evaluate the effect of food on the relative bioavailability of a single 9-mg oral dose of erdafitinib in healthy participants.

Study period — DATE STUDY INITIATED: 14 March 2017

DATE STUDY COMPLETED: 12 May 2017

No. of subjects | All 16 subjects received single oral dose of 9-mg (as one 4-mg tablet and one 5-mg tablet) erdafitinib, administered under fasted (Treatment A) or fed (Treatment B) conditions in a crossover manner.

Treatment | Erdafitinib (JNJ-42756493) was supplied as a 4-mg tablet [G-024] and a 5-mg tablet [G-025].

Results

Cmax, AUClast, and AUC∞ were comparable under fasted and fed conditions. The 90% CIs of the GMRs of Cmax, AUClast, and AUC∞ were within the standard bioequivalence range of 80% to 125%.

Table 19: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Erdafitinib After a Single Dose of 9 mg Erdafitinib Administered as 1x 4 mg (G-024) And 1x 5 mg (G-025) Oral Tablets Under Fasted (Treatment A) and Fed Condition (Treatment B, High-fat Breakfast)

Pharmacokinetic Parameter	Geometric Mean		Geometric Mean Ratio, (%)	90% CI, (%)	Intra-subject CV, (%)
	Treatment A 9 mg erdafitinib fasted (reference)	Treatment B 9 mg erdafitinib fed (high-fat breakfast) (test)			
n	16	16			
C_{max} (ng/mL)	341	294	86.15	80.58 - 92.11	10.8
AUC_{last} (ng.h/mL)	20353	19071	93.70	88.76 - 98.92	8.7
AUC_{∞} (ng.h/mL)	20871	19540	93.62	88.90 - 98.60	8.3

Distribution

Based on the results of Clinical Study EDI1001 (see study design in section "Absorption" above), the mean (CV%) Vd/F of erdafitinib in participants with cancer was 28.8 L (51.2%).

The mean (CV%) Vd/F of erdafitinib in heathy participants (pooled analysis EDI1002-EDI1007) was 37.4 L (33.1%).

Volume of distribution is limited in both populations largely due to AGP binding. The difference of Vd/F in participants with cancer versus healthy participants is also likely due to differences in AGP levels and protein binding of erdafitinib in plasma.

Plasma Protein Binding

The plasma protein binding of erdafitinib was studied *in vitro*. *In vitro*, mean Fraction of drug unbound (Fu) ranged between 0.55% (erdafitinib concentration range of 15 to 150 ng/mL) and 0.74% (concentration range of 750 to 1500 ng/mL) in pooled human plasma from healthy participants. Erdafitinib (15 ng/mL) was more highly bound to AGP (94.1% to 99.5% at AGP concentration from 0.02% to 0.20%) compared with human serum albumin (53.4% to 83.9% at human serum albumin concentration from 1% to 6%), and the percent of the unbound fraction was dependent on the purified protein concentration.

In clinical studies, protein binding was assessed based on predose samples spiked with erdafitinib (similar to *in vitro* analyses) and *ex vivo* using samples obtained around the time of maximum erdafitinib concentrations in both healthy participants and participants with cancer. As erdafitinib Fus

were strongly related to AGP levels, this relationship was modelled and described using a nonlinear relationship in the PopPK model.

Fu was estimated based on AGP concentrations, where IIV on the dissociation constant allowed an influence of measured free concentrations. There was a nonlinear relationship between AGP concentration and Fu, which was well described by the equation Fu=Kd/(Kd+AGP), where Kd, was estimated at 30.3 ng/mL. Mean Fu of erdafitinib in plasma was 0.33% in participants with cancer, corresponding to 99.67% bound.

The relationship between PK parameters and Fu was consistent with erdafitinib being a low extraction ratio drug. Consistent with the expectation for a low extraction ratio drug, changes in total CL/F, AUC, and Cmax of erdafitinib were observed with changes in Fu, while free parameters corrected for these relationships, albeit not completely. The PopPK model was set up based on distribution of free erdafitinib to characterise changes in total and free exposure.

Blood-to-Plasma Ratio

As investigated *in vitro*, blood-to-plasma ratio was 0.60, with no concentration dependency.

Transporters

In vitro transporter studies indicated that erdafitinib is a substrate of P-gp but not of BCRP, OATP1B1, and OATP1B3.

Elimination

Erdafitinib is cleared via multiple pathways. As outlined in the Population Pharmacokinetic-Pharmacodynamic Report (2018) not shown), based on totality of available *in vitro* and clinical PK data, a physiologically-based PK model estimated the clearance of erdafitinib to be composed of metabolism by cytochrome P450 (CYP) 2C9 (39%), CYP3A4 (20%), renal clearance (13%), intestinal secretion (21%), and additional hepatic clearance (8%).

Mean (CV%) total CL/F and unbound CL/F of erdafitinib across all daily doses in the first-in-human Study EDI1001 was 0.362 L/h (51.4%) and 112 L/h (40.8%), respectively, see table below:

Table 20: Individual Dose Normalised PK Parameters, Including Descriptive Statistics (C2D1) - Pooled for All Dose Levels

Pooled results of study 42756493EDI1001

Dose normalized to 8 mg

	Dose normalized PK parameters of erdafitinib - Daily dosing								
Subject	eGFR [mL/min/1.73 m^2]	C2D1 C_{min} [ng/mL]	C2D1 C_{max} [ng/mL]	C2D1 AUC_{24h} [ng.h/mL]	C2D1 Unbound C_{min} [ng/mL]	C2D1 Unbound C_{max} [ng/mL]	C2D1 Unbound AUC_{24h} [ng.h/mL]	C2D1 CL/F [L/h]	C2D1 CL_{free}/F [L/h]
n	50	30	30	21	30	30	21	21	21
Mean	99.3	936	1399	29268	2.69	4.17	81.5	0.362	112
SD	25.7	607	711	17519	1.16	1.66	28.2	0.186	45.6
Min	58	215	439	9995	0.687	1.90	34.8	0.105	59.1
Median	97	755	1240	23068	2.69	3.70	78.8	0.347	101
Max	150	2680	3260	75889	5.53	8.23	135	0.800	230
%CV	25.9	64.9	50.8	59.9	43.1	39.9	34.5	51.4	40.8
Geometric Mean	96.1	774	1238	25220	2.43	3.88	76.7	0.317	104

NAs: Not Assessable.
[a] Excluded from descriptive statistics.

These results are comparable with those estimated in the pooled PopPK model (11 clinical studies, including BLC3001) of 0.321 L/h and 107 L/h, respectively.

Based on pooled data in healthy volunteers after single doses, mean (CV%) t1/2 was 59.3 hours (57.5%).

Dose proportionality and time dependencies

Dose proportionality was assessed using PK data from the first-in-human Study EDI1001 with single and multiple continuous doses ranging between 0.5 and 12 mg once daily, and from the PK Study GAC1001 in Japanese participants receiving single doses ranging between 2 and 12 mg and multiple continuous doses ranging between 2 and 6 mg once daily.

In Study EDI1001, following daily dose administration of 0.5-, 2-, 4-, 6-, 9-, and 12 mg erdafitinib, AUC and Cmax on Cycle 1 Day 1 and Day 21 (Cycle 2 Day 1) increased with dose without showing relevant or consistent deviations from dose proportionality. The slope of the linear regression (on log-log scale) was not significantly different from unity.

Similar observations were made in Study GAC1001. Following single (2 to 12 mg) and multiple (2 to 6 mg) dose administration of erdafitinib, AUC and Cmax increased with dose without showing relevant or consistent deviations from dose proportionality.

The mean (CV%) steady-state accumulation ratio in participants with cancer across all doses (pooled results) was 4.07 (32.0%) based on AUC_{τ}, corresponding to mean effective t1/2 of 58.9 hours.

The effective t1/2 estimate in participants with cancer was consistent with the t1/2 determined after a single dose of 59.3 hours in healthy participants based on dose normalised (to 8 mg) pooled data for HV after SD (N= 105) confirming that erdafitinib PK is time-independent.

Special populations

Impaired renal function

Renal excretion of erdafitinib was low; approximately 13.3% of the total administered dose of erdafitinib was excreted renally, and mean renal CL was 0.0541 (±0.0146) L/h.

In the PopPK analysis, mild (N=422, or 421 excluding paediatric participants) and moderate (N=301) renal impairment did not have a significant impact on erdafitinib oral CL relative to participants with normal renal function.

Limited data are available in participants with severe renal impairment.

A post hoc subgroup analysis was conducted in the first-in-human Study EDI1001 [*study design in section "Absorption" above*], where 36 participants had mild renal impairment and 2 participants had moderate renal impairment compared with 39 participants with normal renal function. Due to the low number of participants with moderate renal impairment in this study, PK parameters from participants with mild and moderate renal impairment were pooled for comparison with normal renal function.

Dose-normalised PK parameters (total or free) are presented in the tables below, for single and steady-state C_{max}, AUC, and C_{min} (steady-state only), stratified by daily or intermittent dose.

Table 21: Comparison of Erdafitinib Exposure on Cycle 1 Day 1 in Participants With Normal Renal Function and Mild/Moderate Renal Impairment (Subgroup Analysis From Study EDI1001

	Dose-Normalised C_{max}					Dose-Normalised unbound C_{max}				
Regimen	**N**	**Normal**	**N**	**Mild + Moderate**	**Ratio**	**N**	**Normal**	**N**	**Mild + Moderate**	**Ratio**
Daily doses	28	405 (154)	21	435 (198)	1.07	28	1.40 (0.481)	20	1.13 (0.490)	0.81
Intermittent doses	10	535 (207)	17	523 (274)	0.98	10	1.35 (0.541)	17	1.90 (0.900)	1.41
All participants	38	439 (177)	38	475 (236)	1.08	38	1.38 (0.490)	37	1.48 (0.799)	1.07

	Dose-Normalised AUC_{0-72}					Dose-Normalised unbound AUC_{0-72}				
Regimen	**N**	**Normal**	**N**	**Mild + Moderate**	**Ratio**	**N**	**Normal**	**N**	**Mild + Moderate**	**Ratio**
Daily doses	21	15129 (7444)	13	15163 (7375)	1.00	21	49.9 (16.3)	12	42.5 (14.4)	0.85
Intermittent doses	0	-	0	-	-	0	/	0	-	-
All participants	21	15129 (7444)	13	15163 (7375)	1.00	21	49.9 (16.3)	12	42.5 (14.4)	0.85

Table 22: Comparison of Erdafitinib Exposure on Cycle 2 Day 1 in Participants With Normal Renal Function and Mild/Moderate Renal Impairment (Subgroup Analysis From Study EDI1001)

	Dose-Normalised C_{max}					Dose-Normalised Unbound C_{max}				
Regimen	**N**	**Normal**	**N**	**Mild + Moderate**	**Ratio**	**N**	**Normal**	**N**	**Mild + Moderate**	**Ratio**
Daily doses	17	1391 (786)	13	1410 (631)	1.01	17	4.40 (1.76)	13	3.86 (1.54)	0.88
Intermittent doses	8	1048 (495)	14	646 (302)	0.62	8	3.37 (2.66)	14	2.45 (1.13)	0.73

Regimen	Dose-Normalised AUC_{0-24}					Dose-Normalised Unbound AUC_{0-24}				
	N	Normal	N	Mild + Moderate	Ratio	N	Normal	N	Mild + Moderate	Ratio
Daily doses	13	28814 (19815)	8	30005 (14240)	1.04	13	81.3 (27.6)	8	81.9 (30.9)	1.01
Intermittent doses	5	18954 (10801)	10	10420 (2906)	0.55	5	48.7 (41.7)	10	38.4 (8.78)	0.79

Regimen	Dose-Normalised C_{min}					Dose-Normalised Unbound C_{min}				
	N	Normal	N	Mild + Moderate	Ratio	N	Normal	N	Mild + Moderate	Ratio
Daily doses	17	958 (680)	13	909 (524)	0.95	17	2.84 (1.10)	13	2.49 (1.24)	0.88
Intermittent doses	8	339 (284)	14	213 (156)	0.63	8	0.941 (0.815)	14	0.775 (0.574)	0.82

The plasma PK of total and free erdafitinib was examined in participants with normal hepatic function (N=8) and with preexisting mild (N=8, Grade A, Child-Pugh score of 5 or 6) or moderate (N=8, Grade B, Child-Pugh score of 7 to 9) hepatic impairment (see below).

EDI1008 (hepatic impairment)

Hepatic impairment has been studied in an open-label, single-dose, non-randomised, Phase 1 PK study of erdafitinib in participants who either had hepatic impairment (mild and moderate) or participants with normal hepatic function who qualified for the healthy control group. Hepatic impairment was classified according to the Child-Pugh Classification of Severity of Liver Disease: mild (Grade A, Child-Pugh score of 5 or 6) and moderate (Grade B, Child-Pugh score of 7 to 9).

Healthy men and women between 18 and 80 years of age (inclusive) who had a body mass index between 18 and 34.9 kg/m² (inclusive) and a body weight of ≥50 kg were eligible.

Severe hepatic impairment

The enrolment of the severe hepatic impairment cohort at 6 mg erdafitinib was to be initiated after review of safety and PK data from the mild and moderate hepatic impairment cohorts. PK and safety data were reported from only 2 patients enrolled in the severe hepatic impairment group.

Moderate and mild hepatic impairment

Table 23: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Total and Free Erdafitinib after Administration of 6 mg of Erdafitinib in Subjects with Mild Hepatic Impairment and in Subjects with Normal Hepatic Function

	Hepatic Function		Geometric Means		
PK Parameter	Normal Hepatic function Impairment (Reference)	Mild Hepatic (Test)	Ratio of Geometric Means (%)	90% CI (%)	Total Variability (%)
C_{max} (ng/mL)	157	130	83.02	59.91-115.04	38.7
AUC_{last} (h*ng/mL)	11152	9208	82.57	55.27-123.37	48.5
AUC_{∞} (h*ng/mL)	11393	9374	82.28	54.98-123.13	48.7
$C_{max,free}$ (ng/mL)	0.71	0.68	96.07	83.43-110.63	16.3
$AUC_{last,free}$ (h*ng/mL)	50.4	48.2	95.56	76.67-119.09	25.6
$AUC_{\infty,free}$ (h*ng/mL)	51.5	49.1	95.22	75.85-119.54	26.5

The ANOVA model included log transformed PK parameters as response variable, fixed effect term as level of hepatic function [normal and mild subjects] and age, body weight, and sex as covariate.
Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Reference: Normal Hepatic Function (n=8)
Test: Mild Hepatic Function (n=8)
Total Variability (%)= 100*sqrt(exp(MSE)-1)

Table 24: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Total and Free Erdafitinib after Administration of 6 mg of Erdafitinib in Subjects with Moderate Hepatic Impairment and in Subjects with Normal Hepatic Function

	Hepatic Function		Geometric Means		
PK Parameter	Normal Hepatic function Impairment (Reference)	Moderate Hepatic (Test)	Ratio of Geometric Means (%)	90% CI(%)	Total Variability (%)
Cmax (ng/mL)	157	126	80.30	56.72-113.70	38.7
AUClast (h*ng/mL)	11152	9315	83.53	54.45-128.15	48.5
AUC∞ (h*ng/mL)	11393	9671	84.89	55.24-130.45	48.7
Cmax,free (ng/mL)	0.71	0.72	100.97	86.87-117.36	16.3
AUClast,free (h*ng/mL)	50.4	53.0	105.03	83.06-132.81	25.6
AUC∞,free (h*ng/mL)	51.5	55.0	106.73	83.75-136.02	26.5

The ANOVA model included log transformed PK parameters as response variable, fixed effect term as level of hepatic function [normal and
moderate subjects] and age, body weight, and sex as covariate.
Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Reference: Normal Hepatic Function (n=8)
Test: Moderate Hepatic Function (n=8)
Total Variability (%)= 100*sqrt(exp(MSE)-1)

Gender

The popPK model predicted regarding exposition (AUCfree) for female patients a geometric mean ratio of 1.12 (90% PI 0.64 – 1.97) compared to 0.94 (90% PI 0.54 – 1.56). Female sex on bioavailability was included as covariate in the popPK model. In addition to that, the popPK-PD analysis revealed that the initial [PO4] baseline was 6.5% higher in women.

Race

GAC1001 study (Asian participants) This was a Phase 1, open-label, multicentre, 2-part, dose escalation (Part 1), and dose expansion (Part 2) study conducted in 19 participants with advanced or refractory solid tumors or lymphoma.

Erdafitinib PK parameters are summarised in the table below:

Table 25: Summary of Single and Multiple Dose Plasma PK Parameters of Erdafitinib for the Continuous and Intermittent Dose Cohorts

Parameter (Unit)	Mean (SD)				
	Continuous Doses			Intermittent Doses	
	2 mg (N=3)	4 mg (N=3)	6 mg (N=3)	10 mg (N=3)	12 mg (N=7)
Cycle 1 Day 1					
t_{max}[a] (h)	3.00 (3.0-6.0)	2.00 (1.0-4.0)	2.92 (1.9-3.9)	2.88 (2.0-3.9)	2.82 (1.0-4.0)
C_{max} (ng/mL)	98.0 (21.2)	162 (52.5)	398 (97.3)	521 (164)	701 (451)
AUC_{τ} (ng.h/mL)	1770 (388)	2458 (563)	6989 (1812)	8935 (1935)	12698 (6698)
Cycle 1 Day 8 (Continuous Dose Cohorts) or Day 7 (Intermittent Dose Cohorts)					
t_{max}[a] (h)	4.05 (4.0-5.9)	2.98 (3.0-4.1)	2.95 (2.8-3.9)	2.95 (2.0-3.9)	5.93 (2.0-23.9)
C_{max} (ng/mL)	283 (37.4)	375 (114)	1146 (294)	1567 (506)	1947 (1106)
AUC_{τ} (ng.h/mL)	5941 (878)	7383 (2537)	22790 (6622)	31425 (10534)	40280 (21049)
Cycle 2 Day 1					
t_{max}[a] (h)	-[b]	5.93 (4.0-7.4)	-[b]	-[b]	6.01 (4.1-23.9)[c]
C_{max} (ng/mL)	662 (-)[b]	524 (181)	1375 (-)[b]	492 (-)[b]	652 (277)[c]
AUC_{τ} (ng.h/mL)	11671 (-)[b]	11552 (4271)	26128 (-)[b]	9990 (-)[b]	13301 (6375)[c]

a Median (range); b N=2; c N=4.

As tabulated above, Cmax and AUC increased with increasing dose on both Days 1 and 8 (Day 7 for the 10 and 12 mg intermittent dose cohorts). The median tmax ranged between 2 and 3 hours after the first dose on Day 1 and between 3 and 6 hours following multiple daily dose administration.

The maximum concentrations of plasma Fu of erdafitinib were seen 3 to 4 hours after the first dose.

Study HCC1001 (Asian participants)

This was an open-label, multicentre, 2-part, Phase 1/2a study conducted at multiple sites in Asia, including South Korea, China Taiwan, and Mainland China. The study had "Part 1 Dose Escalation" and "Part 2 Dose Expansion". A total of 53 (98.1%) participants were treated with erdafitinib, provided as tablets for oral administration in 2 dosing schemes:

a) intermittent dosing (erdafitinib at 8, 10, or 12 mg administered on Days 1 to 7 and Days 15 to 21 of each 28-day cycle), and

b) continuous dosing (erdafitinib at 8 mg administered once daily for 28 days on a 28-day cycle). The 8 mg continuous dose was selected as the final RP2D for further expansion in the HCC indication.

Erdafitinib PK parameters are summarised in the table below:

Table 26: Summary of Single and Multiple Dose Plasma Total PK Parameters of Erdafitinib for the Continuous and Intermittent Dose Cohorts (Study HCC1001)

Parameter (Unit)	Mean (SD)			
	Continuous Doses	Intermittent Doses		
	8 mg (N=6)	8 mg (N=3)	10 mg (N=8)	12 mg (N=4)
Cycle 1 Day 1				
t_{max}[a] (h)	4.1 (2.2-6.0)	3.0 (2.0-3.0)	4.0 (1.0-5.9)	2.3 (1.8-5.1)
C_{max}[b] (ng/mL)	330.50 (26.3)	577 (27.8)	467 (44.2)	662 (49.8)
AUC_{0-24}[b] (ng.h/mL)	6091 (22.7)[c]	13981 (-)[d]	9161 (43.1)[e]	3281 (-)[d]
Cycle 1 Day 8 (Continuous Dose Cohorts) or Day 7 (Intermittent Dose Cohorts)				
t_{max}[a] (h)	3.5 (1.9-7.0)	3.0 (2.0-4.0)	3.05 (2.0-5.7)	4.46 (3.1-5.9)
C_{max}[b] (ng/mL)	749 (20.7)	1553 (30.3)	1329 (58.4)	1768 (52.1)
AUC_{0-24}[b] (ng.h/mL)	15228 (21.1)	32198 (27.5)	26939 (59.3)	34703 (52.6)
Cycle 1 Day 21 (Continuous Dose Cohorts)				
t_{max}[a] (h)	3.0 (2.9-6.0)[c]	-	-	-
C_{max}[b] (ng/mL)	787.00 (17.3)[c]	-	-	-
AUC_{0-24}[b] (ng.h/mL)	15576.18 (15.4)[c]	-	-	-

a Median (range); b Cmax and AUC0-24 are reported as mean (CV%); c N=5; d N=1; e N=7

As tabulated above, systemic exposure of erdafitinib generally increased with increasing doses. However, no clear trend was observed based on the limited sample size.

Median tmax was observed at 2.30 to 4.10 hours post-dose after single dosing and 3.00 to 4.46 hours post-dose after repeated dosing. The accumulation ratios at steady state were 2.57 and 2.84 based on Cmax and AUCτ, respectively. Erdafitinib was characterised by a low total apparent plasma clearance (on average 0.436-0.562 L/h).

Weight

In popPK modelling the relationships between weight and clearance and weight and volumes of distribution were described using allometric scaling. CLfree and the volumes of the central and peripheral compartments (V2, V3, V4) were found to increase with increasing weight, described by power functions with powers of 0.68 and 0.53, respectively.

Elderly

In the PopPK analysis, oral CL decreased with increasing age (range, 12-92 years, or 21-92 years excluding 3 paediatric participants), by -15.2% in the 65 to 75 years old group (N=367) and -20.6% in the >75 years old group (N=111) as compared with the <65 years old group (N=664).

Pharmacokinetic interaction studies

In vitro

Potential for drug interactions: in vitro studies with metabolic enzymes

In vitro studies assessing possible relevance of CYP enzymes for drug interactions of erdafitinib are summarised in Table 27.

Table 27: Overview of *in vitro* studies assessing relevance of metabolic enzymes for drug interactions of erdafitinib

Study nr.	Erdafitinib:	Study system	Enzymes / Receptors	Results / unbound IC_{50} or K_i	Implications
ADME_22183 ADME_31191	inhibitor	human liver microsomes	CYP1A2	IC_{50} > 15 μM	no *in vivo* study needed*
			CYP2C8	IC_{50} > 15 μM	
			CYP2C9	IC_{50} > 15 μM	
			CYP2C19	IC_{50} > 15 μM	
			CYP2D6	IC_{50} > 15 μM	
			CYP3A4 (testosterone)	IC_{50} > 15 μM	
			CYP3A4/5 (midazolam)	IC_{50} > 15 μM	
FK10109	inhibitor, mechanism-based	human liver microsomes	CYP1A2	+ NADPH: no ↓ CYP activity	no irreversible inhibition
			CYP2C9	+ NADPH: no ↓ CYP activity	
			CYP2C19	+ NADPH: no ↓ CYP activity	
			CYP2D6	+ NADPH: no ↓ CYP activity	
			CYP3A4	+ NADPH: 43% ↓ CYP activity	irreversible inhibition
FK11141	inhibitor, mechanism-based	human liver microsomes	CYP3A4	K_I = 1.81 μM k_{inact} = 0.0209 1/min	irreversible inhibition
FK12003	inducer#	human hepatocytes 0.4 – 15 μM ⩾10 μM cytotoxic	CYP1A2	FC > 2 in 2/3 donors not conc.-dependent	inconclusive, concentration range above $15 \times C_{max,u}$ (172 nM)
			CYP2B6	FC > 2 in 3/3 donors not conc.-dependent	
			CYP3A4	FC > 2 in 1/3 donors not conc.-dependent	
			CYP1A2	200 nM: FC < 2 in 3/3 donors	

FK13265	inducer[#]	human hepatocytes 5 – 3000 nM	CYP2B6	200 nM: FC > 2 in 2/3 donors not conc.-dependent	no inducer
			CYP3A4	200 nM: FC > 2 in 1/3 donors (20% pos. ctrl) not conc.-dependent	inconclusive (s. Assessor's comment)

need for *in vivo* study as estimated by the assessor according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) and draft ICH M12 guideline on drug interactions: *in vivo* evaluation is warranted if

at least in one donor a drug increases mRNA expression of a CYP enzyme in a concentration-dependent manner and the fold-change (FC) of CYP mRNA expression is ≥ 2-fold at $15\times C_{max,u}$

*$[I]/K_i \geq 0.02$ where [I] is the unbound mean C_{max} obtained during treatment with the highest recommended dose ([I] = 11.5 nM), for intestinal enzymes $[I]/K_i \geq 10$ where [I] is max. dose taken one occasion (9 mg)/ 250 ml

Potential for drug interactions: in vitro studies with transporters

In vitro studies assessing possible relevance of transport proteins for drug interactions of erdafitinib are summarised in Table 28.

Table 28: Overview of *in vitro* studies assessing relevance of transporters for drug interactions of erdafitinib

Study nr.	Erdafitinib:	Study system	Transporters	Results / unbound IC_{50} or K_i	Implications
FK11162	inhibitor	inside-out vesicles expressing BCRP	BCRP	IC_{50} = 14.9 μM	no *in vivo* study needed*
FK11162	substrate	MDCKII/BCRP cells	BCRP	no effect of BCRP inhibitor	not a transporter substrate
FK11164	inhibitor	LLC-PK1/MDR1 cells	P-gp	IC_{50} = 0.666 μM	*in vivo* study warranted*
ADME14455 ADME24540 FK11164	substrate	LLC-PK1/MDR1 cells	P-gp	P-gp inhibitor reduces transport P-gp transport saturated > 0.3 μM	likely a transporter substrate
FK11163	inhibitor	HEK293 cells overexpressing transporters	OATP1B1	IC_{50} = 36.5 μM	no *in vivo* study needed*
			OATP1B3	IC_{50} = 63.1 μM	
FK11163	substrate	HEK293 cells overexpressing transporters	OATP1B1/3	uptake = wt cells	not a transporter substrate
			OATP1B3	no inhibitor effect	
FK11158	inhibitor	MDCKII cells overexpressing transporters	MATE1	IC_{50} = 2.26 μM	no *in vivo* study needed*
			MATE2-K	IC_{50} = 1.89 μM	

FK11157	inhibitor	CHO cells overexpressing transporters	OAT1	no inhibition up to 20.7 μM	no *in vivo* study needed*
			OAT3	no inhibition up to 68.6 μM	
FK11156	inhibitor	CHO cells overexpressing transporters	OCT1	IC_{50} = 0.73 μM	no *in vivo* study needed*
			OCT2	IC_{50} = 0.043 μM	*in vivo* study warranted*

**need for in vivo study as estimated by the assessor according to the ICH M12 draft guideline on drug interactions: *in vivo* evaluation is warranted if K_i or IC_{50} ≤
- for BCRP and P-gp: 0.1-fold the maximum dose on one occasion (9 mg)/250 ml
- for OATP1B1 and OATP1B3: 10-fold the unbound hepatic inlet concentration (13 nM)
- for OCT2, OAT1 and OAT3: 10-fold unbound C_{max} (11.5 nM)
- for MATE1 and MATE2-K: 50-fold unbound C_{max} (11.5 nM)
- for OCT1 according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**): *in vivo* evaluation is warranted if K_i ≤ 25-fold the unbound hepatic inlet concentration (13 nM)

In vivo

Erdafitinib Effect on Other Drugs (erdafitinib=perpetrator)

CYP induction/inhibition (erdafitinib=perpetrator)

BLC2001: Phase 2 - DDI Substudy

Drug-drug Interaction Substudy to Assess the Effect of Repeated Doses of Erdafitinib on the Single-dose Pharmacokinetics of Midazolam and Metformin in Subjects with Advanced Solid Tumors that Harbor Target FGFR Mutations or FGFR Gene Fusions at Selected Sites.

Results

Figure 2: Mean (Standard Deviation) Plasma Concentration-time Profiles of Midazolam After Single Oral Administration of 2.5 mg of Midazolam Alone (Day -2) and in Combination With Erdafitinib at 8 mg Once Daily (Day 13) (Study 42756493BLC2001: Pharmacokinetic Data Analysis Set)

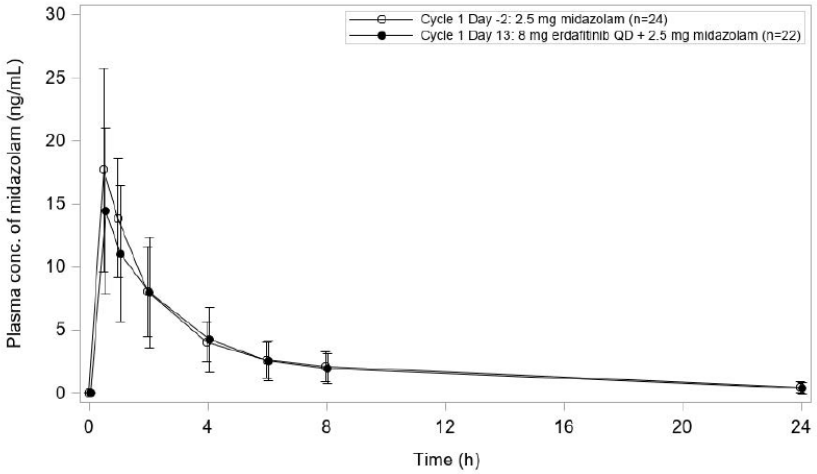


Table 29: Summary of the Statistical Analysis of the PK Parameters of Midazolam after Single Oral Administration of 2.5 mg Midazolam Alone (Day -2) and in Combination With Erdafitinib at 8 mg Once Daily (Day 13) (BLC2001 DDI Substudy: PK Data Analysis Set)

	Geometric Mean				
PK Parameters of Midazolam	Midazolam Alone Day -2 (Reference)	Midazolam+ Erdafitinib Day 13 (Test)	GMR (%)	90% CI (%)	CV (%)
n	21[a]	21[a]			
C_{max} (ng/mL)	16.4	14.2	86.29	73.52-101.28	30.8
AUC_{last} (ng.h/mL)	55.8	49.4	88.46	76.55-102.22	27.7
AUC_{∞} (ng.h/mL)	55.0	45.1	82.11	70.83-95.18	23.3

a n=17 for AUC_{∞}

Figure 3: Linear Mean (Standard Deviation) Plasma Concentration-time Profiles of Metformin after Single Oral Administration of 1000 mg of Metformin Alone (Day -1) and in Combination with Erdafitinib at 8 mg Once Daily (Day 14) (Study 42756493BLC2001: Pharmacokinetic Data Analysis Set)

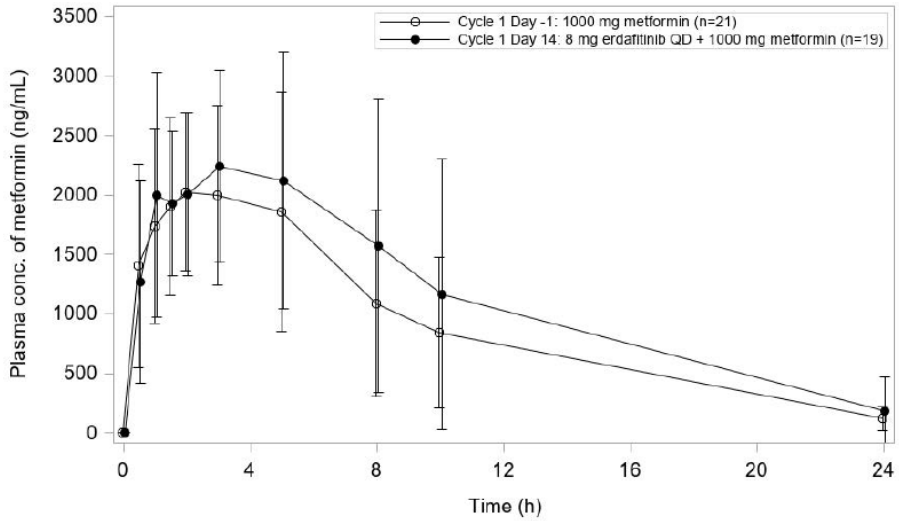


Table 30: Summary of the Statistical Analysis of the PK Parameters of Metformin after Single Oral Administration of 1000 mg of Metformin Alone (Day -1) and in Combination with Erdafitinib at 8 mg Once Daily (Day 14) (BLC2001 DDI Substudy: PK Data Analysis Set)

	Geometric Mean				
PK Parameters of Metformin	Metformin Alone Day -1 (Reference)	Metformin+ Erdafitinib Day 14 (Test)	GMR (%)	90% CI (%)	CV (%)
n	16[a]	16[a]			
C_{max} (ng/mL)	2376	2582	108.66	90.31-130.75	30.5
AUC_{last} (ng.h/mL)	20102	23922	119.01	98.85-143.27	30.6
AUC_{∞} (ng.h/mL)	22225	25319	113.92	93.22-139.23	30.7

a n=14 for AUC∞

Potential for Interactions with Hormonal Contraceptives (erdafitinib=perpetrator)

Not explicitly investigate in clinical DDI studies.

Transporter (erdafitinib=perpetrator)

The potential of erdafitinib to interact with transporters has only been investigated in one clinical study:

In the BLC2001 DDI Substudy discussed in detail above, mean ratios of Cmax and AUC∞ for metformin (a sensitive OCT2 substrate) were 108.66% (90% CI: 90.31-130.75) and 113.92% (90% CI: 93.22-139.23), respectively, when co-administered with erdafitinib relative to metformin alone.

OATP1B3, OAT1, and OAT3

Erdafitinib is not considered an inhibitor of OATP1B3, OAT1, or OAT3.

BCRP and OATP1B

Mean (CV%) steady-state Cmax (Day 21) in participants with cancer at the highest clinical dose of 9 mg was 2018 ng/mL (36.9%), well below the IC50 values of BCRP and OATP1B. Therefore, erdafitinib is not expected to affect the PK of BCRP or OATP1B substrates.

P-gp

Erdafitinib is a P-gp inhibitor with an IC50 of 0.67 µM (299 ng/mL) in LLC-PK1 cells and an unbound intracellular IC50 calculated at 0.026 µM (11.6 ng/mL).

As a P-gp inhibitor, simulated luminal and enterocyte concentration after administration of 9 mg erdafitinib showed a potential risk of P-gp inhibition only in the first 5 hours after administration in the different parts of the intestinal tract.

OCT1, OCT2, MATE-1, and MATE-2

Inhibitory effects were noted for OCT1, OCT2, MATE-1, and MATE-2 with IC50 values in the low micromolar range. Comprehensive analysis based on recommended static models (agency DDI guidelines) indicated that other than OCT2, there were no clinically relevant inhibition-based DDIs expected for OCT1, MATE-1, and MATE-2 by erdafitinib.

OCT2 showed the lowest IC50 of 0.0434 µM (19.4 ng/mL), while mean steady-state unbound Cmax (Day 21) in participants with cancer at the highest clinical dose of 9 mg was 3-fold lower at 6.5 ng/mL (based on mean Cmax of 2018 ng/mL and mean Fu of 0.32%).

Effect of Other Drugs on erdafitinib (erdafitinib=victim)

CYP3A4 Inhibitors (erdafitinib=victim)

EDI1007

A Randomized, Open-Label, Parallel-Group, Drug-Drug Interaction Study to Evaluate the Effect of Fluconazole and Itraconazole on the Pharmacokinetics of Erdafitinib in Healthy Adult Subjects.

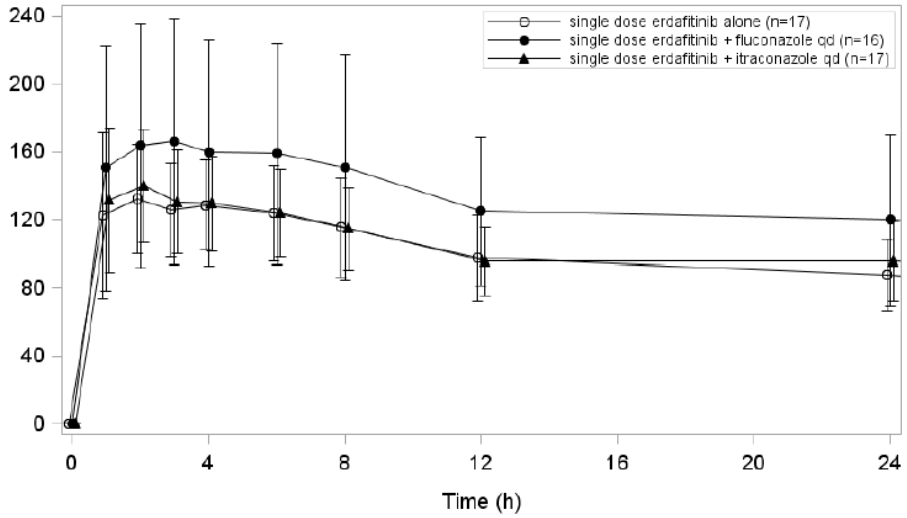
Table 31: GMR and 90% CI for Comparison of Erdafitinib Administered Alone (Reference) Versus Administered with Fluconazole (Test) or with Itraconazole (Test) (Primary Analysis)

Coadministration With Fluconazole			
Parameter (Unit)	**Geometric Mean**		**GMR, % (90% CI)**
	Erdafitinib Alone (Reference) N=17	**Erdafitinib + Fluconazole (Test) N=15**	
$AUC_{0\text{-}168}$ (ng.h/mL)	7490	10306	137.59 (113.56, 166.70)
AUC_{last} (ng.h/mL)	8413	12540	149.05 (120.30, 184.67)
AUC_{∞} (ng.h/mL)	8655	12796	147.85 (119.95, 182.24)
C_{max} (ng/mL)	136	164[a]	121.10 (99.88, 146.84)
Coadministration With Itraconazole			
	Geometric Mean		**GMR, % (90% CI)**
	Erdafitinib Alone (Reference) N=17	**Erdafitinib + Itraconazole (Test) N=17**	
$AUC_{0\text{-}168}$ (ng.h/mL)	7490	9000	120.15 (99.81, 144.62)
AUC_{last} (ng.h/mL)	8413	11198	133.10 (108.21, 163.72)
AUC_{∞} (ng.h/mL)	8655	11585[a]	133.86 (109.05, 164.33)
C_{max} (ng/mL)	136	142	104.79 (86.66, 126.70)

*Note: The analysis was performed based on a mixed effect model, including both genotype and treatment as fixed effects. The primary analysis included CYP2C9 genotype *1/*1 + *1/*2.*

Reference: 4 mg erdafitinib tablet administered alone on Day 1.
Test: 4 mg erdafitinib tablet administered on Day 5 + 400 mg fluconazole administered once daily on Days 1 to 11 or 4 mg erdafitinib tablet administered on Day 5 + 200 mg itraconazole once daily on Days 1 to 11. a N=16.

Figure 4: Mean (SD) Linear Plasma Concentration-time Curves of Erdafitinib after a Single Dose Administration of 4 mg Erdafitinib Alone (Treatment A) or in Combination with Daily Administration of 400 mg Fluconazole (Treatment B, Day 5), or 200 mg Itraconazole (Treatment C, Day 5), in Healthy Subjects with CYP2C9 Genotype *1/*1 or *1/*2



CYP3A4/CYP2C9 Inducers (erdafitinib=victim)

NAP1001

An Open-label, Single-sequence, Drug-drug Interaction Study to Evaluate the Effect of Steady-state Carbamazepine on the Single-dose Pharmacokinetics of Erdafitinib Tablets in Healthy Adult Subjects

Summary PK statistical results are presented in the tables below:

Table 32: Summary of the Statistical Analysis of the PK Parameters of Total Erdafitinib after Single Administration of Erdafitinib Alone at 12 mg and in Combination with Multiple Doses of Carbamazepine; PK Data Statistical Primary Analysis Set

		Geometric Mean		Test versus Reference		Source of Variability	
PK Parameter (Total Erdafitinib)	n	Erdafitinib 12 mg Alone (Reference)	Erdafitinib 12 mg + Carbamazepine (Test)	GMR (%)	90% CI (%)	Intra-participant CV (%)	Inter-participant CV (%)
C_{max} (ng/mL)	13	365	239	65.44	(60.77, 70.46)	10.6	24.6
AUC_{168h} (ng.h/mL)	12	21,616	9,407	43.52	(40.12, 47.21)	11.1	25.8
AUC_{last} (ng.h/mL)	12	24,537	9,714	39.59	(36.28, 43.20)	11.9	26.4
AUC_{∞} (ng.h/mL)	11	26,494	9,993	37.72	(35.35, 40.25)	8.4	24.7

n=number of paired observations.
Note: Log-transformed PK parameters were analysed by a linear model analysis of variance controlling for treatment as fixed effect and participant as a random effect and the results were back-transformed using antilogarithm.

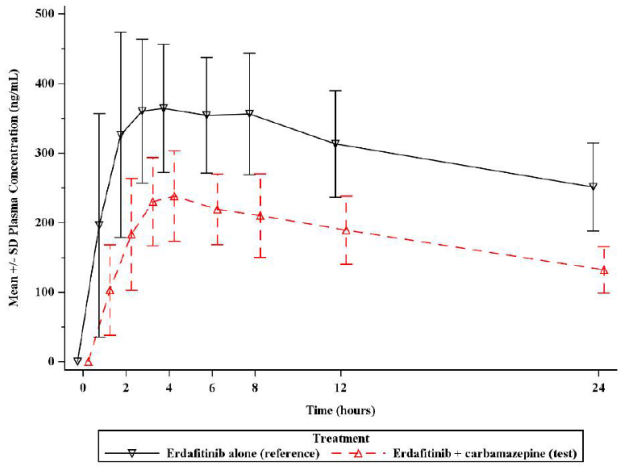
Table 33: Summary of the Statistical Analysis of the PK Parameters of Free Erdafitinib after Single Administration of Erdafitinib Alone at 12 mg and in Combination with Multiple Doses of Carbamazepine; PK Data Statistical Primary Analysis Set

	Geometric Mean			Test versus Reference		Source of Variability	
PK Parameter (Free Erdafitinib)	n	Erdafitinib 12 mg Alone (Reference)	Erdafitinib 12 mg + Carbamazepine (Test)	GMR (%)	90% CI (%)	Intra-participant CV (%)	Inter-participant CV (%)
C_{max} (ng/mL)	12	2.42	1.88	77.76	(72.76, 83.12)	9.1	11.5
AUC_{168h} (ng.h/mL)	11	142	73.8	52.07	(46.14, 58.75)	15.7	12.5
AUC_{last} (ng.h/mL)	11	161	76.5	47.62	(41.91, 54.10)	16.6	13.4
AUC_{∞} (ng.h/mL)	10	173	78.5	45.28	(39.74, 51.59)	16.0	13.3

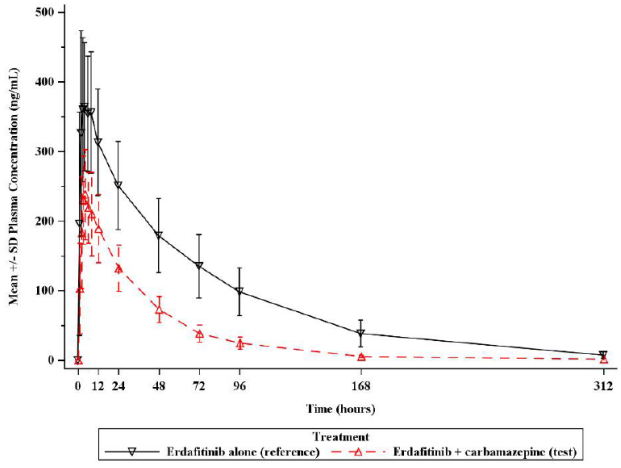
n=number of paired observations.
Note: Log-transformed PK parameters were analysed by a linear model analysis of variance controlling for treatment as fixed effect and participant as a random effect and the results were back-transformed using antilogarithm

Figure PK 1

Figure 5: Mean Plasma Concentrations of Total Erdafitinib vs Time; PK Data Analysis Set



Linear-Linear scale; Reduced X-axis
Erdafitinib alone (reference): Erdafitinib (12 mg as three 4 mg tablets) at Day 1.
Erdafitinib + carbamazepine (test): Erdafitinib (12 mg as three 4 mg tablets) at Day 28 + carbamazepine (300 mg q12h).



Linear-Linear scale
Erdafitinib alone (reference): Erdafitinib (12 mg as three 4 mg tablets) at Day 1.
Erdafitinib + carbamazepine (test): Erdafitinib (12 mg as three 4 mg tablets) at Day 28 + carbamazepine (300 mg q12h).

Inhibitors of Transporters (erdafitinib=victim)

In vitro transporter studies indicated that erdafitinib is a substrate for P-gp but not for BCRP, OATP1B1, and OATP1B3. Based on the expected intestinal concentration in humans at the clinical dose (9 mg once daily), victim-based DDI with concomitant administration of P-gp inhibitors at the intestinal level was excluded, while renal CL was limited (13%) in the total CL of erdafitinib. This was consistent with near complete oral absorption of erdafitinib at the intestinal level and coadministration with itraconazole, an inhibitor of CYP3A4 and P-gp, did not lead to clinically meaningful changes in erdafitinib and metabolite urinary excretion.

Acid Lowering Agents (erdafitinib=victim)

Erdafitinib is a weak base with pKa1 and pKa2 of 9.1 (secondary amine moiety) and 1.9 (quinoxaline moiety), respectively. Erdafitinib is a BCS Class I compound with adequate solubility across the pH range of 1 to 7.4. The solubility of erdafitinib is pH-dependent: solubility decreased from 10 mg/mL at pH 1 to 0.19 mg/mL at pH 7.4. Nevertheless, erdafitinib is still considered highly soluble at pH of 7.4 at the highest clinical dose per regulatory guidance based on dose number. The dose number was calculated as the number of times 250 mL of aqueous media was needed to dissolve the highest

proposed clinical dose of 9 mg, using the lowest solubility (0.19 mg/mL) observed at the highest pH (7.4). When the dose number is 1 or less than 1, the compound is considered highly soluble, and absorption is unlikely to be affected by drugs that increase gastric pH. For erdafitinib, a dose number of 1 was reached at a clinical dose of 47 mg, which was >5 times higher than the maximal dose proposed for clinical use (9 mg).

Interaction of erdafitinib and sevelamer, a phosphate-binding drug (erdafitinib=victim or perpetrator)

Sevelamer, a phosphate-binding drug, is a concomitant medication used in clinical studies to manage hyperphosphataemia, the most common AE upon erdafitinib treatment.

In a cohort-by-cohort analysis of the first-in-human Study EDI1001, erdafitinib exposure was comparable with or without concomitant administration of sevelamer within the same dose regimen (table below).

Table 34: Arithmetic Mean ± SD Plasma Erdafitinib Pharmacokinetic Parameters after 21 Days (C2D1) of Erdafitinib Administration in Subjects Assigned to the Continuous Daily Dosing Regimen (Part 1 and Part 2 of the Study) with or without Sevelamer Coadministration.

	No Sevelamer					With Sevelamer				
	Continuous daily dosing									
	Part 1			Part 2	Part 1	Part 1			Part 2	Part 1
	4 mg	6 mg	9 mg	9 mg	12 mg	4 mg	6 mg	9 mg	9 mg	12 mg
N	2	3	0	1	1	3	5	1	5	2
C_{max} (ng/mL)	639 ± 418	717 ± 429	NA	1970	4890	699 ± 229	879 ± 335	494	2028 ± 831	2140 ± 467
T_{max} (h)	3.15 (2.25-4.05)	3.07 (2.08-8.02)	NA	2.00	8.25	4.00 (2.73-7.00)	2.10 (2.00-3.00)	3.00	3.12 (2.00-23.75)	1.50 (1.00-2.00)
C_{min} (ng/mL)	418 ± 180	548 ± 415	NA	831	4020	437 ± 216	555 ± 348	290	1330 ± 825	1465 ± 559
AUC_{τ} (ng.h/mL)	7421[a]	14974 ± 10261	NA	24064	113833	19610[a]	12621 ± 3892[b]	NA	43468 ± 17648[c]	39211 ± 8889
AR_{Cmax}	3.01 ± 0.151	4.41 ± 1.33	NA	4.56	4.14	3.30 ± 0.146	2.88 ± 0.754	4.15	3.42 ± 0.786	3.83 ± 1.54
$AR_{AUC\tau}$	2.73[a]	5.32 ± 1.67	NA	3.52	5.42	3.44[a]	3.00 ± 1.36[b]	NA	3.85± 0.336[d]	4.12 ± 1.37
CL/F (L/h)	0.539[a]	0.528 ± 0.289	NA	0.374	0.105	0.204[a]	0.515 ± 0.192[b]	NA	0.237± 0.0988[c]	0.314 ± 0.0712
$t_{1/2eff}$ (h)	36.5[a]	79.9± 27.9	NA	49.7	81.5	48.3[a]	40.9 ± 23.0[b]	NA	55.3± 5.64[d]	59.8 ± 22.9
C_{maxu} (ng/mL)	1.51 ± 0.224	3.26 ± 1.00	NA	9.26	6.06	2.67 ± 0.842	2.73 ± 1.09	4.01	4.29± 2.26	8.96 ± 2.91
$AUC_{\tau u}$ (ng.h/mL)	36.1[a]	65.0 ± 15.4	NA	113	141	39.4[a]	42.5 ± 23.8[b]	NA	95.1± 41.1[c]	164 ± 54.8

Tmax is reported as median (min-max).The 0.5 and 2 mg doses in C2D1 of Part 1 Continuous Dosing did not have any Sevelamer so they are not shown in this table. Mean±SD values and median for Tmax are not reported in cohorts with n=1, instead the individual value is presented.
NA: not assessable
a:n=1; b:n=3; c:n=4; d:n=2

In addition, a pooled analysis across all doses demonstrated comparable dose-normalised Cmax and AUC on Cycle 1 Day 1; Cmax values with (N=31) or without (N=45) sevelamer were 465 and 451

ng/mL, respectively, and AUC0-24 values with (N=29) or without (N=43) sevelamer were 8073 and 7377 ng/h/mL, respectively. Similar results were observed with free parameters and on Cycle 1 Day 8 [data not shown].

Population PK Modelling

Erdafitinib dosing is individualised based on serum PO4 concentrations, therefore popPK and popPK-PD models were developed for erdafitinib. The previously developed models for erdafitinib PK and erdafitinib effects on phosphate levels were further refined using additional clinical data.

The final PopPK dataset included data from 11 clinical studies: Studies EDI1001, EDI1002, EDI1003, EDI1005, GAC1001, BLC2002, CAN2002, HCC1001, LUC2001, updated data from Study BLC2001, and the primary study of focus, Study BLC3001. In the final popPK model 8,566 total and 839 free erdafitinib plasma concentrations from 1,145 subjects were included. The relationship between total and free erdafitinib concentrations appears to be linear, except at very low concentrations and the free fraction is strongly related to AGP concentrations.

The following changes to the previous model were tested and incorporated in the updated base model:

1. The relationship between the free fraction, Fu, and AGP was fitted to the data instead of calculated based on a fixed Kd. IIV on the Kd parameter was incorporated, to use both AGP measurements and measurements of free and total concentrations in the estimation of Fu. Kd was estimated at 30.3 ng/mL, with an IIV of 17%.

2. The volume of the central compartment, V2, and the relative bioavailability, F1, were found to increase with increasing Fu, described by power functions, with respective powers of 0.77 and 0.27, respectively.

3. CLfree and the volumes of the central and peripheral compartments (V2, V3, V4) were found to increase with increasing weight, described by power functions with powers of 0.68 and 0.53, respectively.

4. The Fu was found to be approximately 20% higher in spiked predose samples than for other samples.

5. F1 for the capsule formulation was found to be 6% higher than for the other formulations.

6. IIV was applied to CLtotal, F1, V3, Ka, and Kd.

Model parameters of the updated base model (run391) and the final model (run393) are presented in Table 35. The model resulting from the backward step was selected as the final model. CLfree was estimated at 107 L/h, corresponding to a CLtotal of 0.321 L/h at the median Fu, 0.30%. The volume of the central compartment, for total drug, was estimated at 25.9 L. Ka and lag times varied between formulations, with the solution having the shortest lag time and fastest Ka, as expected. The lag time for Study GAC1001 using capsule formulation was longer than for the other studies. IIV was modest for CLfree (32%), F1 (21%), and Kd (17%), but higher for V3 (78%) and Ka (178%).

Table 35: Parameters of Base and Final PopPK Models

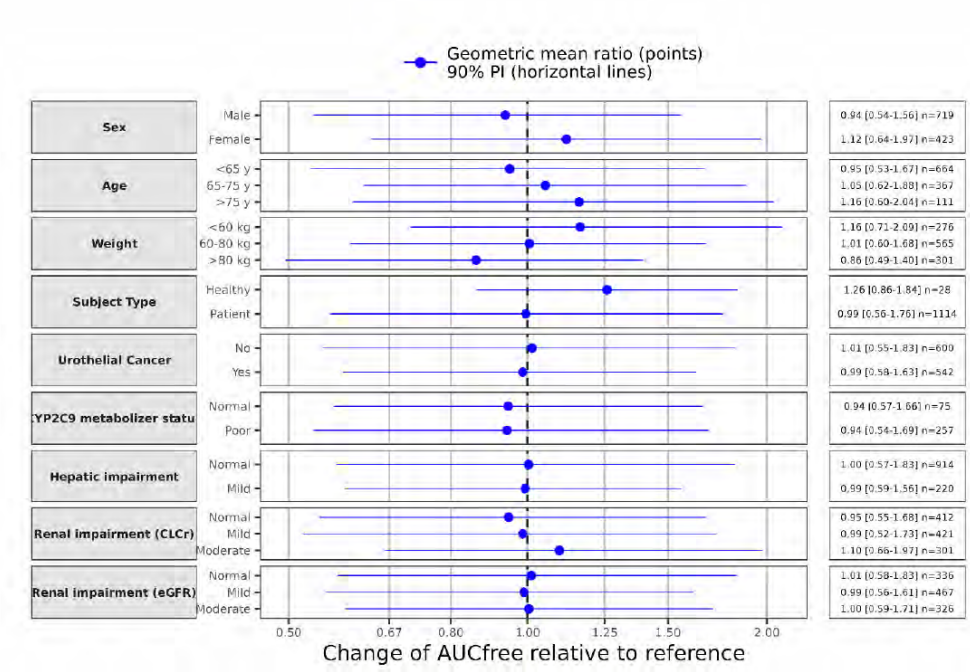
			Base Model (run391)			Final Model (run393)		
Parameter	Unit	Description	Parameter Estimate	RSE (%)	95% CI	Parameter Estimate	RSE (%)	95% CI
MVOF		Minimum value of objective function	[redacted]	-	-	[redacted]	-	-
Cl_{free}/F	L/h	Clearance of free drug		1.72	(91.4 – 97.8)		2.01	(103 – 111)
$V2_{total}$/F	L/h	Volume of central compartment of total drug		1.64	(23.7 – 25.3)		1.77	(25.0 – 26.8)
V3/F	L	Volume of first peripheral compartment (only free drug distributes)		7.71	(1740 – 2360)		6.43	(1861 – 2399)
Q3/F	L/h	Inter-compartmental clearance of free drug to first peripheral compartment		8.47	(41.5 – 58.1)		12.3	(40.5 – 66.3)
V4/F	L	Volume of second peripheral compartment (only free drug distributes)		12	(512 – 826)		7.24	(584 – 778)
Q4/F	L/h	Inter-compartmental clearance of free drug to second peripheral compartment		18.6	(1.04 – 2.24)		11.2	(1.29 – 2.01)
K_d	ng/mL	Dissociation constant to AGP used to estimate Fu		1.66	(29.3 – 31.3)		1.63	(29.3 – 31.3)
Ka solution	h^{-1}	Absorption rate constant for solution		18.9	(2.98 – 6.48)		13.5	(3.38 – 5.82)
Ka capsule	h^{-1}	Absorption rate constant for capsules		12.3	(0.888 – 1.45)		10.9	(0.913 – 1.41)
Ka tablet	h^{-1}	Absorption rate constant for tablets		14	(1.35 – 2.37)		10.2	(1.47 – 2.19)
Lagtime solution	h	Lagtime for solution		5.85	(0.166 – 0.21)		5.33	(0.167 – 0.207)
Lagtime capsule	h	Lagtime for capsules		0.29	(0.244 – 0.246)		0.292	(0.244 – 0.246)
Lagtime tablet	h	Lagtime for tablets		1.91	(0.22 – 0.238)		1.93	(0.22 – 0.238)
Lagtime Study GAC1001	h	Lagtime for Study GAC1001		0.511	(0.411 – 0.419)		0.675	(0.41 – 0.42)
F1 capsule	%	Bioavailability change for capsules		42.9	(0.964% – 11.2%)		52.7	(-0.158% – 9.88%)

			Base Model (run391)			Final Model (run393)		
Parameter	Unit	Description	Parameter Estimate	RSE (%)	95% CI	Parameter Estimate	RSE (%)	95% CI
Fu on $V2_{total}$		Power of effect of Fu on the volume of the central compartment	[redacted]	4.29	(0.706 – 0.836)	[redacted]	4.26	(0.732 – 0.866)
Fu on F1		Power of effect of Fu on bioavailability		9.70	(0.219 – 0.323)		9.67	(0.222 – 0.326)
Spiking on Fu	%	change in Fu in spiked samples		12.8	(15.0% – 25.0%)		13.0	(14.7% – 24.7%)
WT on $V2_{total}$, V3, V4		Power of weight effect on volumes		7.50	(0.577 – 0.777)		9.15	(0.483 – 0.695)
WT on Cl_{free}		Power of weight effect on clearance of free drug		10.0	(0.428 – 0.636)		12.0	(0.342 – 0.552)
CLAGECAT1	%	Effect of age 65 – 75y compared to <65y on clearance of free drug		-	-		14.1	(-19.4% – 11.0%)
CLAGECAT2	%	Effect of age >75y compared to <65y on clearance of free drug		-	-		15.5	(-26.9% – 14.3%)
F1SEX1	%	Effect of female sex compared to male on bioavailability		-	-		17.2	(8.61% – 17.4%)
F1HLTH1	%	Effect of healthy subjects compared to patients on bioavailability		-	-		27.0	(8.60% – 28.0%)
IIV Cl_{total}		IIV on clearance of total drug		5.00	(0.329 – 0.35)		5.07	(0.314 – 0.334)
IIV F1		IIV of bioavailability		6.59	(0.209 – 0.23)		6.78	(0.198 – 0.218)
IIV V3		IIV of the volume of the first peripheral compartment		13.4	(0.686 – 0.873)		12.9	(0.695 – 0.873)
IIV Ka		IIV of absorption rate (all formulations)		8.59	(1.72 – 1.89)		7.83	(1.71 – 1.86)
IIV K_d		IIV on the AGP dissociation constant		11.8	(0.149 – 0.187)		11.7	(0.15 – 0.187)

			Base Model (run391)			Final Model (run393)		
Parameter	Unit	Description	Parameter Estimate	RSE (%)	95% CI	Parameter Estimate	RSE (%)	95% CI
RUV_{tot}	%	Residual unexplained variability of total concentrations	[redacted]	4.27	(27.3% – 28.6%)	[redacted]	4.3	(27.3% – 28.6%)
RUV_{free}	%	Residual unexplained variability of free concentrations		6.72	(25.1% – 27.6%)		7.82	(24.9% – 28.1%)
Correlation CL, F1	%			-	-		-	-
Correlation CL, V3	%			-	-		-	-
Correlation F1, V3	%			-			-	-

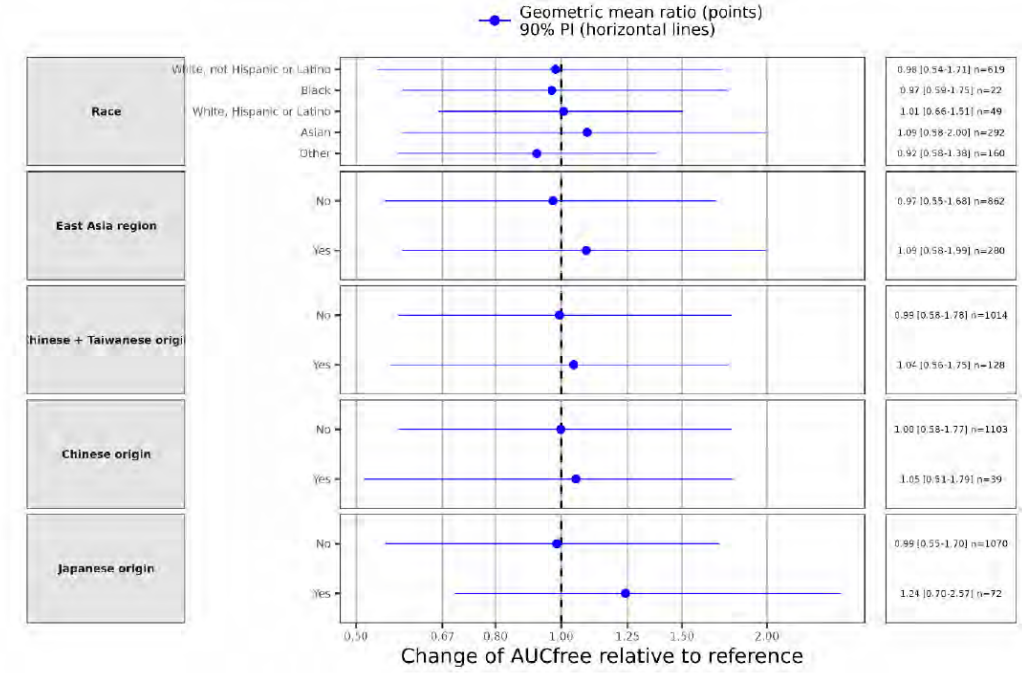
The following covariates were selected for evaluation: For CL: age category, weight category, sex, patient/healthy status, hepatic impairment, renal impairment, race, East Asian region, Chinese origin, Chinese or Taiwanese origin, Japanese origin, CYP2C9 polymorphism and for F1: weight category, sex, patient/healthy status, race, East Asian region, Chinese origin, Chinese or Taiwanese origin, Japanese origin. The covariate effects are shown in the forest plots presented in Figure 3 and Figure 4, where the summaries of individual predictions of the steady state AUCfree were plotted by covariate categories. Overall, the observed effects were modest, as expected from the covariate effect estimates in the final model and median predicted AUCfree across all covariate subgroups was within the 86% to 126% range of the population median.

Figure 6: Summary of Individual Predicted Normalised Steady State AUCfree by Covariate Categories



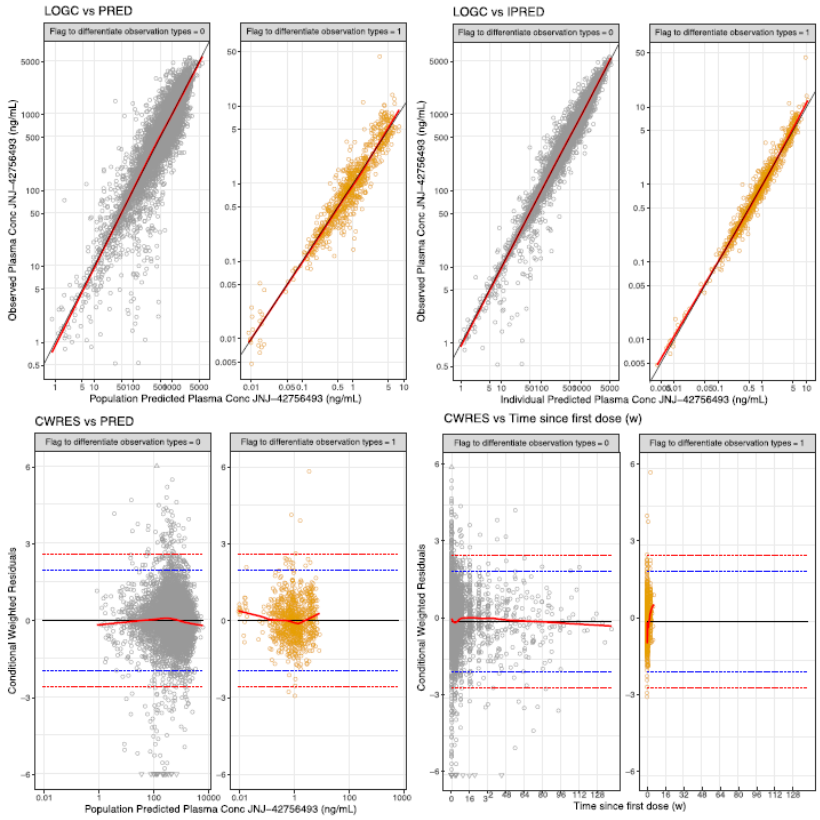
Numbers indicate geometric mean ratio (5th to 95th percentile); PI=prediction interval. Steady state AUC_{free} normalized by overall median steady state AUC_{free}. Dots indicate the geometric mean ratio by category; horizontal lines indicate 5th to 95th percentile range. Groups with fewer than 20 subjects excluded. Pediatric population (n=3) excluded.

Figure 7: Summary of Individual Predicted Normalised Steady State AUCfree by Race and Region Covariate Categories



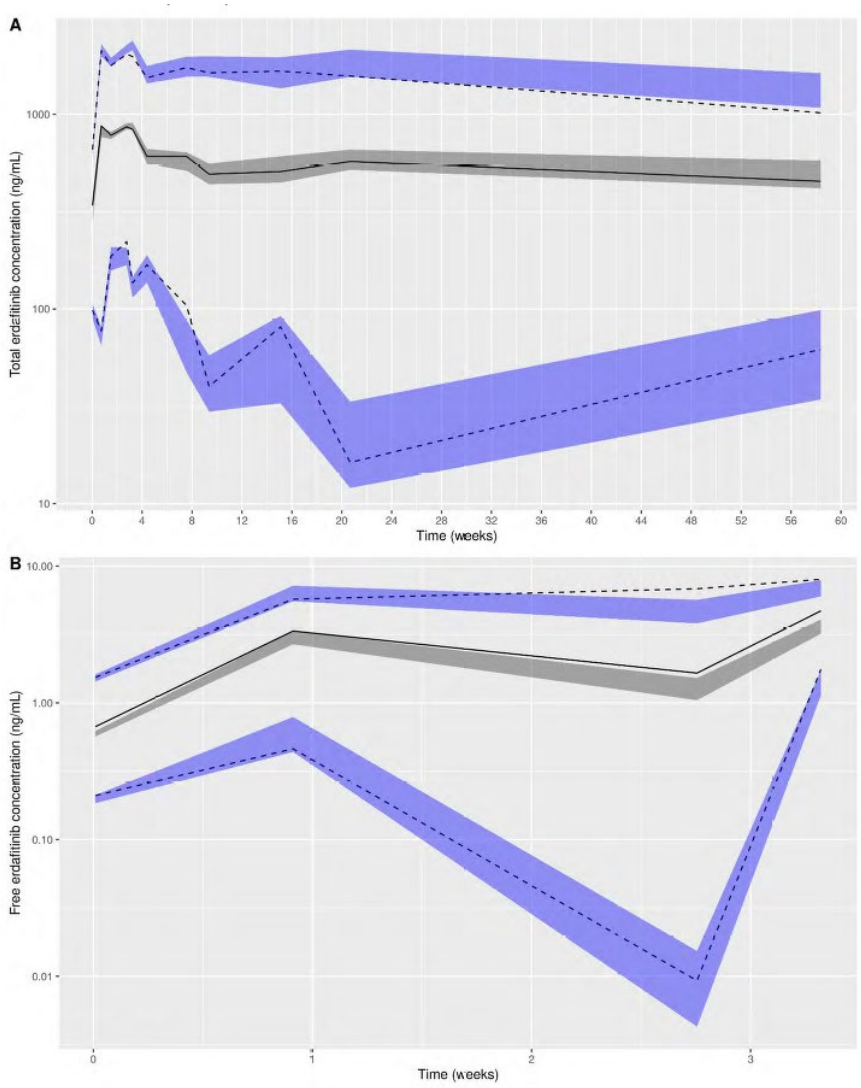
Numbers indicate geometric mean ratio (5th to 95th percentile); PI=prediction interval.
Steady state AUC_{free} normalized by overall median steady state AUC_{free}. Dots indicate geometric mean ratio by category; horizontal lines indicate 5th to 95th percentile range. Groups with fewer than 20 subjects excluded. Pediatric population (n=3) excluded.

Figure 8: GOF Plots, Final Model (run393) for Erdafitinib Total (Flag=0) and Free (Flag=1) Concentrations



Symbols represent observations/predictions (upper panels), conditional weighted residuals (lower panels) for erdafitinib total (flag=0, grey symbols) and free (flag=1, orange symbols) concentrations. Solid black lines represent the identity lines; solid red lines represent a smooth of the data. Blue dashed lines represent 95th percentile of residual probability. Red dashed lines represent 99th percentile of residual probability.

Figure 9: pcVPC of Total and Free Erdafitinib Concentrations Versus Time Since First Dose, Final Model (run393)



Population PK-PD Modelling

The final PopPK-PD dataset was comprised of a subset of the PopPK dataset with patient data from subjects with cancer obtained from 8 studies: Studies EDI1001, GAC1001, BLC2002, CAN2002, HCC1001, LUC2001, and BLC3001. In the final popPK-PD model data from 1,132 subjects receiving continuous once daily doses (range, 0.5-12 mg) or intermittent once daily doses (range, 10-12 mg) of erdafitinib, contributing 15,494 serum [PO4], were included in the analysis.

An Emax model described the erdafitinib effect on PO4 driven by free concentrations in the effect compartment, with an attenuation of the erdafitinib effect on serum [PO4] with time, used to describe the relationship between erdafitinib free plasma concentrations and serum [PO4]. This model characterised serum [PO4] and their variability in subjects with cancer treated with different dosing regimens of erdafitinib. The initial [PO4] baseline was estimated to be 6.5% higher in women. Emax was 26.9% higher in subjects who received PO4-lowering drugs. Emax decreased with increasing age (decreasing by 8.1% when age went from 60 to 80 years) and was 12.6% lower in subjects of Japanese origin.

Model parameters are presented in Table 36, goodness-of-fit plots and pcVPCs are depicted in Figure 10 and Figure 11, respectively.

Table 36: Parameters of Base and Final PopPK-PD Models

			Base Model (run469)			Final Model (run462)		
Parameter	Unit	Description	Parameter Estimate	RSE (%)	95% CI	Parameter Estimate	RSE (%)	95% CI
MVOF		Minimum value of objective function	[redacted]	-	-	[redacted]	-	-
Baseline	mg/dL	Initial [PO_4] baseline		0.59	(3.25 – 3.33)		1.87	(3.10 – 3.34)
Plateau baseline	mg/dL	Post-treatment interruption [PO_4] baseline plateau		0.993	(2.65 – 2.75)		1.83	(2.59 – 2.79)
kbase	h^{-1}	Rate constant for treatment interruption change of [PO_4] baseline		43	(0.00227 – 0.0267)		43.5	(0.00193 – 0.0241)
tlag	h	Post-treatment interruption lagtime before [PO_4] baseline decline		26.8	(50.3 – 162)		24.2	(45.1 – 126)
ke0	h^{-1}	Effect compartment rate constant		5.23	(0.0115 – 0.0141)		35.9	(0.00389 – 0.0223)
EC_{50}	ng/mL	Effect compartment free erdafitinib concentration giving half maximal effect		40.6	(0.923 – 8.10)		22.2	(2.12 – 5.36)
E_{max}	mg/dL	Maximal erdafitinib effect on [PO4]		29.6	(2.93 – 11.0)		13.6	(4.13 – 7.13)
Power		Power in Hill equation		9.16	(1.07 – 1.55)		11.2	(1.02 – 1.60)
kin	h^{-1}	Rate constant describing attenuation of drug effect over time		3.20%*	(8.32E-05- 1.10E-04)		3.45*	(8.12E-5 – 1.12E-4)
Sex effect on baseline	%	Effect of female sex on initial baseline	[redacted]			[redacted]	39.4	(0.0148 – 0.116)
CORENA on E_{max}	%	Effect of coadministration of PO_4-lowering drugs on E_{max}					10.6	(0.213 – 0.325)
Age on E_{max}		Effect of age on E_{max}, power					42.2	(-0.537 - -0.051)
JPNS on E_{max}	%	Effect of Japanese origin on E_{max}					41.6	(-0.229 - -0.0233)
IIV Baseline		IIV, initial baseline		4.37	(0.466 – 0.488)		4.27	(0.449 – 0.471)
IIV E_{max}		IIV, E_{max}		4.86	(0.331 – 0.351)		5.04	(0.282 – 0.3)
IIV ke0		IIV, effect compartment rate constant		6.99	(1.03 – 1.12)		15.1	(0.934 – 1.22)
IIV kin		IIV, attenuation of drug effect over time		7.21	(1.15 – 1.25)		6.96	(1.15 – 1.25)
IIV final baseline		IIV, post-treatment interruption baseline		7.62	(0.495 – 0.552)		8.89	(0.488 – 0.561)
Correlation IIV ke0 – kin		Correlation between individual ke0 and kin						
Residual error		Additive residual error on log scale		2.9	(0.138 – 0.142)		3.05	(0.137 – 0.141)

*sd on log scale.

Figure 10: GOF Plots, PK-PD Final Model

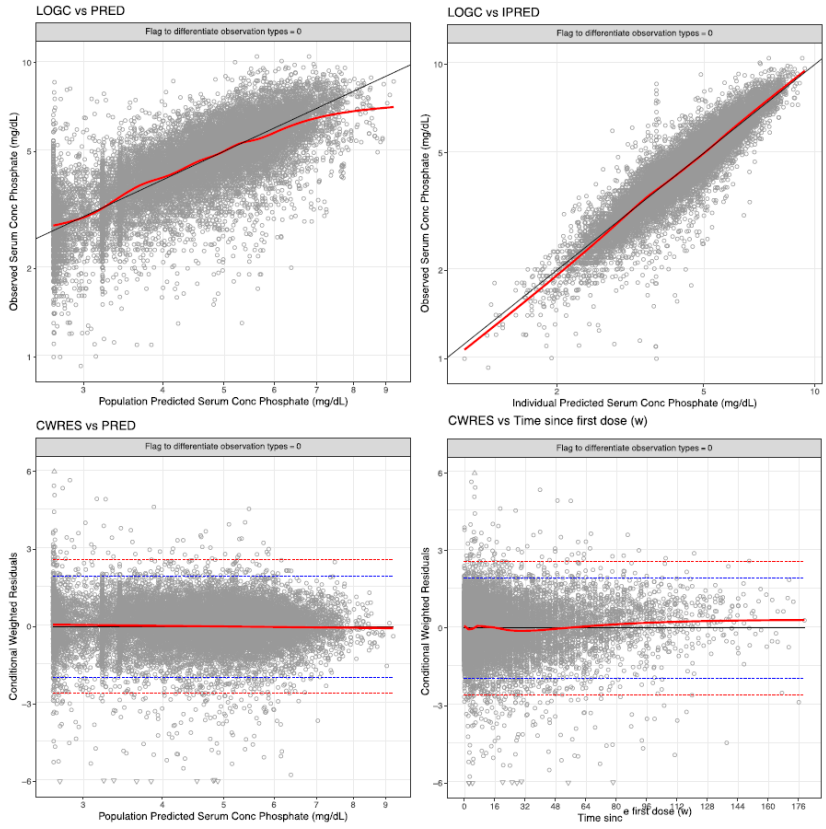
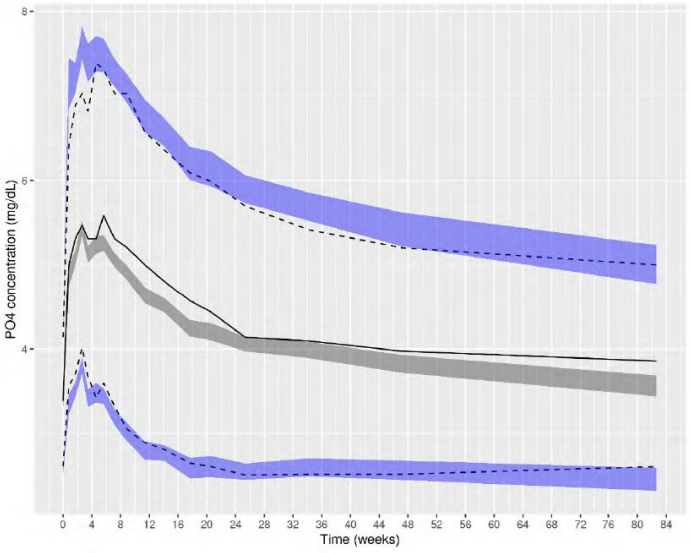


Figure 11: pcVPC of [PO4] Concentrations Versus Time Since First Dose, Final PK-PD Model



Median (solid line), 5th and 95th (dashed lines) of observed data; Percentiles of the simulated data with their 95% CI (grey and blue shaded areas).

PBPK Modelling

The DDI potential for erdafitinib was further investigated using PBPK modelling. The aim was to assess DDI potential of CYP3A4 inhibitors, CYP2C9 inhibitors, as well as CYP3A4/CYP2C9 inducers on the

pharmacokinetics of erdafitinib in patients and in poor CYP2C9 metabolising populations. In addition, the DDI potential of erdafitinib as perpetrator for transporter inhibition (Pgp and OCT2/MATE2) and for mechanism based inhibition and/or induction of CYP3A was assessed.

2.8.2.2. Pharmacodynamics

Mechanism of action

Erdafitinib is a highly selective and potent oral pan-FGFR tyrosine kinase inhibitor with high affinity and inhibitory activity at low nanomolar levels for all FGFR family members, FGFR 1, 2, 3 and 4. In FGFR pathway activated cancer cell lines, the concentration required for 50% tumour growth inhibition (IC50) is in the low nanomolar range 0.1 to 129.2 nM.

Erdafitinib demonstrated antitumour activity in FGFR-driven cell lines and xenograft models derived from multiple tumour types, including bladder cancer.

Primary and Secondary pharmacology

FIH Study EDI1001 [study design is described in section "Absorption" above]

Systemic PD, including serum phosphate concentrations, vitamin D, FGFR ligand FGF-23, calcium levels, and PTH secretion were characterised in the first-in-human Study EDI1001.

Figure 12: Mean Pharmacodynamic Markers in Blood – 1, 25-Dihydroxyvitamin D

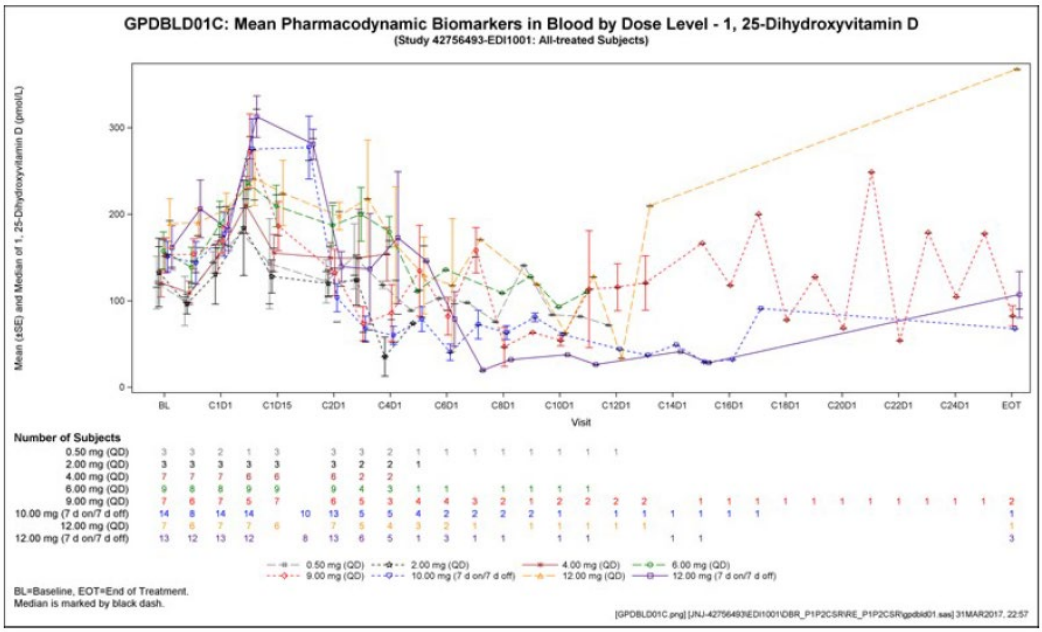


Figure 13: Mean Pharmacodynamic Markers in Blood – Intact Fibroblast Growth Factor 23

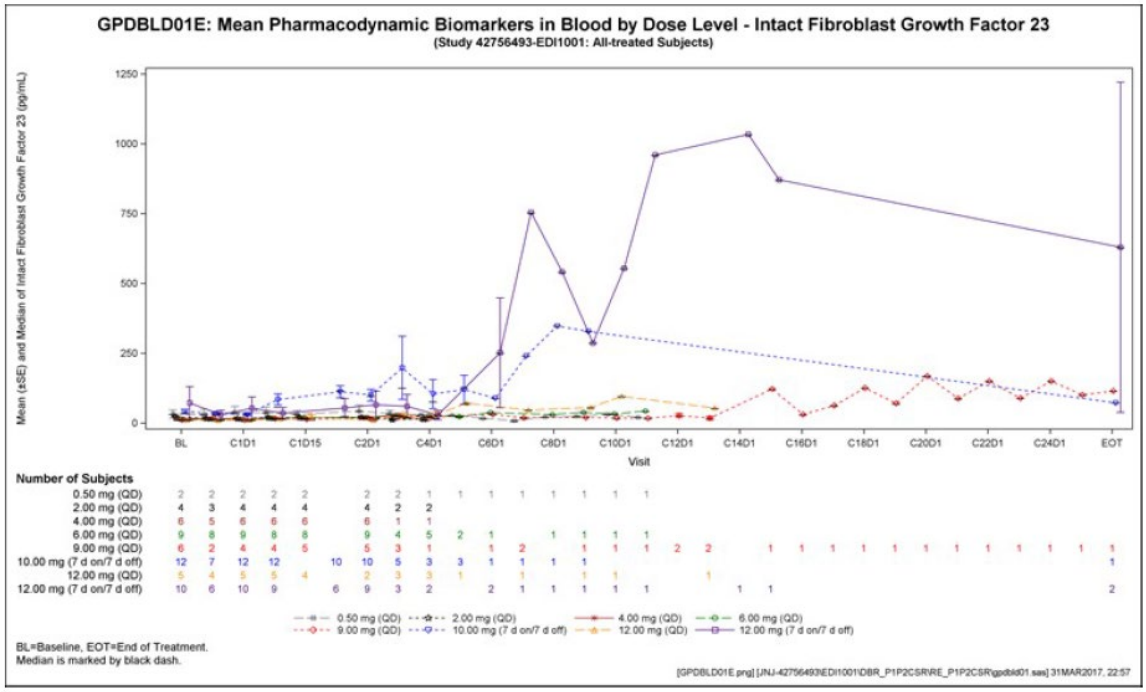


Figure 14: Mean Percent Change of Pharmacodynamic Markers in Blood – Intact Fibroblast Growth Factor 23

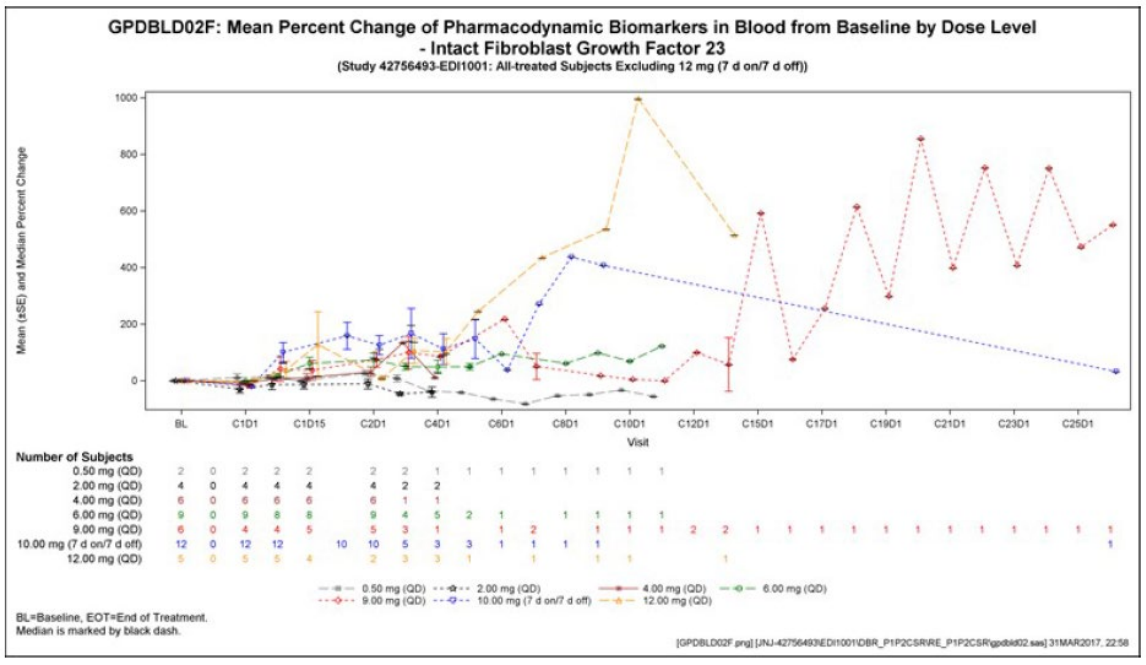


Figure 15: Mean Pharmacodynamic Markers in Blood – Calcium

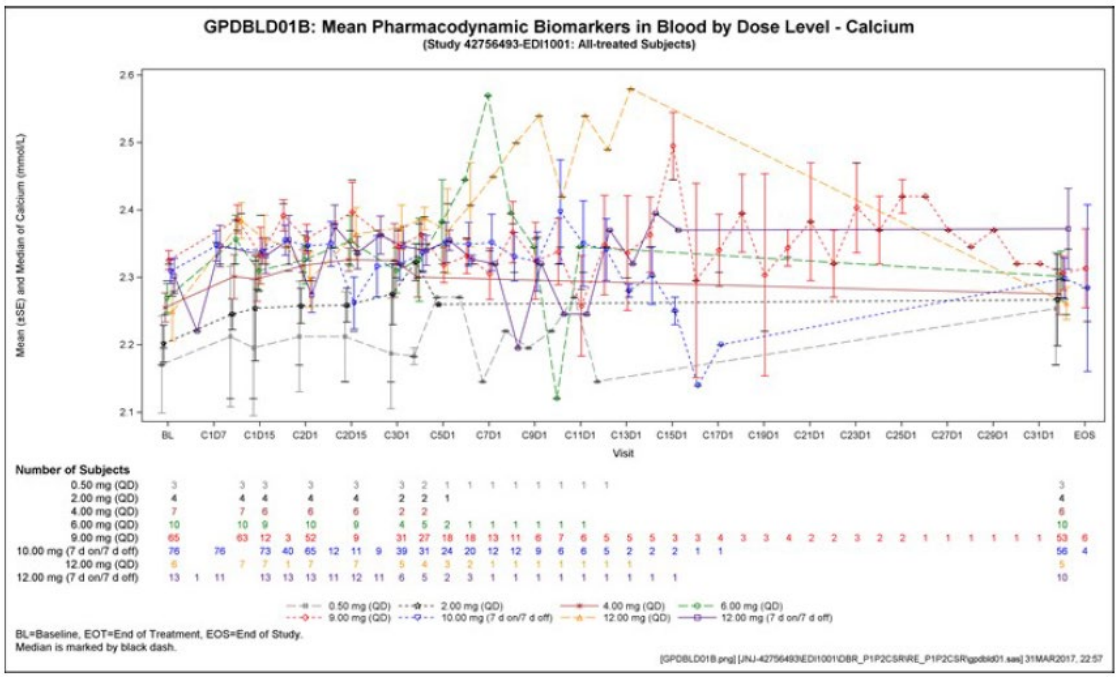


Figure 16: Mean Pharmacodynamic Markers in Blood – Intact Parathyroid Hormone

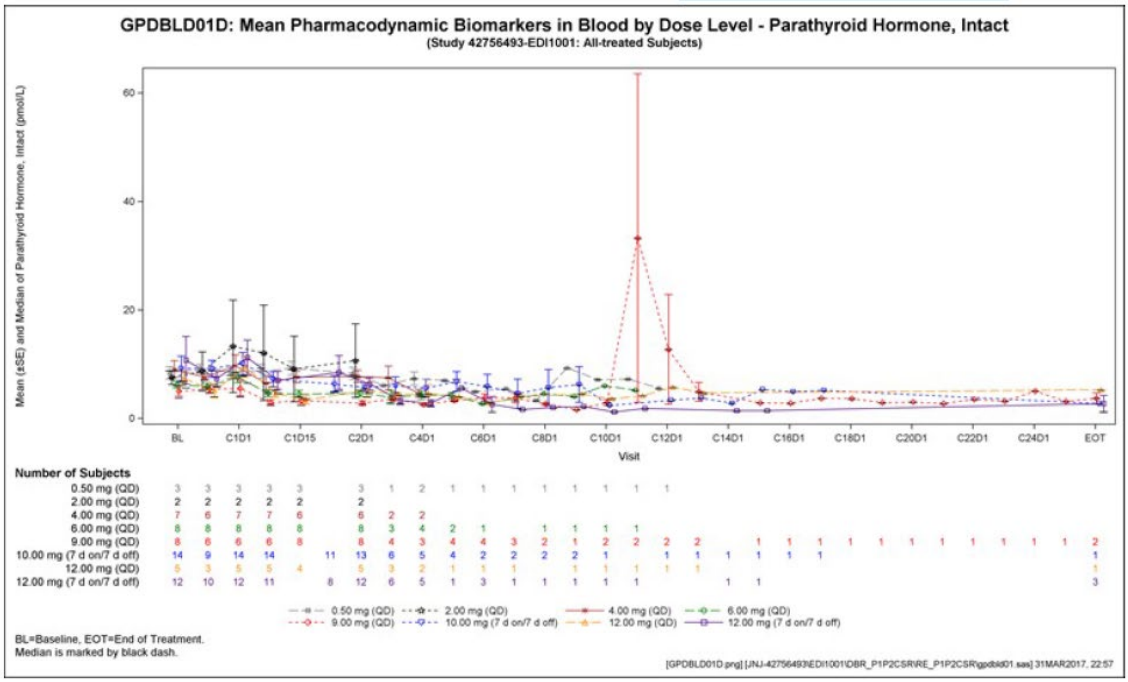
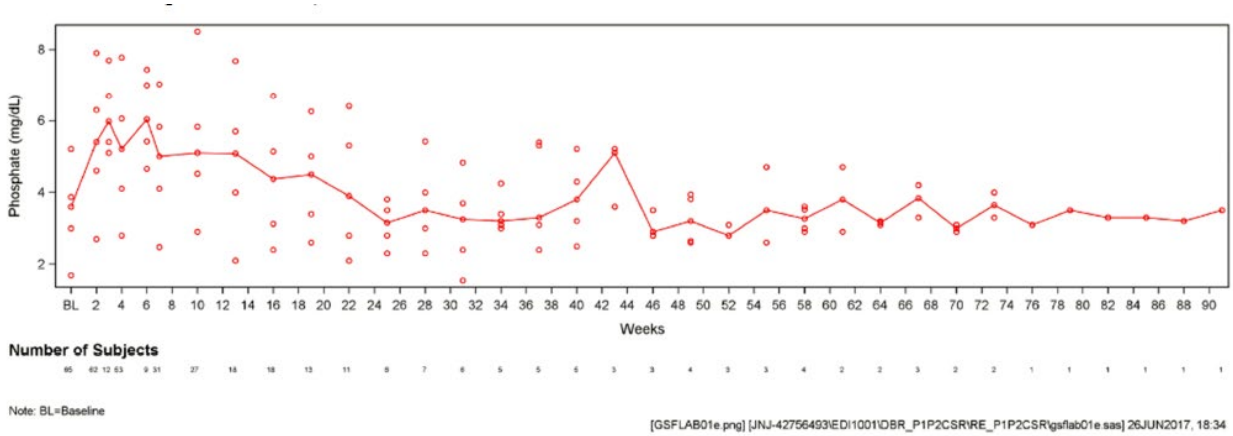


Figure 17: Phosphate Over Time (9 mg Once Daily) (Min, First Quartile, Median [Solid Line], Third Quartile, Max)



Cardiac Electrophysiology

Exposure-response analyses were conducted based on data from Study EDI1001 over a dose range from 0.5 to 12 mg from 187 subjects, including ECG obtained during study, manually read ECG by a central reader [I], and ECG extracted from Holter monitor with matching baseline [II].

The exposure-response analyses consistently indicated no significant relationship between erdafitinib plasma concentration (total and free) and change in QTc. The 2 sided 90% upper CIs at Cmax from the highest clinical dose (9 mg) was ≤2.5 ms, lower than the accepted threshold of 20 ms for oncology compounds.

Pharmacokinetic-Pharmacodynamic Relationship of Serum Phosphate

Serum phosphate concentration was identified as a relevant PD marker of target engagement with erdafitinib and selected as the metric of exposure for the E-R analysis, as it reflects both variability in the PK of free erdafitinib and individual responses to FGFR inhibition (Dosne 2022; E-R Report 2018). Serum phosphate was stated to directly reflect erdafitinib target engagement and to be closely related to erdafitinib PK-based exposure metrics: AUCfree, AUCtotal, Cmax, and Cmin.

Exposure-response Analyses of Efficacy and Safety

Serum phosphate concentration was used as the primary measure of erdafitinib exposure in analyses to describe the erdafitinib effect on both efficacy and safety endpoints.

To account for dose titration and dose interruptions and reductions, daily serum phosphate concentrations were simulated based on the individual patient's observations and the final post hoc PK-PD model parameters (Mod5.3.3.5/PopPK-PD Report 2023), and the associated exposure metrics were predicted for each participant to assess their relationship with efficacy or safety endpoints.

E-R Report 2023 quantifying the relationship between serum phosphate and OS, the primary efficacy endpoint of Study BLC3001, as well as for the secondary endpoints PFS and ORR.

The exposure-efficacy analysis was performed using Study BLC3001 Cohort 1 data collected in subjects following 1 or 2 prior line(s) of systemic therapy, with at least 1 line containing anti-PD-(L)1 treatment.

Individual average serum phosphate concentrations up to Week 6, as well as individual average serum phosphate concentrations up to an event, were evaluated and compared for the efficacy endpoints OS and PFS as exposure metrics for participants enrolled and treated in Cohort 1 (erdafitinib arm) of Study BLC3001. In addition, a time-dependent serum phosphate analysis, assuming a direct effect of

serum phosphate concentrations on the OS or PFS hazard, were performed to further investigate how variations of individual phosphate concentrations over time could affect the risk of disease progression and/or death. For participants randomly assigned to the chemotherapy-comparator arm, baseline serum phosphate levels were used as an exposure metric, given the limited fluctuation over time. A Kaplan-Meier analysis of OS, stratified by serum phosphate concentration into 4 groups ([1] chemotherapy with baseline serum phosphate concentration and [2] low, [3] medium, and [4] high average erdafitinib phosphate concentration up to Week 6 based on phosphate terciles). Univariate and multivariate Cox regression analysis models were also applied to assess the relationship with serum phosphate after adjusting by baseline prognostic factors: haemoglobin, ECOG performance status, and race. Similar analyses were conducted for PFS.

For the ORR endpoint, univariate and multivariate logistic regression models were applied to assess the relationship between serum phosphate and ORR accounting for potential baseline prognostic factors. ORR was defined as the proportion of participants achieving complete response or PR with response dichotomised as best confirmed and unconfirmed investigator-assessed response. For ORR, average serum phosphate up to Week 6 was evaluated as an exposure metric because erdafitinib is associated with an early clinical response (Dosne 2022) and because of the fluctuations in serum phosphate concentration over this period.

Results

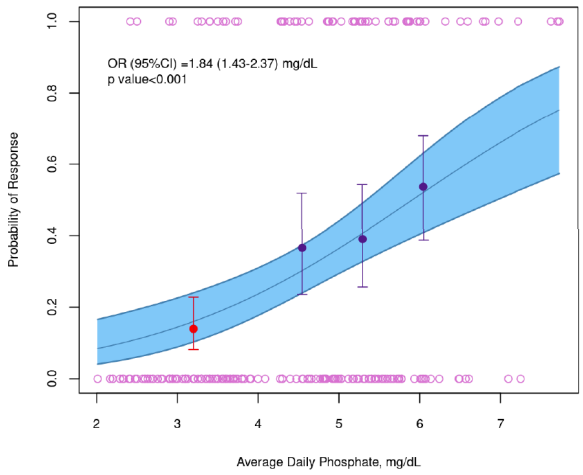
OS/PFS

The Cox proportional hazard analyses indicated that the weekly average of daily serum phosphate concentration (*PO4-Time dependent*) predicted OS and PFS better than *PO4avg 6 weeks* and *PO4avg up to event* (lowest AIC). Data not shown.

ORR

The relationship between ORR and average serum phosphate concentrations up to Week 6 (planned time of first response assessment) is shown in the figure below:

Figure 18: Probability of ORR by Investigator as a Function of $PO4_{ave,\ 6\ weeks}$ of data of Cohort 1 in Study BLC3001



The upper and lower open circles represent the presence or absence of response across the range of serum PO4 concentrations. The purple dots depict the observed incidence for the terciles of average daily serum PO4 up to Week 6 of subjects receiving erdafitinib and the corresponding vertical bars represent the 95% CI. The red dot depicts the observed incidence of median baseline serum PO4 of subjects receiving chemotherapy and the corresponding vertical bars represent the 95% CI. The full blue line and the associated

shaded area represent the model-based exposure-efficacy relationship and its 95% CI. Unconfirmed partial responses were considered as partial responses for this analysis.

The ORR increased with higher serum phosphate concentrations and resulted in an OR of 1.84 (95% CI: 1.43-2.37; p<0.001) per 1 mg/dL change in average serum phosphate concentration (see table above). The submitted report highlighted that the results obtained from Study BLC3001 Cohort 1 data are in line with the previous analysis of Study BLC2001 data, for which an OR of 1.38 was obtained (95% CI: 1.02-1.86; p=0.04).

E-R Report 2023 quantifying the relationship between serum phosphate and selected clinical safety endpoints: eye disorders (excluding CSR), CSR disorders, nail disorders, skin disorders, and GI disorders.

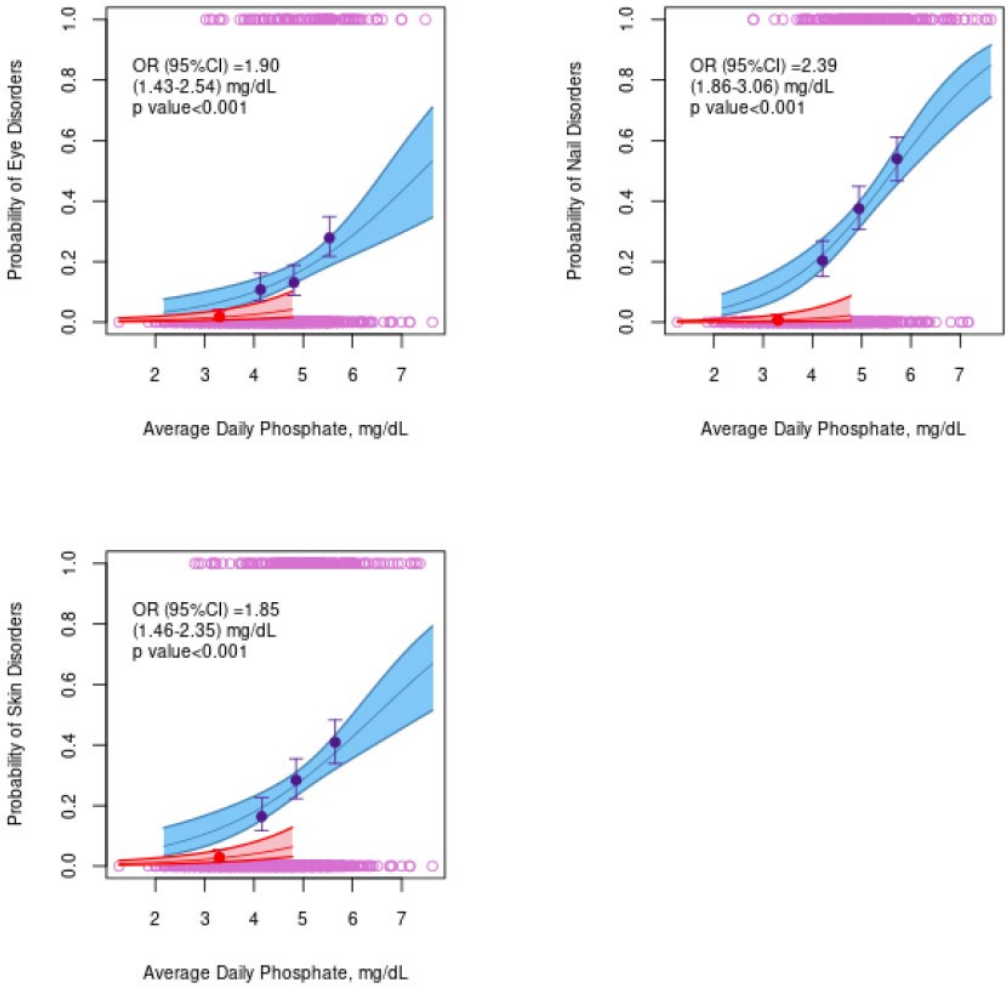
The exposure-safety analysis was performed using data obtained from 6 mg or 8 mg once daily erdafitinib monotherapy dosed patients harbouring susceptible FGFR aberrations, collected in a locally advanced or metastatic urothelial cancer population. In this context, pooled data from 814 participants in 3 studies were included. These data were from the 6 and 8 mg once daily regimens of Study BLC2001 (end of main study, 27 July 2021 clinical data cut), the erdafitinib monotherapy arm data of Study BLC2002 (30 September 2022 data cut), and data collected in Cohort 1 and Cohort 2 of Study BLC3001.

For the safety analysis, the relationships between erdafitinib serum phosphate and the incidence of the selected clinical safety endpoints were investigated using univariate logistic regression models. Participants were dichotomised into the presence or absence of the TEAEs that are at the first occurrence at such severity as to require a potential dose adaptation in the protocol: Grade ≥2 for eye disorders, Grade ≥1 for CSR disorders, Grade ≥2 for nail disorders, Grade ≥2 for skin disorders, and Grade ≥2 for GI disorders. Average serum phosphate concentration up to an event (PO4avg, event) was selected as the exposure metric for the safety analysis.

Results

The incidence of eye disorders (other than CSR), nail disorders, skin disorders, GI disorders at Grade ≥2 of severity, and CSR disorders at Grade ≥1 of severity, with a potential to require dose interruption, show a statistically significant relationship with the serum phosphate level associated with erdafitinib treatment. The incidence of eye disorders, nail disorders, and skin disorders had a positive and statistically significant relationship with average serum phosphate concentrations up to the day the disorder appeared, see figure below:

Figure 19: Probability of Experiencing Eye (Upper Left), Nail (Upper Right), and Skin (Bottom) Disorders as a Function of $PO4_{avg, event}$

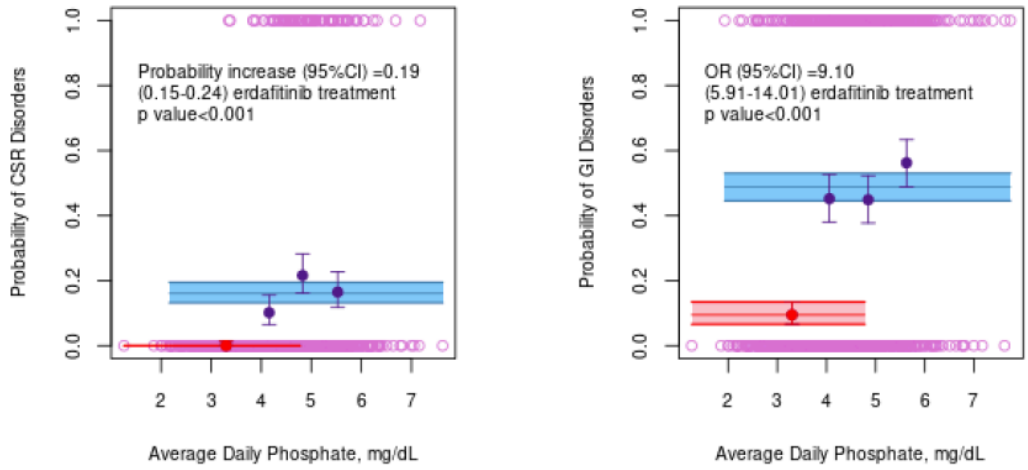


Upper and lower open circles represent the presence or absence of disorder across the range of serum PO4 concentrations. The purple dots depict the observed incidence for the terciles of average serum PO4 up to event of subjects receiving erdafitinib and the corresponding vertical bars represent the 95% CI. The red dot depicts the observed incidence of median baseline serum PO4 of subjects receiving chemotherapy and the corresponding vertical bars represent the 95% CI. The full blue and red line and the associated shaded area represent the model based exposure-efficacy relationship and its 95% CI.

Within the range of average serum phosphate concentrations observed in erdafitinib-treated participants (0.93 mg/dL to 10.5 mg/dL) in the analysis dataset, the magnitude of the association varied across the different disorders and was strongest for nail disorders, with an OR of 2.39 for a 1 mg/dL increase in serum phosphate concentrations up to the day of event, with a slightly lower OR for eye disorders (1.90) and skin disorders (1.85).

The incidence of Grade ≥1 CSR and Grade ≥2 GI disorders showed a statistically significant effect of erdafitinib treatment ($p<0.001$), but no effect of phosphate, see figure below:

Figure 20: Probability of Experiencing CSR (left) and GI (right) Disorders as a Function of $PO4_{avg, event}$



Upper and lower open circles represent the presence or absence of disorder across the range of serum PO4 concentrations. The purple dots depict the observed incidence for the terciles of average serum PO4 up to event of subjects receiving erdafitinib and the corresponding vertical bars represent the 95% CI. The red dot depicts the observed incidence of median baseline serum PO4 of subjects receiving chemotherapy and the corresponding vertical bars represent the 95% CI. The full blue and red line and the associated shaded area represent the model based exposure-efficacy relationship and its 95% CI.

The relationship of serum phosphate with CSR, significant for Study BLC2001 with OR of 1.97, was not statistically significant for the current analysis.

The probability of CSR disorders (a known class effect of FGFR inhibitors) in the erdafitinib arm was 19% compared with pembrolizumab or chemotherapy, where there was no observed incidence of CSR disorders. The OR of GI disorders comparing erdafitinib to treatment with pembrolizumab or chemotherapy was 9.1.

Exposure-response Analyses of Safety E-R relationship between the change from baseline in QTc intervals (QTcF and QTcB) and total and unbound plasma concentration of erdafitinib [*Analysis I*]

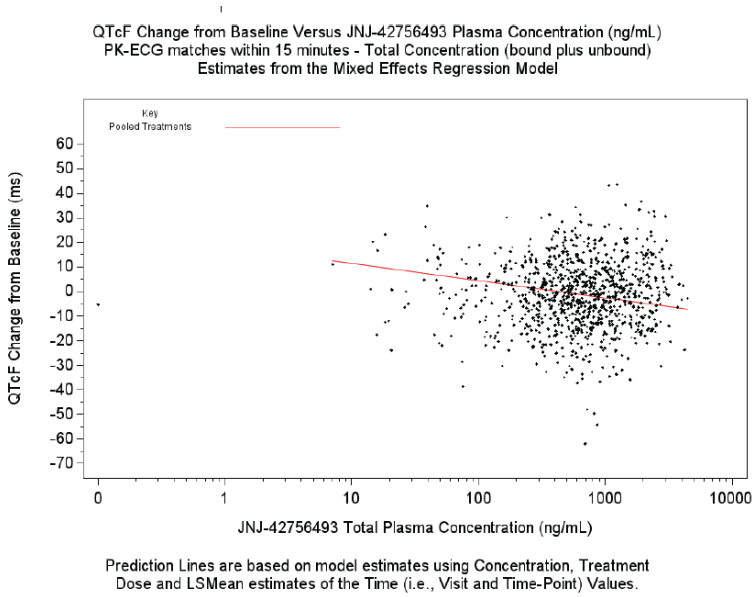
A pharmacokinetic-pharmacodynamic (PK-PD) analysis was performed using all subjects who had time-matched ECG and plasma concentrations for JNJ-42756493 [*erdafitinib*]. The primary analysis was performed using ECGs (mean of triplicates or whatever number of ECGs are available at a timepoint) and PK assessments which were collected within a +/- 15 minute window. A secondary analysis was performed using a wider +/- 60 minute window. The primary analyses were performed using the total plasma concentration of JNJ-42756493, and the secondary analyses were performed using the unbound plasma concentration of JNJ-42756493.

The PK-PD analysis was a concentration response analysis of a baseline-adjusted QTc (ΔQTc) (QTcF and QTcB) against the independent variables of plasma concentration of JNJ-42756493, and time (i.e., the nominal time post dose categorically). The primary endpoint for this trial was the change from baseline in QTcF. A negative result (i.e., no evidence of a QTc prolongation) was defined as a model based upper bound of the two-sided 90% CI of the predicted mean ΔQTcF less than 20 ms at the observed mean Cmax for the therapeutic dose of JNJ-42756493. If modelling was completed with plasma concentration on the log scale, the geometric mean Cmax was used for this calculation.

A linear mixed effects modelling approach was used to examine the E-R relationship between the change from baseline in QTc intervals (QTcF and QTcB) and total and unbound plasma concentration of erdafitinib. The model included plasma concentration, time (categorical), and treatment with random subject effects on plasma concentration and the intercept included in the model. This model was used to estimate the population slope and the standard error of the slope of the relationship between change from baseline in QTc intervals and other ECG continuous parameters (QTcF and QTcB) and plasma concentration of erdafitinib.

The results of this PK-PD model showed that the slope for QTcF for erdafitinib was negative, see figure below:

Figure 21: Relationship between Total Plasma Concentration of Erdafitinib and ΔQTcF (ECG and PK collections within +/- 15 minute window) by Pooled Treatment



The overall predicted baseline-corrected QTcF value at the geometric mean Cmax (1263 ng/mL) was -4.0 ms with an upper bound of the 2-sided 90% CI of -1.2 ms, see details in the table below:

Table 37: Treatment-Specific Change from Baseline versus the Total Plasma Concentration of erdafitinib - Predicted from Mean Cmax QTc Fridericia (msec). Pharmacokinetic-Pharmacodynamic Population; +/- 15 Minute Window for ECGs and PK

Treatment Dose	Geometric Mean C_{max} (arithmetic scale) (ng/mL) [1]	Mean C_{max} (log scale) [1]	Predicted Mean Effect at Mean C_{max} (ms) [3]	Lower CI (ms) [2]	Upper CI (ms) [2]
0.50 mg Liquid	63.52	1.803	6.378	-7.214	19.481
2.00 mg Liquid	370.34	2.569	-7.758	-14.12	-1.997
4.00 mg Liquid	569.82	2.756	-0.720	-3.504	1.973
6.00 mg Liq/Cap	852.29	2.931	-8.438	-11.49	-5.544
9.00 mg Capsule	1453.46	3.162	-0.849	-2.831	0.990
10.00 mg Capsule (7d on/7d off)	1499.03	3.176	-2.136	-4.192	-0.096
12.00 mg Capsule	2206.04	3.344	-3.047	-5.749	-0.366
12.00 mg Capsule (7d on/7d off)	2060.57	3.314	-0.710	-3.356	1.878
Pooled Treatments	1262.56	3.101	-4.031	-6.992	-1.205

[1] Geometric Mean Cmax and Mean Cmax (log scale) were estimated as the geometric mean of Cmax values and arithmetic mean of the logtransformed
Cmax values, respectively, of the absolute maximum concentration observed in each individual (i.e., in any PK occasion).
[2] Lower/Upper Confidence = upper one-sided 95% linear mixed model based confidence limit, based on bootstrap methods using
percentile confidence intervals with 1000 replicates.
[3] Estimates include the mean values for time included in the model. This varies from the Garnett et al. 2016 model specifications

For the highest dose group, 12 mg daily, the overall predicted baseline-corrected QTcF value at the geometric mean Cmax (2206 ng/mL) was -3.0 ms with an upper bound of the 2-sided 90% CI of -0.4 ms. Similar results were obtained using free concentrations.

Exposure-response analysis to describe the exposure-response (ER) relationships between total and free erdafitinib plasma concentration and QT/QTc interval changes extracted from Holter monitors from Part 1 of the Phase 1 Study EDI1001 [*Analysis II*]

Holter recordings were obtained from Part 1 of Study EDI1001 at screening, on Cycle 1 Day 1, and at steady state on Cycle 2 Day1, and Cycle 3 Day 1. ECG measurements were obtained at the same time as total and free erdafitinib plasma concentrations, resulting in paired PK-ECG measurements. The time-matched QT measurements at screening were used as baseline. ΔQTcI was selected as the dependent variable since Fridericia's correction was not sufficient to correct for heart rate. After confirming the lack of hysteresis and the linearity of the drug effect, the linear mixed effect model including ΔQTcI as the dependent variable, the erdafitinib plasma concentration (total or free), Cp, as a continuous covariate and each nominal post-dose timepoint (timei) as categorical factors was used to analyse the data.
The outcome of this analysis was compared with the results obtained when QTcF was used.

The final dataset included 62 subjects with 704 paired PK and Holter ECG data for the analysis based on total concentrations. A total of 1142 Holter ECG measurements were used with 438 ECGs included as baseline time-matched (Screening), and 375, 324, and 5 ECGs obtained on Cycle 1, Cycle 2, and

Cycle 3, respectively. For the analysis based on free concentrations, a total of 685 free erdafitinib concentrations from 60 subjects were available. The number of Holter ECG measurements at baseline, Cycle 1, Cycle 2, and Cycle 3 were 424, 362, 318, and 5, respectively.

A linear mixed-effect model was fitted to the data with ΔQTcI as dependent variable, erdafitinib plasma concentrations as continuous independent variable, and each $time_i$[1] as categorical covariate. While the inclusion of a random intercept term improved model fit both for total and free concentration models, the addition of a random slope of the erdafitinib plasma concentration effect did not improve model fit. This finding was consistent for the models where total and free erdafitinib plasma concentrations were used as independent variables.

The estimated parameters of the final model for total and free erdafitinib plasma concentrations and QTcI are shown in the tables below:

Table 38: Final Parameter Estimates for the Exposure-Response Model with Erdafitinib Total Plasma Concentrations and ΔQTcI

	Estimate	Lower Limit 95% CI[a]	Upper Limit 95% CI[a]	Pr(>|t|) [b]
Intercept (ms)	2.783	-2.413	7.975	0.297
Slope (ms/(ng/mL))	**-0.00269**	**-0.00498**	**-0.000387**	**0.0229**
Timepoint 1 h (ms)	-0.469	-6.223	5.308	0.874
Timepoint 2 h (ms)	1.171	-4.625	6.995	0.694
Timepoint 3 h (ms)	0.469	-5.291	6.262	0.874
Timepoint 4 h (ms)	-4.196	-9.885	1.521	0.151
Timepoint 6 h (ms)	-3.529	-9.173	2.143	0.224
Timepoint 8 h (ms)	-2.396	-8.028	3.264	0.408
Timepoint 24 h (ms)	-2.810	-9.971	4.373	0.445

Pr(>|t|): p-value
a Model parameters were reported with a 95% CI for significance in the model.
b Calculated with Kenward-Roger approximations to degrees of freedom.

Table 39: Final Parameter Estimates for the Exposure-Response Model with Erdafitinib Free Plasma Concentrations and ΔQTcI

	Estimate	Lower Limit 95% CI[a]	Upper Limit 95% CI[a]	Pr(>|t|) [b]
Intercept (ms)	3.355	-1.941	8.646	0.217
Slope free (ms/(ng/mL))	**-1.138**	**-1.968**	**-0.308**	**0.00813**
Timepoint 1 h (ms)	-0.473	-6.295	5.365	0.874
Timepoint 2 h (ms)	0.796	-5.080	6.688	0.792
Timepoint 3 h (ms)	0.720	-5.119	6.582	0.810
Timepoint 4 h (ms)	-4.405	-10.165	1.375	0.137
Timepoint 6 h (ms)	-3.165	-8.879	2.568	0.281
Timepoint 8 h (ms)	-2.645	-8.344	3.073	0.366
Timepoint 24 h (ms)	-3.056	-10.234	4.135	0.408

Pr(>|t|): p-value
a Model parameters were reported with a 95% CI for significance in the model.
b Calculated with Kenward-Roger approximations to degrees of freedom.

Model parameters were reported with 95% CI to evaluate the significance in the model. The slopes for total and free erdafitinib plasma concentrations were the only significant parameters and were

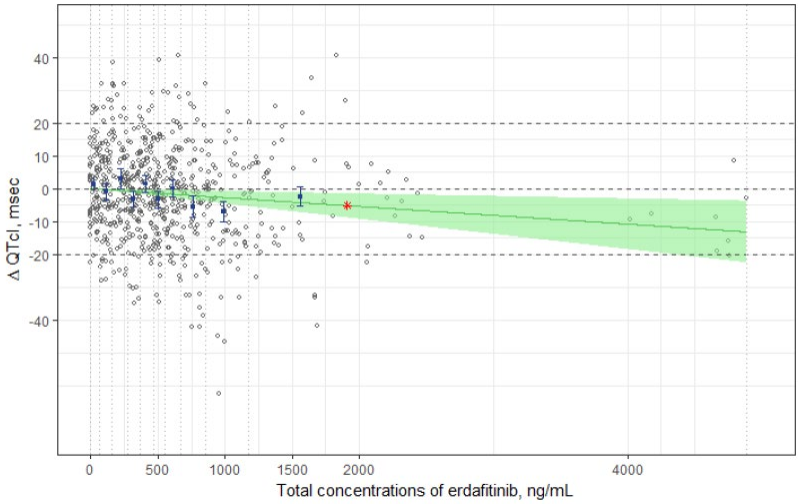
[1] $time_i$: nominal post-dose timepoint

estimated at -0.00269 ms/(ng/mL) and -1.138 ms/(ng/mL), respectively, indicating that increases in erdafitinib plasma concentrations resulted in decreased QTcI. The ratio of the slopes for total and free erdafitinib plasma concentrations, 0.00236, was consistent with the free fraction estimated for erdafitinib. The results obtained with the final model when using ΔQTcF as the dependent variable were comparable.

The model-predicted mean ΔQTcI at the observed geometric mean of the Cmax for total (1911 ng/mL) and free (4.51 ng/mL) plasma concentration at steady state following a 9-mg dose of erdafitinib was -5.1 ms (90% CI: -8.8, -1.5 ms) and -5.1 ms (90% CI: -8.3, -2.0 ms), respectively.

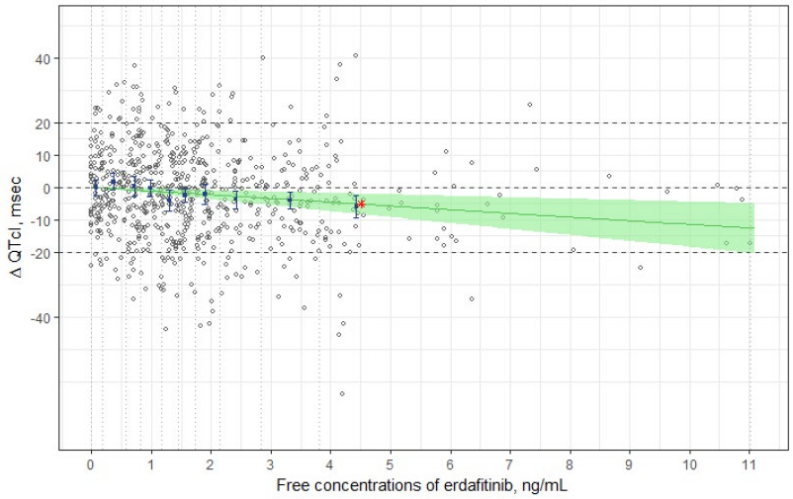
See figures below:

Figure 22: ΔQTcI versus Erdafitinib Total Concentrations



Solid green line (+shaded area): model-predicted mean ΔQTcI (+90% CI). Blue boxes (+vertical bars): observed arithmetic means (+90% CI) for the ΔQTcI within each plasma concentration decile. Red star represents ΔQTcI predicted for the geometric Cmax at steady state of a 9-mg dose (1911 ng/mL). Observed ΔQTcI were corrected by the estimated individual intercept and the effect of each timepoints, which were not considered to be related to the plasma concentration effect of erdafitinib.

Figure 23: ΔQTcI versus Erdafitinib Free Concentrations



Solid green line (+shaded area): model-predicted mean ΔQTcI (+90% CI). Blue boxes (+vertical bars): observed arithmetic means (+90% CI) for the ΔQTcI within each plasma concentration decile. Red star represents ΔQTcI predicted for the geometric Cmax at steady state of a 9-mg dose (4.51 ng/mL). Observed ΔQTcI were corrected by the estimated individual intercept and the effect of each timepoints, which were not considered to be related to the plasma concentration effect of erdafitinib.

The upper limit of the 2-sided 90% CI of the model-predicted mean ΔQTcI was below 20 ms at the observed geometric mean of the total and free Cmax at steady state following a 9-mg dose of erdafitinib.

Consistent with the results on ΔQTcI, the model-predicted mean ΔQTcF at the observed geometric mean of the Cmax for total (1911 ng/mL) and free (4.51 ng/mL) plasma concentration at steady state following a 9-mg dose of erdafitinib was -4.4 ms (90% CI: -8.0, -0.8 ms) and -4.5 ms (90% CI: -7.5, -1.4 ms), respectively. Since the upper limit of the 2-sided 90% CI of the model-predicted mean ΔQTcF was below 20 ms at the observed geometric mean of the total and free Cmax at steady state following a 9-mg dose of erdafitinib, the provided CSR concluded that erdafitinib does not prolong the QTcF.

2.8.3. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetic data from study EDI1005 (ADME) in healthy volunteers showed that erdafitinib is readily absorbed after administration as oral solution, with T_{max} values around 2.5 hours. The t_{max} value in the SmPC including range is taken from EDI1006 which was adequately justified.

In subjects with advanced or refractory solid tumours or lymphoma in study EDI1001 (FTIH), after a single dose (Cycle 1 Day 1) in the 76 participants with serial PK sampling, t_{max} values ranged between 1.00- and 3.44-hours post-dose across the different cohorts and was independent of dose.

After multiple doses at steady state in the continuous dose cohorts, mean accumulation ratios based on Cmax ranged between 2.74 and 3.94 and based on AUC_{τ} between 3.08 and 4.96.

For SD and MD, Cmax and AUCs increased with increasing dose without consistent or significant deviations from the dose-proportionality across the range of dose levels and results are reported in section 5.2 of the SmPC.

The SmPC´s information "*Following administration of 8 mg once daily, the proposed starting dose, mean (coefficient of variation [CV%]) erdafitinib steady-state Cmax, AUC_{τ}, and minimum observed*

plasma concentration (Cmin) were 1399 ng/mL (50.8%), 29268 ng.h/mL (59.9%), and 936 ng/mL (64.9%). Daily fluctuations in erdafitinib plasma concentrations were low, with a mean (CV%) peak-to-trough ratio of 1.47 (23%) at steady state upon daily dosing." are based on additional pharmacokinetic analyses of individual dose normalised PK parameters pooled over dose levels based on results of Clinical Study EDI1001.

Based on non-clinical data, erdafitinib was 99.7% bound to human plasma proteins. The plasma to blood ratio was 0.60, with no concentration dependency. The mean apparent volume of distribution of erdafitinib in patients with cancer was 0.411 L/kg (see SmPC 5.2).

The results of mass balance study EDI1005 indicate that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway: Excretion of radioactivity was primarily via faeces (68.7%), with unchanged drug representing 14.1% to 20.8% of the total dose. Radioactivity was also excreted in the urine (18.7%), with unchanged drug being the major entity (11.3%). Statements in the SmPC in section 5.2 on excretion are adequately justified.

Results from *in vitro* studies suggest that mainly CYP2C9 and CYP3A4 are responsible for erdafitinib biotransformation in human (refer to Non-Clinical Part of the dossier): Erdafitinib metabolism in human liver microsomes was low. Therefore, human hepatocytes were considered a more suitable system to investigate the involvement of CYP enzymes. The formation of M6 was inhibited by ketoconazole by 22% and by sulphaphenazole by 90.6% indicating that CYP2C9 is mainly involved in M6 metabolic pathway with a minor contribution of CYP3A4. The formation of M8 is largely mediated by CYP3A4 as it was inhibited by ketoconazole by 73%. These results were further confirmed by metabolic profile in CYP-specific supersomes.

Possible influence of CYP2C9 polymorphism on erdafitinib exposure was investigated as part of Clinical DDI study EDI1007 and via PBPK and PopPK analysis. Results from Clinical Study EDI1007 do not indicate clinically significant effects on PK in patients with CYP2C9*1/*2, and CYP2C9*1/*3 genotype compared to wild type CYP2C9*1/*1. The popPK analysis supports that there is no significant effect of CYP2C9 status on clearance. However, these results are based on n=75 for intermediate and n=11 for poor metabolisers. Based on the aforementioned results, it is agreed that no need for an individualised dose adjustment based on CYP2C9 polymorphism is indicated. As outlined above, predictions from PBPK modelling should not be used in the SmPC.

Food effect

Food effects were investigated in cross-over study EDI1006. Cmax, AUClast, and AUC∞ were comparable under fasted and fed conditions. The 90% CIs of the GMRs of Cmax, AUClast, and AUC∞ were within the standard bioequivalence range of 80% to 125%. Based on the provided study results from study EDI1006 investigating the phase III formulation it is agreed that no clinically relevant effect of food on erdafitinib PK would be expected. According to the Clinical Study Protocol in the pivotal Phase III study, subjects were to avoid consuming grapefruit or Seville oranges due to CYP450 3A4/5 inhibition and this information is also stated in section 4.5 of the SmPC.

The SmPC does not include information for patient who cannot take the whole tablets. According to the applicant nothing is known about reported "swallowability issues" from any of the studies in the adult clinical development programme, including the mUC population. The combination of the small size of the tablets and the film coating would improve swallowability in the elderly subject population. The reason for not breaking or crushing the tablet seems to be due to avoiding unnecessary inhalation of the tablet particles during the process. In conclusion, section 4.2 of the SmPC clarifies that the tablets should be swallowed whole. For the future the applicant is to consider the Reflection paper on "Pharmaceutical-development of medicines-for use-in the older-population".

Special Populations

Clinical pharmacology studies were conducted to evaluate the effect of race and hepatic impairment but not the role of impaired renal function, age and gender.

Hepatic impairment

A formal dedicated Study EDI1008 investigating the effect of mild and moderate hepatic impairment (HI) on the PK of erdafitinib has been performed. With regard to hepatic status, subjects were graded according to the Child-Pugh Classification. This is acceptable as the recommended metric for hepatic function classification was used. As per the provided results, compared to normal hepatic function group, Cmax and AUCs of total erdafitinib decreased by 17.0% and 17.7% respectively for mild HI, and by 26.4% to 38.6% respectively for the moderate HI group. However, Cmax and AUCs of free erdafitinib were comparable in both mild and moderate HI groups, compared to those observed in the normal hepatic group with a maximum decrease of 12.6%. As reflected in 5.2 of the SmPC, no clinically meaningful differences were observed. For the severe HI group, PK of erdafitinib was not characterised as only very limited numbers of subjects (n=2) were available; therefore no formal conclusion could be drawn for this subgroup of patients (see section 4.2 of the SmPC).

Impact of HI on erdafitinib PK was also investigated as part of the Pop-PK analysis using ALT and AST values as a marker of hepatic function. As per the provided classification, the majority of subjects, 914 (80%) and 220 (19.3%) were graded as normal hepatic function and mild HI respectively. The number of patients with moderate and severe hepatic impairment was too limited (n=3, n=1, respectively) to allow meaningful conclusions. The analysis indicated that there was no clinically meaningful effect of mild HI on the systemic exposure of erdafitinib. However, such results should be regarded with caution as the recommended Child-Pugh metric for hepatic function was not used.

Overall, based firstly on results from the formal study, no dose adjustment is required for patients with mild or moderate hepatic impairment (see SmPC 4.2). Alternative treatment should be considered in patients with severe hepatic impairment.

Renal impairment

No dedicated study was performed in subjects with renal impairment, and this appears acceptable given the low renal excretion of erdafitinib observed in the mass balance study EDI1005 (approximately 13.3% of the total administered dose) and since a major impact of renal impairment on erdafitinib PK does not seem likely.

Impact of renal impairment on erdafitinib PK was investigated as part of the Pop PK analysis using both creatinine clearance (CLCR expressed in mL/min) and estimated glomerular filtration rate (eGFR expressed in mL/min/1.73m2). CLCR was tested in the model and was not found to be statistically significant at the predetermined significance level (p>0.001). The Pop-PK dataset included n=412 (36.1%), n=421 (36.9%), n=301 (26.4%) and n=8 (0.7%) subjects with normal renal function, mild, moderate and severe renal impairment, respectively. It is noted that the numbers of patients included in the severe category is too low and not considered sufficient to detect a potential clinically relevant change in clearance. Therefore, no formal conclusion could be drawn for this subgroup of patients. Overall, no dose adjustment is needed in patients with mild and moderate RI, as reflected in SmPC 4.2.

Information regarding renal impairment is presented in section 5.2 of the SmPC.

With regard to renal impairment, pcVPCs stratified by renal impairment were also submitted and further supported that no dose adjustment is required for patients with mild or moderate renal impairment (data not shown).

Race

Results from studies in Asian patients (GAC1001 and HCC1001) were generally in line with results from non-Asian participants.

Even though race/ethnicity did not have a significant effect on erdafitinib PK in the population PK analysis, it should be noted that races other than Asian and Caucasian were minimally represented in the dataset.

Body weight

The mean (range) body weight (BW) was 72.0 kg (36-166 kg, excluding 3 paediatric participants). In the Pop-PK analysis, BW was identified as a statistically significant covariate on the clearance CLfree and the central and peripheral compartments (V2, V3, V4) for erdafitinib with exponent effects (allometric scaling) of 0.589 and 0.447, respectively (both lower than the classical values of 0.75 and 1). Therefore, CLfree and the volumes parameters of erdafitinib were found to increase with increasing BW; range of78.3-157 L/h for CL and 17-43 L for volume among the range of bodyweight observed in the pooled population dataset.

To investigate the effect of BW categories on erdafitinib steady state AUCfree BW was categorised in 3 different categories: <60 kg, 60 to 80 kg (reference), and >80 kg. Based on provided Pop-PK model simulations, predicted mean ratio [CI: 5th-95th] of normalised steady state AUCfree was 1.16 [0.71-2.09] for BW <60 kg and 0.86 [0.49-1.40] for BW >80 kg relative to the reference group of weight [60-80 kg]. Thus, patients with lower body weight will have relatively higher exposure and in the contrary patients with higher body weights will have lower exposure relative to the reference BW. A significant increase on the systemic exposure to free erdafitinib, up to 209% (doubling), is expected in patients with extreme lower BW and a significant decrease, up to reduction by half, is expected in patients with extreme higher BW relative to the reference BW. Simulations of AUCfree for the extreme low [30-40 kg], [40-50 kg] and high [120-130 kg], [130-140 kg] and [>140 kg] body weight ranges in comparison to the reference systemic exposure were presented. Based on the results, there is no need for dose adjustment in obese and underweighted patients.

Age

No or very limited PK / clinical data are provided in the paediatric population <18 years. Erdafitinib is not indicated for the treatment of locally advanced unresectable or metastatic urothelial cancer. Only adult population is claimed. This is clearly stated in section 4.2 of the SmPC and is agreed.

The mean (range) age was 60.9 years (21-92 years, by excluding 3 paediatric participants.

In the Pop-PK analysis, age was identified as a statistically significant covariate on the oral clearance CL. Age was categorised in 3 different subgroups: <65 years old (reference, n=664), 65 to 75 years old (n=367) and >75 years old (N=111). In elderly, oral CL is expected to decrease with age by 15.2% in the [65-75 years] group and by 20.6% in the >75 years group in comparison to patients <65 years old. Overall, the applicant’s conclusion that no dose adjustment is needed in elderly could be agreed.

DDIs

Erdafitinib is a substrate for P-gp. P-gp inhibitors are not expected to affect the PK of erdafitinib in a clinically relevant manner. Erdafitinib has adequate solubility across the pH range of 1 to 7.4. Acid lowering agents (e.g., antacids, H2-antagonists, or proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib. No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed in patients taking sevelamer.

Drug-drug interactions have been discussed based on the provided results of *in vitro* studies using human biomaterial, clinical DDI studies in healthy volunteers and patients (*in vivo*) as well as PBPK modelling (*in silico*). Overall, potential DDIs with erdafitinib as a victim or perpetrator have been adequately investigated and relevant information are included in sections, 4.4 and 4.5 of the SmPC.

Pharmacodynamics

Mechanism of action

Activating mutations and translocations in FGFR genes have been associated with neoplastic progression and tumour vascularisation in multiple cancer types including, most commonly, UC (Dienstmann 2014; Parker 2014). Several lines of evidence point to deregulation of FGFR signalling (e.g., via FGFR mutation and gene fusion) being involved in bladder cancer pathogenesis (Babina 2017; Dienstman 2014; Touat 2015). Recurrent FGFR mutations and gene fusions are observed in urothelial cancer (Robertson 2017).

Preclinical models have shown that expression of FGFR mutations and gene fusions leads to increased cellular proliferation, and FGFR altered bladder cancer cell lines have shown sensitivity to FGFR inhibition *in vitro* and *in vivo (*Dienstmann 2014;Touat 2015).

Targeting FGFRs is aiming on simultaneously inhibiting tumour cell growth, survival, and migration, as well as tumour angiogenesis (Beenken 2009; Turner 2010; Wesche 2011).

Erdafitinib is a highly selective and potent oral pan-FGFR tyrosine kinase inhibitor with high affinity and inhibitory activity at low nanomolar levels for all FGFR family members, FGFR 1, 2, 3 and 4.

Primary pharmacology

Systemic PD, including serum phosphate concentrations, vitamin D, FGFR ligand FGF-23, calcium levels, and PTH secretion were characterised in the first-in-human Study EDI1001.

Pharmacodynamic biomarkers measured in the blood showed that:

- Vitamin D3 levels started to increase by 24 hours after the first dose, peaked in average with a change of approximately 100% across doses and then began to decline with average levels returning to near baseline levels around cycle 4.
- FGF23 overall increased mildly compared to baseline.
- Calcium levels remained overall stable.
- PTH levels, after a very modest initial peak, mildly decreased compared to baseline.
- Dose dependent increases in phosphate levels were observed at the first assessed time points. Phosphate levels peaked between Cycles 1 and 2 of treatment. Phosphate level changes from baseline declined over time beginning at approximately Cycle 3 of treatment.

Population PK-PD modelling used an Emax model to describe the erdafitinib effect on PO4 driven by free concentrations in the effect compartment, with an attenuation of the erdafitinib effect on serum [PO4] with time, used to describe the relationship between erdafitinib free plasma concentrations and serum [PO4]. This model characterised serum [PO4] and their variability in subjects with cancer treated with different dosing regimens of erdafitinib. Diagnostic plots showed an underprediction for the first 6 months of the study as well as an underprediction of the variability but overall described the effect of erdafitinib on [PO4] reasonably well.

Secondary Pharmacology / Exposure-response Analyses of Safety E-R relationship between the change from baseline in QTc intervals (QTcF and QTcB) and total and unbound plasma concentration of erdafitinib

Exposure-response analyses were conducted based on data from Study EDI1001 over a dose range from 0.5 to 12 mg from 187 subjects, including ECG obtained during study, manually read ECG by a central reader [I], and ECG extracted from Holter monitor with matching baseline [II].

The submitted analysis [I and II] are based on data for exposures after doses of up to 12 mg erdafitinib per day in clinical study EDI1001. Analysis I is based on preliminary data (Jan 26, 2015 data cut-off, see eRT report). For Analysis II, mean ΔQTcI was always calculated for the observed mean of the Cmax for total (1911 ng/mL) and free (4.51 ng/mL) plasma concentration at steady state following a 9-mg dose of erdafitinib. The submitted exposure-response analysis based on time-matched QTc Holter data do not indicate a critical effect of erdafitinib on cardiac repolarisation.

Nevertheless caution is advised when administering Balversa with medicinal products known to prolong the QT interval or medicinal products with a potential to induce torsades de pointes, such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, ibutilide) antiarrhythmic medicinal products, macrolide antibiotics, SSRIs (e.g., citalopram, escitalopram), methadone, moxifloxacin, and antipsychotics (e.g., haloperidol and thioridazine) (SmPC section 4.4).

Pharmacodynamic interactions

During the procedure, a discussion on whether concomitant use of medicinal products that can alter serum phosphate levels might be problematic in the initial dose increase period based on serum phosphate levels have been submitted (Data not shown). Based on the data presented it is reasonable to advise against the use of concomitant medications with the potential to alter serum phosphate levels during the period up to the up-titration decision and proposed to add respective information in section 4.5 of the SmPC.

Exposure-response analyses of efficacy following treatment with erdafitinib

This exposure-response analysis quantifies the relationship between serum phosphate and OS, the primary efficacy endpoint of Study BLC3001, as well as for the secondary endpoints PFS, ORR, and DOR. The exposure-efficacy analysis was performed using Study BLC3001 Cohort 1 data.

The Cox proportional hazard analyses indicated that the weekly average of daily serum phosphate concentration (PO4-Time dependent) predicted OS and PFS better than PO4avg 6 weeks and PO4avg up to event (lowest AIC).

For ORR, an increase in average serum PO4 concentrations up to 6 weeks was found to significantly increase ORR as assessed by the investigator.

As reflected in SmPC 4.2, daily doses can be up-titrated to 9 mg once daily if the serum phosphate level is <9.0 mg/dL (serum phosphate level should be assessed between 14 and 21 days after initiating treatment) and there is no drug-related toxicity. However, patients should not be actively further up-titrated based on phosphate levels. Therefore, the relevance of information about phosphate as an indicator of PD activity (reflects target engagement) for the prescriber could be regarded minor.

Exposure-response analysis of safety following treatment with erdafitinib

This exposure-response analysis quantifies the relationship between serum phosphate and selected clinical safety endpoints: eye disorders (excluding CSR), CSR disorders, nail disorders, skin disorders, and GI disorders.

The exposure-safety analysis was performed using data obtained from 6 mg or 8 mg once daily erdafitinib monotherapy dosed patients harboring susceptible FGFR aberrations, collected in a locally advanced or metastatic urothelial cancer population. In this context, pooled data from 814 participants in 3 studies were included. These data were from the 6 and 8 mg once daily regimens of Study BLC2001 (end of main study, 27 July 2021 clinical data cut), the erdafitinib monotherapy arm data of Study BLC2002 (30 September 2022 data cut), and data collected in Cohort 1 and Cohort 2 of Study BLC3001.

For the safety analysis, the relationships between erdafitinib serum phosphate and the incidence of the selected clinical safety endpoints were investigated using univariate logistic regression models.

The incidence of eye disorders (other than CSR), nail disorders, skin disorders, GI disorders at Grade ≥2 of severity, and CSR disorders at Grade ≥1 of severity, with a potential to require dose interruption, show a statistically significant relationship with the serum phosphate level associated with erdafitinib treatment.

The incidence of Grade ≥1 central serous retinopathy and Grade ≥2 gastrointestinal disorders had no such associations.

2.8.4. Conclusions on clinical pharmacology

Pharmacokinetic and pharmacodynamic properties of erdafitinib have been overall adequately described and support the use in the intended indication.

2.8.5. Clinical efficacy

2.8.5.1. Dose response study(ies)

The recommended starting dose of erdafitinib is 8 mg daily, with individualised up-titration to 9 mg once daily based on serum phosphate levels and drug-related toxicity, and a stepwise dose reduction to 6, 5, or 4 mg and/or interruption for tolerability.

The 8 mg once daily dose was evaluated in Study BLC2001 as Regimen 3 in participants with urothelial carcinoma. Study BLC2001 was started with 2 treatment regimens, to which participants were randomly assigned: Regimen 1 (intermittent dosing 10 mg daily with pharmacodynamically guided up-titration to 12 mg daily 7 days on/7 days off) and Regimen 2 (continuous dosing 6 mg daily with pharmacodynamically guided up-titration to 8 mg daily). At Interim Analysis 1, intermittent dosing was discontinued due to a low response rate (21.2%, 95% CI: 7.3-35.2). Based on further analysis of safety and efficacy data for the continuous daily dosing regimen and PK-PD modelling, a starting dose of 8 mg daily with pharmacodynamically guided up-titration to 9 mg (Regimen 3) was predicted to be superior to Regimen 2, which was also discontinued and, following implementation of Amendment 3, all subsequently enrolled participants received Regimen 3.

Based on the final analysis, the 8 mg daily regimen demonstrated higher investigator-assessed ORR than the 6 mg once daily regimen (40.2% versus 34.6%). PFS and OS data also showed a consistent trend of superior efficacy for the 8 mg once daily regimen.

In Study BLC2001, a serum phosphate concentration threshold of 5.5 mg/dL was used for up-titration of erdafitinib. Safety data from that study demonstrated no increased risk of AEs considered potential sequelae of prolonged hyperphosphataemia (more than 1 month) in participants with phosphate levels >5.5 mg/dL. Furthermore, increased serum phosphate levels correlated with improved clinical efficacy

with a requirement for concomitant increased dose interruptions or reductions. Consequently, in Study BLC3001, the threshold for individualised up-titration serum phosphate concentration was increased to 9 mg/dL. In Study BLC3001, all participants in the erdafitinib treatment group started erdafitinib 8 mg once daily from Day 1 to Day 14 of Cycle 1, and serum phosphate concentrations were measured on Day 14 of Cycle 1. Participants with serum phosphate concentrations <9.0 mg/dL with no significant toxicity could increase the erdafitinib dose to 9 mg daily. Dose interruption and dose reduction guidelines were also provided based on tolerability and AEs in Study BLC3001.

In Study BLC3001 Cohort 1 (N=266; erdafitinib n=136, chemotherapy n=130), erdafitinib significantly prolonged OS (primary endpoint) compared with chemotherapy (median OS of 12.1 months versus 7.8 months; HR=0.64, p=0.0050). The results of the primary endpoint are reinforced by superiority of erdafitinib versus chemotherapy for the key secondary endpoints of PFS and ORR. The exposure-efficacy analysis demonstrated that treatment with erdafitinib resulted in increased serum phosphate concentrations, which were associated with statistically significant improvements in OS, PFS, and ORR, thereby supporting the individualised dose titration used in Study BLC3001 Cohort 1.

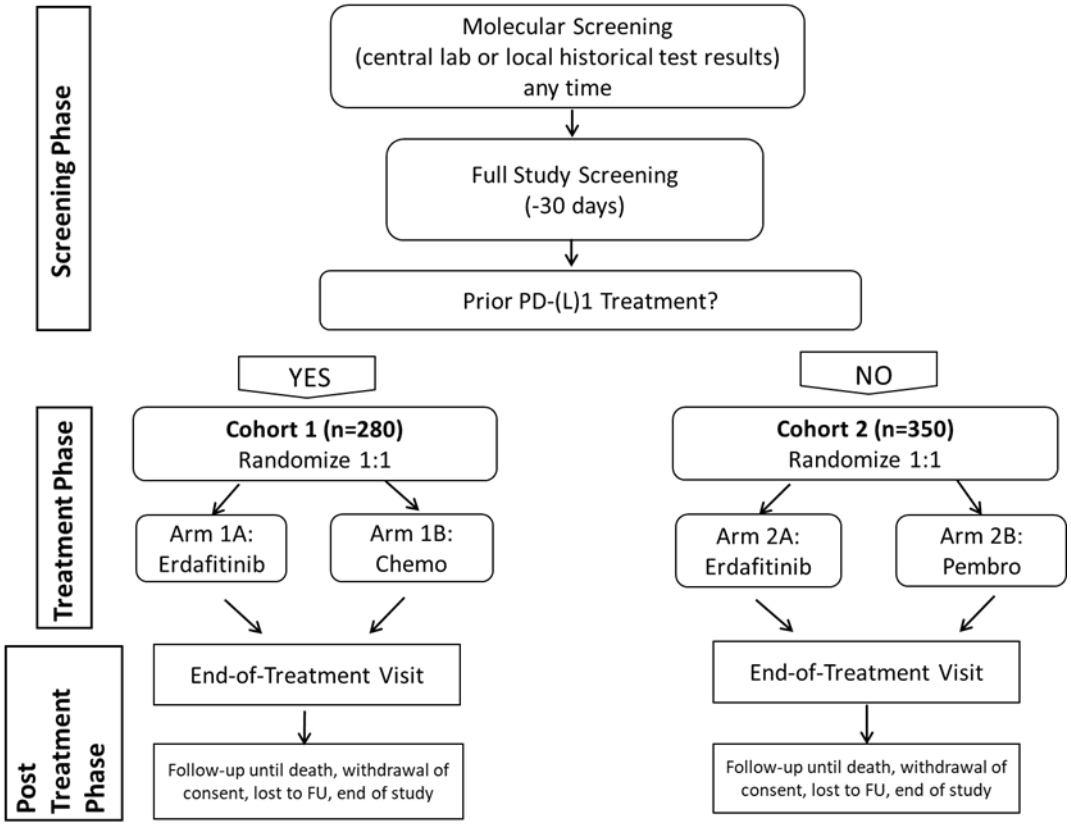
2.8.5.2. Main study

Study BLC3001 (cohort 1): A Phase 3 Study of Erdafitinib Compared with Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations

Study BLC3001 was a randomised (1:1) controlled open-label phase 3 study with two independent cohorts.

- Cohort 1 (object of this application) evaluated erdafitinib monotherapy versus investigator's choice of chemotherapy (docetaxel or vinflunine) in patients with advanced urothelial cancer and susceptible FGFR alterations, who had progressed on or after 1 or 2 prior line(s) of therapy, with at least 1 line including anti-PD-(L)1 as monotherapy or as combination therapy; and no more than 2 prior lines of systemic treatment. The choice of the type of chemotherapy (i.e. docetaxel or vinflunine) was made at the site level by the investigator prior to enrolment of subjects.
- Cohort 2 evaluated erdafitinib monotherapy versus pembrolizumab in patients with advanced urothelial cancer and susceptible FGFR alterations, who had progressed on or after 1 prior line of systemic treatment and who had no prior treatment with an anti-PD-(L) 1 agent.

Figure 24: schematic study design of study BLC3001



Chemo=Chemotherapy; FU=follow-up; lab=laboratory; PD (L)1= programmed death-ligand 1; Pembro=Pembrolizumab

Note: Treatment until disease progression, intolerable toxicity, withdrawal of consent, or decision by investigator. An IDMC was commissioned for this study. A review of one predefined interim analysis for each cohort was performed by the IDMC on both safety and efficacy data.

Source: figure 1, CSR BLC3001 cohort 1

Methods

- **Study Participants**

Key inclusion criteria for cohort 1

1) ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)
2) Histologic demonstration of transitional cell carcinoma of the urothelium. Minor components (<50% overall) of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable.
3) Metastatic or surgically unresectable urothelial cancer
4) Documented progression of disease, defined as any progression that requires a change in treatment, prior to randomisation
5) Prior treatment with an anti-PD-(L)1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment. Prior treatment with an anti-PD-(L)1 agent could have been given as neo-adjuvant, adjuvant, or in metastatic line of treatment as frontline or maintenance therapy, as follows:
   - Together with chemotherapy or as maintenance therapy
   - Together with chemotherapy in metastatic setting

- For superficial cancer (early disease/non-muscle invasive bladder cancer), OR in neo-adjuvant OR adjuvant setting. If these subjects did not relapse within a year of their last dose of anti-PD-(L)1, this will not be counted as a prior line of systemic treatment. These subjects will however still be eligible only for Cohort 1.

Note: Subjects who received neoadjuvant or adjuvant chemotherapy or immunotherapy and showed disease progression within 12 months of the last dose are considered to have received systemic therapy in the metastatic setting.

6) Subjects must meet appropriate molecular eligibility criteria, as determined by central laboratory screening or by local historical test results (from tissue or blood) performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or regional equivalent laboratory using the following methods: local next-generation sequencing (NGS), direct digital counting methods, or the Qiagen *therascreen* FGFR Rotor-Gene Q (RGQ) reverse transcription polymerase chain reaction (RT-PCR) test; see Section 9.1.2 for details.

Tumours must have at least 1 of the following translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or 1 of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C.

Key exclusion criteria for cohort 1

1. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to randomisation
2. Active malignancies (that is, requiring treatment change in the last 24 months). The only allowed exceptions are: urothelial cancer, skin cancer treated within the last 24 months that is considered completely cured, localised prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance) and localised prostate cancer with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence.
3. Symptomatic central nervous system metastases
4. Received prior fibroblast growth factor receptor (FGFR) inhibitor treatment
5. Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients
6. Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade.
7. History of uncontrolled cardiovascular disease
8. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions

- **Treatments**

Patients randomised to the experimental arm received erdafitinib orally with or without food at a starting dose of 8 mg once daily for 21 days in a 21-day cycle. Erdafitinib dose should be up-titrated to 9 mg once daily if the serum phosphate level on Cycle 1 Day 14 is <9.0 mg/dL, and there was no drug-related toxicity. For eye, skin/nail, dry mouth/mucositis, and phosphate toxicity, specific recommendations for dose modifications or dose delays were provided in the study protocol.

Patients randomised to the control arm received either vinflunine or docetaxel by investigator's choice (choice was made at the site level by the investigator prior to enrolment of subjects). Vinflunine was administered at a dose of 320 mg/m² as a 20-minute intravenous infusion once every 3 weeks. Docetaxel was administered at a dose of 75 mg/m² as a 1-hour intravenous infusion every 3 weeks. All

patients should continue treatment with the study drug until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment.

- **Objectives**

The primary objective was to show superiority on the effect of erdafitinib monotherapy vs investigator's choice chemotherapy (i.e. vinflunine or docetaxel) by assessment of OS.

- **Outcomes/endpoints**

Primary endpoint

- **Overall survival (OS)** as measured from the date of randomisation to the date of the subject's death. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.

Key secondary endpoints (hierarchically tested if superiority of erdafitinib to chemotherapy is established for the primary endpoint; testing order as listed)

- **Progression free survival (PFS) as** duration in days from the date of randomisation to the date of disease progression (or relapse from CR) assessed per RECIST v1.1 by the investigator or death, whichever is reported first.
- **Objective response rate (ORR)** → the proportion of subjects who achieve CR or PR, as assessed per RECIST v1.1 by the investigator.
- **Time to urinary bladder cancer symptom deterioration (TUSD-3) (subset of 3 FACT-Bl items)** → urinary bladder cancer Symptoms (US) score from 3 items from the FACT-Bl (BL1: urinary incontinence, BL2: urinary frequency, BL3: urinary pain) and is defined as the first time to increase in US score from the day of randomisation beyond a meaningful change threshold compared to baseline.

Tumour assessments were performed every 6 weeks for the first 6 months and then every 12 weeks for the next 6 months (±7-day window) using date of randomisation as reference. After the first year, assessments were to be performed as clinically indicated. Assessment of responses for solid tumours were to be performed according to RECIST (Version 1.1) by investigators. More frequent radiological assessments were allowed, if clinically indicated/desirable. Identical methodology (CT scan or MRI) was to be used for disease assessment at baseline, and throughout the course of the study, to characterise each identified and reported lesion to document disease status. If symptomatic deterioration (on the basis of global deterioration of health status) occurred without documentation of radiographic progression, the clinical findings used to make this determination must be specified in the eCRF and documented in the source documents. For subjects who discontinued study therapy without documented disease progression, monitoring of their disease status by tumour imaging according to the imaging schedule were to be continued, until the start of new anti-cancer treatment, disease progression, withdrawal of consent, death, or the end of the study, whichever occurs first.

- **Sample size**

Approximately 280 subjects (approximately 140 subjects to each arm) were planned to be enrolled in cohort 1 of study BLC3001. The data cut-off date for the final analysis was planned when approximately 208 death events had occurred. Assuming a 53% improvement in median OS of the erdafitinib arm over the chemotherapy arm (a hazard ratio [HR] of 0.65 for the erdafitinib group relative to chemotherapy group, under the exponential distribution assumption), the study had at least 85% power to detect a HR of 0.65 at a statistical significance level of 5% (2-sided) with one interim analysis for efficacy at an approximately 65% information fraction (approximately 136 deaths) and a final analysis.

- **Randomisation and Blinding (masking)**

Eligible patients were randomised in a 1:1 ratio to each arm. The randomisation was stratified by

- Region (North America vs EU vs rest of world)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2)
- Disease distribution (presence vs. absence of visceral metastases) (yes, no).

Study BLC3001 was an open-label study.

- **Statistical methods**

Estimand (Target of estimation)

Study intervention:

- Erdafitinib
- Chemotherapy (Cohort 1)

Population: Subjects with advanced urothelial cancer harboring selected FGFR aberrations who have progressed on or after 1 or 2 prior treatments, at least 1 of which includes an anti-PD-(L)1 agent (Cohort 1)

Variable: Overall survival (OS)

Summary measure (Population-level summary): HR of erdafitinib vs. chemotherapy

Intercurrent events: The intercurrent events of treatment discontinuation and subsequent anti-cancer therapy were accounted for by a treatment policy strategy.

The planned analyses and determination of sample size are described in the final version of the SAP. Cohort 1 and Cohort 2 were assessed independently, i.e., as if there were 2 separate studies.

The Intent-to-Treat (ITT) population was defined as all randomised subjects.

Subjects lacking data beyond randomisation have their OS censored at the date of randomisation.

The primary efficacy analysis was based on the ITT analysis set. The distribution of OS for each treatment group, including estimated median (in months) and 95% CI, was estimated using the Kaplan-Meier method. The log-rank test was used to compare the treatment groups (within each cohort) at an overall alpha level of 0.05 for the primary analyses. Additionally, the HR for erdafitinib relative to the control and its associated 95% CI was calculated based on a Cox proportional hazards model.

The three stratification factors separated the total subjects into 24 subgroups when treatment arm is taken into consideration. Due to a limited number of events by treatment group per strata (ie, <10 events) for OS and PFS per treatment group, a pre-specified pooling algorithm was applied resulting in unstratified analysis for OS and PFS.

The ITT analysis set was used for the analyses of all secondary endpoints. PFS and time to urinary bladder symptom deterioration were analysed using the same methods as the primary endpoint.

Inference for ORR was accomplished using the stratified Cochran-Mantel-Haenszel test.

The Type 1 error rate was controlled at 5% (2-sided) for the primary and key secondary endpoints. All tests were conducted at a 2-sided alpha level of 0.05, and 95% CIs were provided, unless stated otherwise. The familywise Type 1 error rate was strongly controlled at 5% (2-sided) for the secondary endpoints. A hierarchical testing approach was utilised for testing the secondary endpoints. At both interim and final analyses, the secondary endpoints were to be tested at the same significance levels as specified for testing the primary endpoint (OS) based on the O'Brien-Fleming alpha-spending

function to control the overall Type 1 error rate. The testing order of these endpoints was as follows: PFS; ORR; Time to urinary bladder cancer symptom deterioration.

The interim analysis for Cohort 1 was planned after an approximately 65% information fraction. Both superiority and futility were assessed at the interim analysis. The classical O'Brien-Fleming boundaries were used for these assessments. The stopping boundaries were implemented by Lan-DeMets spending function to control the Type 1 error rate at the 0.05 significance level overall. The Cohort 1 interim analysis occurred after 155 death events had been observed (at approximately 75% information fraction), and the significance level was determined using the O'Brien-Fleming alpha-spending function to control the Type 1 error rate at the 0.05 significance level (2-sided). The efficacy boundary p-value was predetermined to be 0.019 (2-sided). The IDMC recommended that Cohort 1 be stopped due to superiority of erdafitinib over chemotherapy and that subjects be allowed to crossover to erdafitinib treatment. As Cohort 1 was stopped, the interim analysis of Cohort 1 is considered the final analysis.

To evaluate the impact of the asymmetry in the number of patients randomized to chemotherapy vs erdafitinib who did not receive treatment, sensitivity analyses, including a tipping point analysis, were conducted. This included an analysis where OS for the 10 censored subjects due to dropout in the chemotherapy arm were imputed using multiple imputation with two approaches: a) by applying the top 20% OS values observed across both erdafitinib and chemotherapy arms and b) by applying the top 20% OS values observed in the chemotherapy arm alone. In the tipping point analysis, the OS hazard rate for the 10 censored subjects on the chemotherapy arm was incrementally improved until a null result was achieved, ie, the hazard ratio was no longer statistically significant at the 0.05 (2-sided) level.

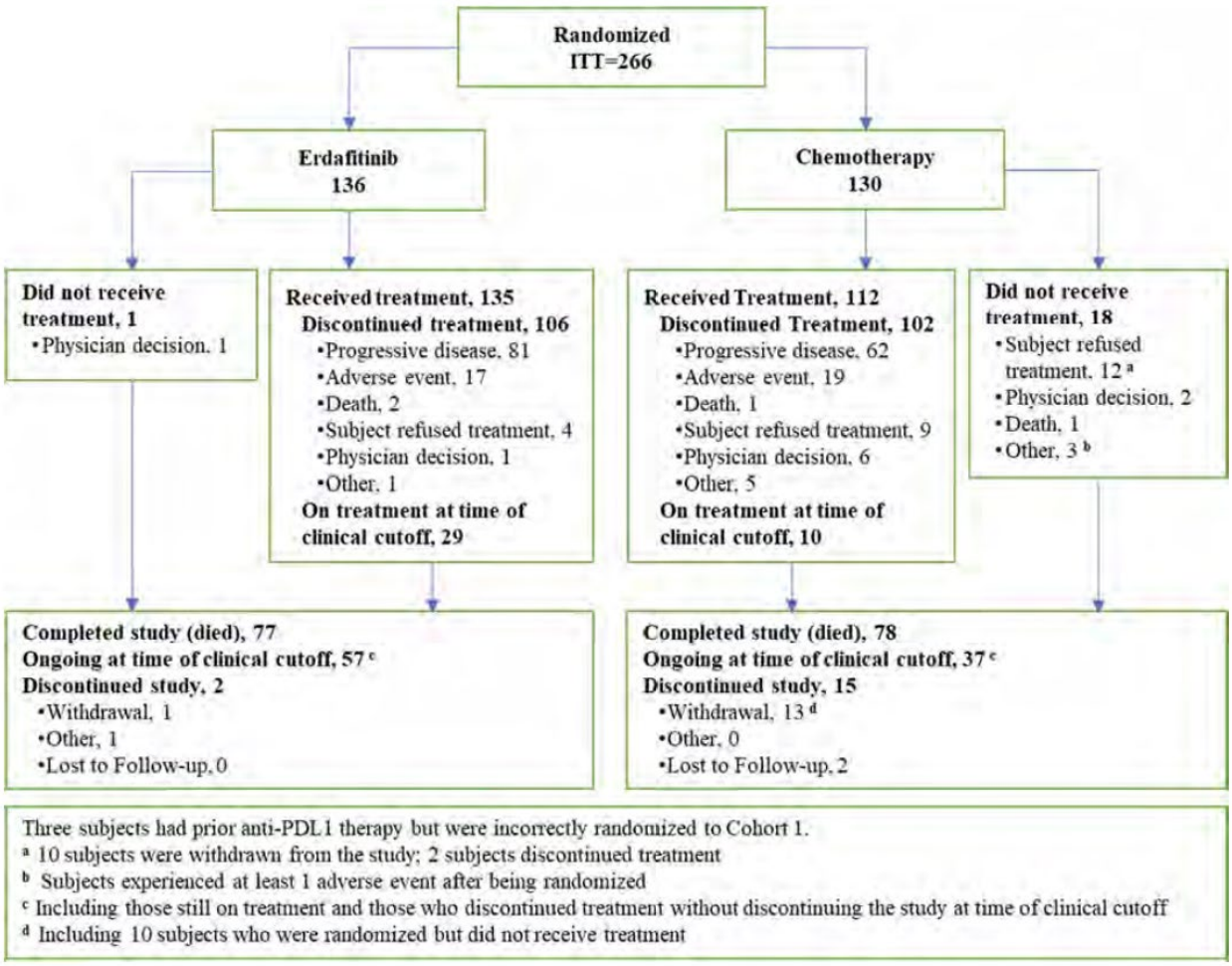
Results

- **Participant flow**

Figure 25: disposition of subjects cohort 1 study BLC3001

A total of 824 patients entered full study screening for the study BLC3001 (Cohorts 1 and 2), 619 (75.1%) passed and 207 (24,9%) failed full study screening.

Although cohort 1 and cohort 2 were performed and assessed independently, patient screening for both cohorts was combined and it is not possible to provide an analysis of screening failures for the pivotal 'study BLC3001 cohort 1' specifically.



- **Recruitment**

Initiation date: 6 August 2018 (first patient signed informed consent)

Primary completion date: 15 January 2023 (stopped for superiority in OS in interim analysis; clinical cut-off date)

Study completion date: N/A (study ongoing)

Data lock: 2 March 2023

Release date of CSR: 7 August 2023

Patients were recruited in 121 study sites in 23 countries (Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, Russia, South Korea, Spain, Taiwan, Turkey, UK, USA).

- **Conduct of the study**

Protocol amendments

The original study protocol (Version 1.0, dated 29 September 2017) was amended 6 times:

- **Amendment 1 (26 October 2017) (before study start of cohort 1)**
  The overall reason for the amendment was to clarify collection time-points for biomarker samples and correct numbering of exclusion criteria.

- **Amendment 2 (1 May 2018) (before study start of cohort 1)**
  The overall reason for the amendment was to address feedback from health authorities.
- **Amendment 3 (18 January 2019)**
  The overall reason for the amendment was to expand the subject population eligible for cohort 1 and to align with current standard of care following FDA and EMA label restrictions of the patient population eligible for treatment with anti-PD-(L)1 at frontline to those with high PD-L1 status and common practice to administer a platinum-based treatment as standard of care as a second-line treatment in this patient population.
- **Amendment 4 (29 Mar 2020)**
  The overall reason for the amendment was to allow subjects to meet appropriate molecular eligibility for the study by local historical test results for selected FGFR aberrations; ie, subjects can meet molecular eligibility criteria as determined by central laboratory screening as previously specified, or by local historical test results. However, if a subject is enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrolment for retrospective confirmation of FGFR status, diagnostic development, and biomarker research.
- **Amendment 5 (25 March 2021)**
  The overall reason for this amendment was to revise the timing of the interim analysis to occur at a higher percentage of total events (65% information fraction), ie, allow for more mature data. Also, the possible sample size re-estimation was removed and guidance on the futility boundary was provided.
- **Amendment 6 (20 January 2023) (after clinical cut-off for IA cohort 1)**
  The overall reason for the amendment was to add the Long-term Extension (LTE) Phase. The addition of the LTE Phase modifies the overall end of study definition. Study completion is distinct from end of study. Study completion is defined as the end-of-data-collection time-point for both cohorts, which is defined as when the clinical cut-off at for the final analysis has been achieved. End of study is defined as when the last subject receives the last dose of study drug on the study.

Protocol deviations / protocol compliance

Table 40: Summary of Subjects with Major Protocol Deviations

	Erdafitinib	Chemotherapy	Total
Analysis set: ITT	136	130	266
Subjects with major protocol deviations	8(5.9%)	3(2.3%)	11 (4.1%)
Entered but did not satisfy criteria	4 (2.9%)	2 (1.5%)	6 (2.3%)
Received wrong treatment or incorrect dose	2 (1.5%)	0	2 (0.8%)
Other	2 (1.5%)	1 (0.8%)	3(1.1%)

Note: Subjects may appear in more than one category.
Source: Table 7, CSR BLC3001 cohort 1

GCP inspection findings

To date one GCP inspection of a site in Korea was conducted by the Korean health authority with no observations. In the context of this inspection, the clinical site and the sponsor site were inspected. In addition, US FDA conducted 3 post-submission investigator site inspections in Spain, Italy and US with no observations noted.

- **Baseline data**

Table 41: Summary of demographic characteristics at baseline (ITT)

	Erdafitinib	Chemotherapy	Total
Analysis set: ITT	136	130	266
Age, years			
N	136	130	266
Mean (SD)	64.8 (10.40)	67.9 (9.07)	66.3 (9.87)
Range	(32; 85)	(35; 86)	(32; 86)
< 65 years	59 (43.4%)	45 (34.6%)	104 (39.1%)
65 - 69 years	30 (22.1%)	23 (17.7%)	53 (19.9%)
70 - 74 years	21 (15.4%)	32 (24.6%)	53 (19.9%)
≥75 years	26 (19.1%)	30 (23.1%)	56 (21.1%)
Sex			
N	136	130	266
Female	40 (29.4%)	36 (27.7%)	76 (28.6%)
Male	96 (70.6%)	94 (72.3%)	190 (71.4%)
Geographic region			
N	136	130	266
North America	8 (5.9%)	5 (3.8%)	13 (4.9%)
Europe	82 (60.3%)	80 (61.5%)	162 (60.9%)
Rest of the World	46 (33.8%)	45 (34.6%)	91 (34.2%)
Weight, kg			
N	136	130	266
Mean (SD)	73.24 (17.867)	72.51 (15.261)	72.88 (16.617)
Range	(41.0; 166.0)	(44.0; 113.0)	(41.0; 166.0)
Height, cm			
N	135	130	265
Mean (SD)	168.77 (9.281)	168.10 (9.711)	168.45 (9.483)
Range	(145.5; 192.0)	(144.0; 190.0)	(144.0; 192.0)

Note: N for each parameter reflects non-missing values.
Source: Table 3, 'summary of clinical efficacy'

Table 42: Summary of disease characteristics at baseline (ITT)

	Erdafitinib	Chemotherapy	Total
Analysis set: ITT	136	130	266
Time from progression/relapse on the last line of prior therapy to randomisation (months)			
N	128	124	252
Mean (SD)	2.72 (4.715)	1.82 (1.993)	2.28 (3.660)
Range	(0.2; 41.1)	(0.2; 19.7)	(0.2; 41.1)
Time from diagnosis of surgically unresectable or metastatic disease to randomisation (months)			
N	135	130	265
Mean (SD)	17.53 (13.158)	14.15 (10.415)	15.87 (11.989)
Range	(0.6; 74.6)	(1.8; 63.5)	(0.6; 74.6)
Primary tumour location			
N	136	130	266
Lower tract	95 (69.9%)	82 (63.1%)	177 (66.5%)
Bladder	90 (66.2%)	74 (56.9%)	164 (61.7%)
Urethra	5 (3.7%)	8 (6.2%)	13 (4.9%)
Upper tract	41 (30.1%)	48 (36.9%)	89 (33.5%)
Renal Pelvis	19 (14.0%)	20 (15.4%)	39 (14.7%)
Ureter	22 (16.2%)	28 (21.5%)	50 (18.8%)
Type of histology			
N	136	130	266
Transitional Cell Carcinoma	128 (94.1%)	124 (95.4%)	252 (94.7%)

	Erdafitinib	Chemotherapy	Total
Transitional Cell Carcinoma with minor components (<50% overall) of variant histology	8 (5.9%)	6 (4.6%)	14 (5.3%)
Bladder Cancer Stage at initial diagnosis			
N	102	102	204
0a	7 (6.9%)	8 (7.8%)	15 (7.4%)
0is	2 (2.0%)	2 (2.0%)	4 (2.0%)
I	14 (13.7%)	16 (15.7%)	30 (14.7%)
II	19 (18.6%)	8 (7.8%)	27 (13.2%)
III	32 (31.4%)	35 (34.3%)	67 (32.8%)
IV	28 (27.5%)	33 (32.4%)	61 (29.9%)
Baseline ECOG			
N	136	130	266
0	63 (46.3%)	51 (39.2%)	114 (42.9%)
1	61 (44.9%)	66 (50.8%)	127 (47.7%)
2	12 (8.8%)	13 (10.0%)	25 (9.4%)
Disease distribution at study entry			
N	136	130	266
Presence of visceral metastases[a]	101 (74.3%)	97 (74.6%)	198 (74.4%)
Lung	71 (52.2%)	67 (51.5%)	138 (51.9%)
Liver	31 (22.8%)	38 (29.2%)	69 (25.9%)
Bone	36 (26.5%)	39 (30.0%)	75 (28.2%)
Absence of visceral metastases(lung, liver, or bone)	35 (25.7%)	33 (25.4%)	68 (25.6%)
PD-(L)1 Status			
N	96	79	175
CPS >= 1	38 (39.6%)	38 (48.1%)	76 (43.4%)
CPS < 1	58 (60.4%)	41 (51.9%)	99 (56.6%)
PD-(L)1 Status			
N	96	79	175
CPS >= 10	7 (7.3%)	11 (13.9%)	18 (10.3%)
CPS < 10	89 (92.7%)	68 (86.1%)	157 (89.7%)
Number of prior systemic therapy lines			
1	45 (33.1%)	33 (25.4%)	78 (29.3%)
2	90 (66.2%)	97 (74.6%)	187 (70.3%)
3	1 (0.7%)	0	1 (0.4%)
Creatinine Clearance			
N	136	130	266
< 30 mL/min	2 (1.5%)	1 (0.8%)	3 (1.1%)
30 - <60 mL/min	57 (41.9%)	73 (56.2%)	130 (48.9%)
>= 60 mL/min	77 (56.6%)	56 (43.1%)	133 (50.0%)
Haemoglobin			
N	136	130	266
< 10 g/dL	24 (17.6%)	20 (15.4%)	44 (16.5%)
>= 10 g/dL	112 (82.4%)	110 (84.6%)	222 (83.5%)

ECOG = Eastern Cooperative Oncology Group.
Percentages are based on the number of subjects in a specified group with non-missing values for the relevant parameter.
Time from date of initial diagnosis to randomisation (months)=(randomisation date - date of initial diagnosis)/30.4375.
Time from progression/relapse on the last line of prior therapy to randomisation (months)=(randomisation date - date of progression/relapse on the last line of prior therapy)/30.4375.
[a] Number and percentages for lung, liver, and bone are based on subjects marked with "Yes" in the eCRF question "Are there currently any metastatic disease sites involving liver, lung, and/or bone?"

Table 43: Summary of prior anti-cancer therapy by line of therapy (ITT)

	Erdafitinib	Chemotherapy	Total
Analysis Set: ITT	136	130	266
One line of prior systemic therapy	45 (33.1%)	33 (25.4%)	78 (29.3%)
Chemotherapy+Anti-PDL1	32 (23.5%)	14 (10.8%)	46 (17.3%)
Anti-PDL1	9 (6.6%)	13 (10.0%)	22 (8.3%)
Anti-PDL1+Other	2 (1.5%)	3 (2.3%)	5 (1.9%)
Chemotherapy	1 (0.7%)	2 (1.5%)	3 (1.1%)
Chemotherapy+Anti-PDL1+Other	1 (0.7%)	1 (0.8%)	2 (0.8%)
Two lines of prior systemic therapy	90 (66.2%)	97 (74.6%)	187 (70.3%)
Chemotherapy; Anti-PDL1	75 (55.1%)	74 (56.9%)	149 (56.0%)
Chemotherapy+Anti-PDL1; Chemotherapy	5 (3.7%)	6 (4.6%)	11 (4.1%)
Anti-PDL1; Chemotherapy	4 (2.9%)	5 (3.8%)	9 (3.4%)
Anti-PDL1+Other; Chemotherapy	1 (0.7%)	3 (2.3%)	4 (1.5%)
Chemotherapy; Chemotherapy+Anti-PDL1	2 (1.5%)	1 (0.8%)	3 (1.1%)
Chemotherapy+Anti-PDL1; ADC	0	2 (1.5%)	2 (0.8%)
Anti-PDL1; Other	2 (1.5%)	0	2 (0.8%)
Other; Anti-PDL1	0	2 (1.5%)	2 (0.8%)
Chemotherapy+Anti-PDL1; Chemotherapy+Anti-PDL1	0	1 (0.8%)	1 (0.4%)
Chemotherapy+Anti-PDL1; Chemotherapy+Other	0	1 (0.8%)	1 (0.4%)
Chemotherapy+Anti-PDL1; Anti-PDL1	1 (0.7%)	0	1 (0.4%)
Chemotherapy; Anti-PDL1+Other	0	1 (0.8%)	1 (0.4%)
Anti-PDL1; Chemotherapy+Anti-PDL1+Other	0	1 (0.8%)	1 (0.4%)
Two lines of prior systemic therapy (categorised by first and second line)			
First line of therapy			
Chemotherapy	77 (56.6%)	76 (58.5%)	153 (57.5%)
Chemotherapy+Anti-PDL1	6 (4.4%)	10 (7.7%)	16 (6.0%)
Anti-PDL1	6 (4.4%)	6 (4.6%)	12 (4.5%)
Anti-PDL1+Other	1 (0.7%)	3 (2.3%)	4 (1.5%)
Other	0	2 (1.5%)	2 (0.8%)
Second line of therapy			
Anti-PDL1	76 (55.9%)	76 (58.5%)	152 (57.1%)
Chemotherapy	10 (7.4%)	14 (10.8%)	24 (9.0%)
Chemotherapy+Anti-PDL1	2 (1.5%)	2 (1.5%)	4 (1.5%)
ADC	0	2 (1.5%)	2 (0.8%)
Other	2 (1.5%)	0	2 (0.8%)
Chemotherapy+Anti-PDL1+Other	0	1 (0.8%)	1 (0.4%)
Chemotherapy+Other	0	1 (0.8%)	1 (0.4%)
Anti-PDL1+Other	0	1 (0.8%)	1 (0.4%)

Percentages are based on the number of subjects in analysis set of the corresponding treatment group.

Table 44: Summary of prior anti-cancer therapy

	Erdafitinib	Chemotherapy	Total
Analysis Set: ITT	136	130	266
Radiation therapy	39 (28.7%)	44 (33.8%)	83 (31.2%)
Prior urinary surgery	122 (89.7%)	116 (89.2%)	238 (89.5%)
Chemotherapy	123 (90.4%)	114 (87.7%)	237 (89.1%)
Any Platinum-based therapy	122 (89.7%)	111 (85.4%)	233 (87.6%)
Cisplatin	76 (55.9%)	59 (45.4%)	135 (50.8%)
Gem-cisplatin	69 (50.7%)	55 (42.3%)	124 (46.6%)
Carboplatin	37 (27.2%)	41 (31.5%)	78 (29.3%)
Gem-carboplatin	36 (26.5%)	40 (30.8%)	76 (28.6%)
Multiple platinum-based therapy	8 (5.9%)	10 (7.7%)	18 (6.8%)
No platinum based therapy	1 (0.7%)	3 (2.3%)	4 (1.5%)
Antibody drug conjugate	0	2 (1.5%)	2 (0.8%)
Enfortumab Vedotin	0 (0.0%)	2 (1.5%)	2 (0.8%)
Anti-PD-(L)1 therapy	135 (99.3%)	128 (98.5%)	263 (98.9%)
Prior systemic therapy indication			
Metastatic Urothelial Cancer	128 (94.1%)	122 (93.8%)	250 (94.0%)
Adjuvant	17 (12.5%)	15 (11.5%)	32 (12.0%)
Neoadjuvant	11 (8.1%)	14 (10.8%)	25 (9.4%)

Percentages are based on the number of subjects in analysis set of the corresponding treatment group.

Table 45: Summary of subsequent anti-cancer therapy

	Erdafitinib	Chemotherapy	Total
Analysis Set: ITT	136	130	266
Number of subjects with any subsequent therapy	44 (32.4%)	48 (36.9%)	92 (34.6%)
Number of subsequent systemic therapy lines			
1	33 (24.3%)	40 (30.8%)	73 (27.4%)
2	9 (6.6%)	8 (6.2%)	17 (6.4%)
3	0	0	0
>3	2 (1.5%)	0	2 (0.8%)
Chemotherapy	21 (15.4%)	21 (16.2%)	42 (15.8%)
Immunotherapy	9 (6.6%)	9 (6.9%)	18 (6.8%)
FGFR inhibitors	3 (2.2%)	10 (7.7%)	13 (4.9%)
Antibody drug conjugate	22 (16.2%)	14 (10.8%)	36 (13.5%)
Other systemic therapy	2 (1.5%)	1 (0.8%)	3 (1.1%)
Investigational systemic therapy	0	3 (2.3%)	3 (1.1%)

Modified from Source: Table 7, 'summary of clinical efficacy'

Table 46: Summary of FGFR genetic alterations

	Erdafitinib	Chemotherapy	Total
Analysis Set: ITT	136	130	266
Subjects with any FGFR alterations	135 (99.3%)	129 (99.2%)	264 (99.2%)
Mutations (excluding fusions)	108 (79.4%)	107 (82.3%)	215 (80.8%)
Fusions (excluding mutations)	25 (18.4%)	19 (14.6%)	44 (16.5%)
Mutations and fusions	2 (1.5%)	3 (2.3%)	5 (1.9%)

Percentages are based on the number of subjects in analysis set of the corresponding treatment group.
FGFR genetic alterations from local laboratory are used if no central laboratory data available.

Gene (Exon) **CDS point mutation** Amino acid variant	**pathophysiological impact of alteration**	**number of subjects BLC3001 (n = 266)***
FGFR3(7) c.746C>G p.**S249C**	Ligand – independent constitutive phosphorylation and proliferation	124 (46.6%)
FGFR3(7) c.1118A>G p.**Y373C**	Ligand- independent dimerisation and proliferation	45 (16.9%)
FGFR3(10) c.742C>T p.**R248C**	Ligand- independent proliferation	25 (9.4%)
FGFR3 (10) c.1108G>T p.**G370C**	Constitutive activation of FGFR3	13 (4.9%)
Fusion – ID (Exons) Genomic breakpoints		
FGFR3-TACC3v1 (17,11) chr4: 1:1808661 C; G chr4: 1741428	Promotes dimerisation, anchorage - independent proliferation	26 (9.8%)
FGFR3-TACC3		11 (4.1%)
FGFR3-TACC3v3 (17, 10) chr4: 1:1808661 C, G chr4: 1739324	Promotes dimerisation, anchorage - independent proliferation	4 (1.5%)
FGFR3-BAIAP2L1+ (17, 2) chr4: 1:1808661 C A chr7: 97991744	Ligand – independent receptor activation	1 (0.4%)
FGFR2-BICC1+ chr10: 123243211 G; A chr10: 60461834	Anchorage - independent cell - growth	-
FGFR2-CASP7+ chr10:123243211G A chr10:115457252	Anchorage - independent cell - growth	-

\+ *therascreen* FGFR Kit is clinically not validated to detect these fusions
* subjects with more than one alteration not shown (n=17)

For further details on biomarker and companion diagnostics (CDx) please refer to section 3.6 'In vitro biomarker test for patient selection for efficacy'.

- **Numbers analysed**

Table 47: Number of subjects in each analysis set

	Erdafitinib	Chemotherapy	Total
Intention-to-treat population (ITT) (i.e. all randomised subjects)	136	130	266
Safety population (i.e. all randomised subjects who received at least 1 dose of study drug)	135	112	247

Source: Table 8, CSR BLC3001 cohort 1

- **Outcomes and estimation**

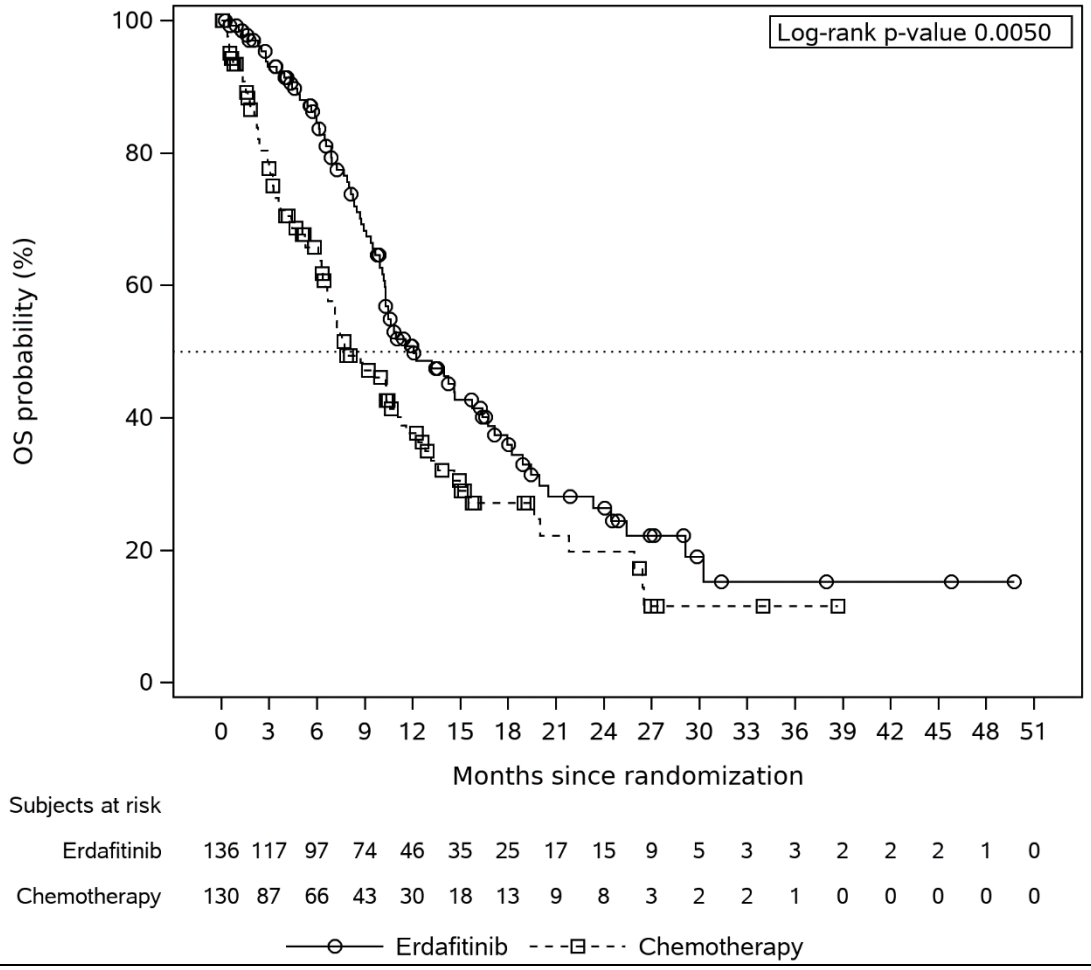
Primary endpoint (OS)

Table 48: Summary of Overall Survival – unstratified analysis (ITT)

	Erdafitinib	Chemotherapy
Analysis set: ITT	136	130
Overall survival[a]		
Number of events (%)	77 (56.6%)	78 (60.0%)
Number censored (%)	59 (43.4%)	52 (40.0%)
Kaplan-Meier estimates (months)		
25% Percentile (95% CI)	8.02 (6.14, 9.40)	3.25 (2.30, 5.22)
Median (95% CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)
75% Percentile (95% CI)	24.48 (18.23, NE)	19.61 (13.17, 26.51)
Min, Max	(0.2+, 49.7+)	(0.0+, 38.7+)
6-month Survival rate (95% CI)	0.85 (0.77, 0.90)	0.66 (0.56, 0.74)
9-month Survival rate (95% CI)	0.68 (0.59, 0.76)	0.47 (0.37, 0.56)
12-month Survival rate (95% CI)	0.51 (0.41, 0.60)	0.38 (0.28, 0.47)
24-month Survival rate (95% CI)	0.26 (0.17, 0.36)	0.20 (0.11, 0.31)
Hazard ratio (95% CI)[b]	0.64 (0.47, 0.88)	
P-value[c]	0.0050	

Key: CI = confidence interval; NE = not estimable.
a Overall survival (OS) in months is calculated as (date of death – date of randomisation+1)/30.4375. If the subject is alive or the vital status is unknown (for example, lost to follow-up or withdrew consent etc.), OS is censored at the date the subject was last known to be alive. Subjects lacking data beyond randomisation have their OS censored at the date of randomisation.
b Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the only explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the chemotherapy (vinflunine or docetaxel) arm.
c P-value is 2-sided and is based on a log-rank test.
+ indicates censored observation.

Figure 26: Kaplan-Meier Plot of Overall Survival – unstratified analysis (ITT)



Source: Figure 3, CSR BLC3001 cohort 1

Key secondary endpoints (PFS, ORR, TUSD-3)

Progression Free Survival (PFS)

Table 49: Summary of Progression Free Survival – unstratified analysis (ITT)

	Erdafitinib	**Chemotherapy**
Analysis set: ITT	136	130
Progression-free survival[a]		
Number of events (%)	101 (74.3%)	90 (69.2%)
Number censored (%)	35 (25.7%)	40 (30.8%)
Withdrawal by subject	1 (0.7%)	11 (8.5%)
Start Subsequent Anti-cancer Therapy	2 (1.5%)	14 (10.8%)
No progression until data cut-off	32 (23.5%)	15 (11.5%)
Kaplan-Meier estimates (months)		
25% Percentile (95% CI)	3.09 (2.69, 4.14)	1.35 (1.25, 1.51)
Median (95% CI)	5.55 (4.40, 5.65)	2.73(1.81, 3.68)
75% Percentile (95% CI)	10.71 (7.03, 11.30)	6.74 (4.50, 8.11)
Min, Max	(0.0+, 35.4)	(0.0+, 26.3+)
6-month Survival rate (95% CI)	0.37 (0.28, 0.46)	0.27 (0.19, 0.37)
9-month Survival rate (95% CI)	0.25 (0.18, 0.34)	0.12 (0.06, 0.20)
12-month Survival rate (95% CI)	0.17 (0.10, 0.25)	0.08 (0.03, 0.15)
24-month Survival rate (95% CI)	0.05 (0.01, 0.12)	0.04 (0.00, 0.13)

Hazard ratio (95% CI)[b]	0.58 (0.44, 0.78)
P-value[c]	0.0002

Key: CI = confidence interval; NE = not estimable.

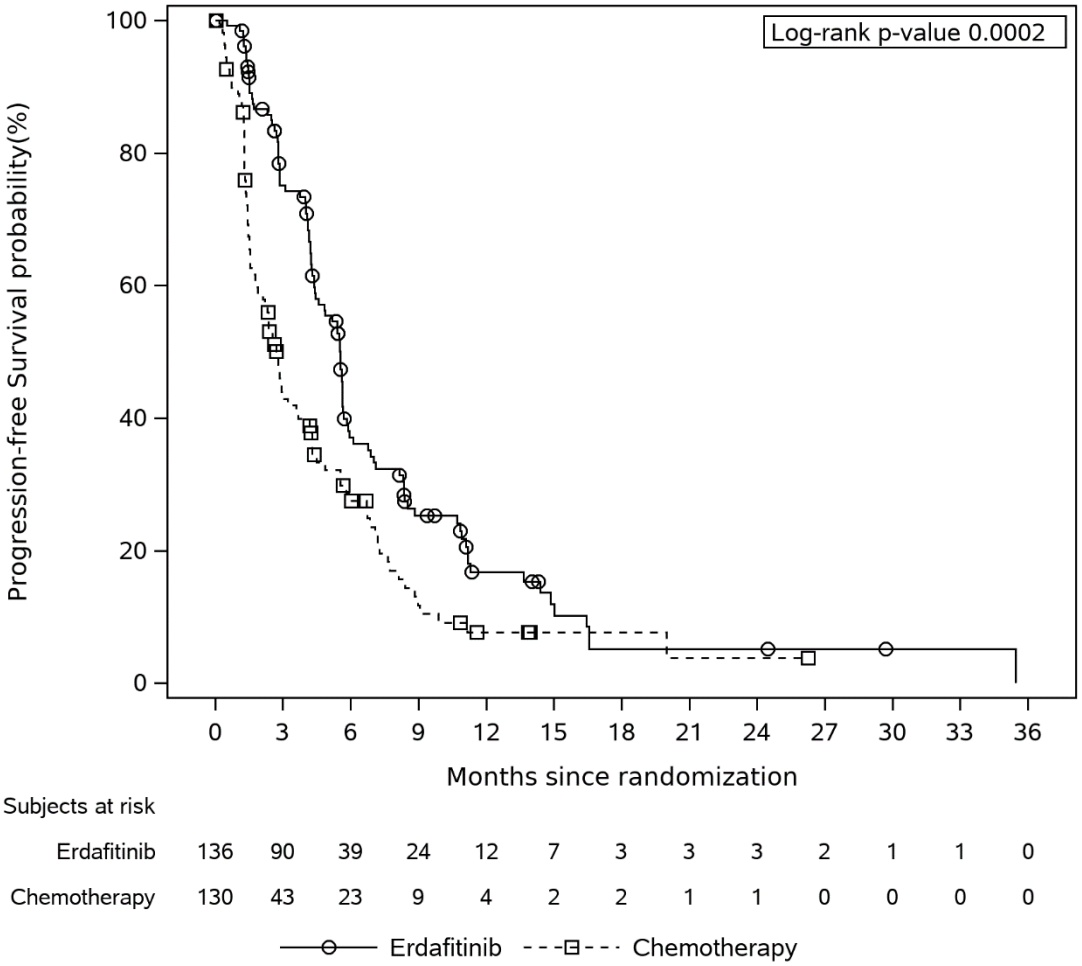
a PFS in months is defined as time from the date of randomisation to the date of disease progression (assessed per RECIST v1.1 by the investigator) or relapse from complete response or death, whichever is reported first divided by 30.4375. PFS is censored at the date of the last adequate disease assessment for subjects who do not have disease progression and are alive, as well as for subjects with unknown disease progression or unknown survival status as of the clinical cut-off date. Also, if there is no post baseline tumour assessment for a subject, PFS is censored on the date of randomisation. Subjects who die or have disease progression after starting subsequent anti-cancer therapy will be censored at the last tumour assessment date.

b Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the chemotherapy (vinflunine or docetaxel) arm.

c P-value is 2-sided and is based on a log-rank test.

\+ indicates censored observation.

Figure 27: Kaplan-Meier Plot Progression Free Survival (ITT)



To evaluate the impact of the asymmetry in the number of subjects randomised to chemotherapy vs erdafitinib who did not receive treatment, a post-hoc sensitivity analysis using the safety population was performed showing consistent results (PFS: HR=0.60; 95% CI: 0.45, 0.81).

Objective response rate (ORR)

Table 50: Summary of best objective response – stratified analysis (IWRS defined stratification factors) (ITT)

	Erdafitinib	Chemotherapy
Analysis set: ITT	136	130
Best overall response		
Complete response (CR)	9 (6.6%)	1 (0.8%)
Partial response (PR)	53(39.0%)	14 (10.8%)
Stable disease (SD)[a]	50 (36.8%)	41 (31.5%)
Progressive disease (PD)	14 (10.3%)	31 (23.8%)
Not evaluable (NE)	10 (7.4%)	43(33.1%)
Objective response rate (CR + PR)	62 (45.6%)	15 (11.5%)
Relative risk (95% CI)[b]	3.94 (2.37, 6.57)	
P-value[b]	<.001	

Key: CI = confidence interval; NE = not estimable.
a Minimum duration requirement for SD is 6 weeks from the date of randomisation. Stable disease includes subjects with no measurable disease at baseline and their best response was Non-CR/Non-PD.
b Relative risk, 95% CI and p-value are estimated using Cochran-Mantel-Haenszel (CMH) test with ECOG performance status (0 or 1 vs 2) as a stratification factor.
All p-values are 2-sided.
ORR: Relative risk greater than 1 indicates that the probability of achieving an objective response (PR or CR) is higher on the Erdafitinib arm compared to the chemotherapy arm.

As of the clinical cut-off, of 9 subjects in the erdafitinib group with a best overall response of CR, 7 subjects were ongoing in study follow-up (4 of these subjects discontinued study treatment due to progression of disease), and 2 subjects died. One subject in the chemotherapy group with a best overall response of CR was ongoing in the study.

The confirmed ORR by investigator assessment was 35.3% for the erdafitinib treatment group and 8.5% for the chemotherapy treatment group (observed relative risk of 4.16 [95% CI: 2.27, 7.64]).

The median duration of response (DoR) determined by the investigator was 4.86 (95% CI: 3.84, 7.46) months for the erdafitinib treatment group and 5.55 (95% CI: 2.14, 6.01) months for the chemotherapy treatment group. Consistently, the median duration of confirmed response determined by the investigator was 5.55 (95% CI: 4.17, 8.31) months for the erdafitinib treatment group and 5.75 (95% CI: 4.86, 7.16) months for the chemotherapy treatment group.

Ancillary analyses

Sensitivity analyses (OS)

To evaluate the impact of the asymmetry in the number of subjects randomised to chemotherapy vs erdafitinib who did not receive treatment, a post-hoc sensitivity analysis using the safety population was performed showing results consistent with the ITT analysis (OS: HR=0.68; 95% CI: 0.49, 0.94).

Results of the OS analyses in which the best 20% OS distribution was used to impute the survival times of the 10 subjects censored due to dropout in the chemotherapy arm are provided below:

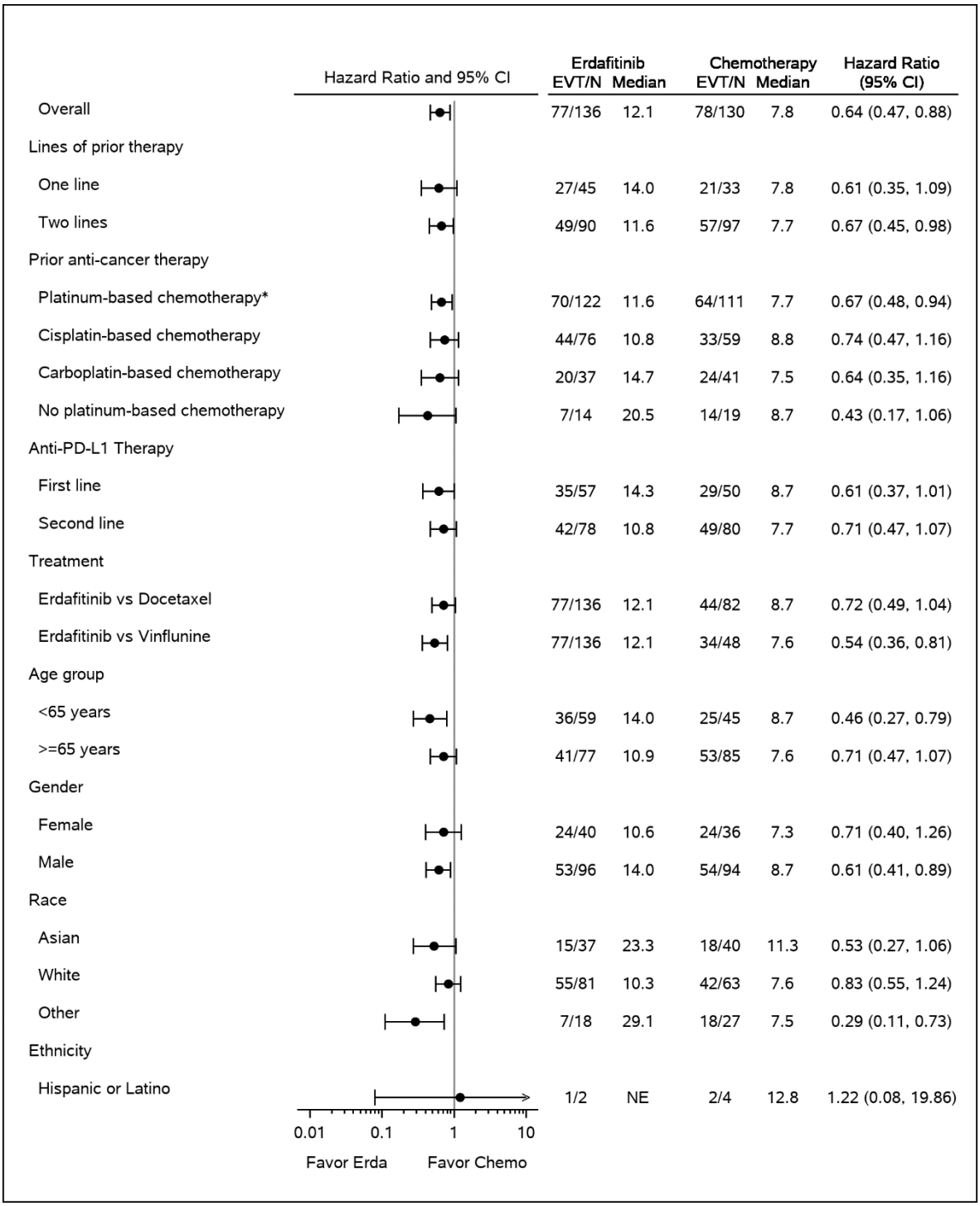
Table 51: Analysis of Multiple Imputation for 10 Droopouts from Best 20% of OS

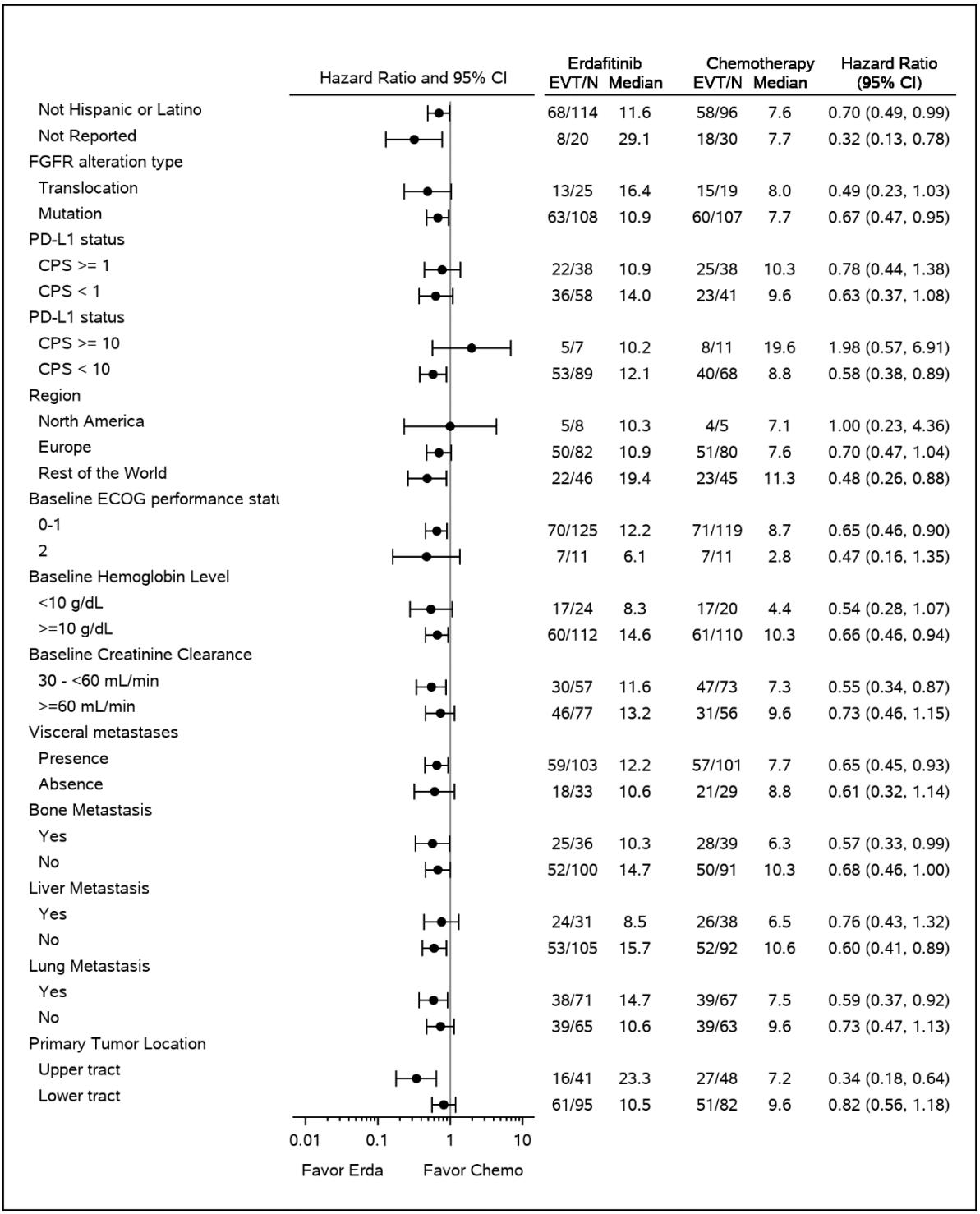
Imputation Pool	# of Dropouts Imputed [a]	% of Best OS	HR (95% CI)	2-sided P-value
Across arms	10	20%	0.712 (0.519, 0.977)	0.0355
Chemo arm	10	20%	0.706 (0.514, 0.969)	0.0310
[a] KM in imputation and Cox model in analysis				

In the OS tipping point analysis for these 10 censored patients, with the observed OS hazard rate in the erdafitinib arm fixed, at least 95% reduction in the hazard rate for the 10 subjects, randomised but not treated, in the chemotherapy arm was needed to obtain a null result i.e., the corresponding 2-sided p-value from less than 0.05 to 0.05 or above.

Subgroup analyses (OS)

Figure 28: Forest Plot of Overall Survival - Subgroup Analysis (ITT)





* Include cisplatin, carboplatin, and multiple platinum-based chemotherapy.

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 52: Summary of efficacy for the single pivotal study BLC3001 (Cohort 1)

Title: A Phase 3 Study of Erdafitinib Compared with Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations (Cohort 1).			
Study identifier	Study Number: 42756493BLC3001 EudraCT Number: 2017-002932-18 ClinicalTrials.gov Identifier: NCT03390504		
Design	A randomised, controlled, open-label Phase 3 study.		
	Duration of main phase:		6 August 2018 (first subject in Cohort 1 signed informed consent) to 15 January 2023 (clinical cut-off for analysis of Cohort 1). The Treatment Phase extended from administration of first dose until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment or study completion (ie, end of data collection time-point).
	Duration of Run-in phase:		n/a
	Duration of Extension phase:		The post-treatment follow-up Phase extended from the End-of-Treatment Visit until the subject died, withdrew consent, was lost to follow-up, or the end of study data collection time-point, whichever came first. Extension phase is still ongoing.
Hypothesis	Erdafitinib treatment prolongs overall survival (OS) in subjects with advanced urothelial cancer harbouring selected FGFR aberrations following 1 or 2 prior line(s) of systemic therapy, with at least 1 line containing anti-PD-(L)1, compared with the OS of those treated with chemotherapy (docetaxel or vinflunine).		
Treatment groups	Erdafitinib		Erdafitinib was administered orally in a tablet form once daily for 21 days in 21-day cycles. All subjects randomised to erdafitinib received a starting dose of erdafitinib 8 mg once daily from Day 1 to Day 14 of Cycle 1. Subjects with Cycle 1, Day 14, serum phosphate levels less than or equal to 8.99 mg/dL (≤ 2.90 mmol/L) had the option to increase the dose to 9 mg once daily. Subjects with toxicity or consistent hyperphosphataemia had specific dose modification rules where lower doses of erdafitinib were to be considered (ie, 6 mg, 5 mg, or 4 mg once daily). 136 patients randomised.
	Chemotherapy		Vinflunine was administered at a dose of 320 mg/m^2 as a 20-minute intravenous infusion once every 3 weeks. Docetaxel was administered at a dose of 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. 130 patients randomised.
Endpoints and definitions	Primary endpoint	Overall Survival (OS)	OS was measured from the date of randomisation to the date of the subject's death.

	Key secondary endpoints	Progression-Free Survival (PFS)	PFS was measured as duration in days from the date of randomisation to the date of disease progression (or relapse from complete response [CR]) assessed per RECIST v1.1 by the investigator or death, whichever is reported first.
		Objective Response Rate (ORR)	ORR was measured as the proportion of subjects who achieve complete response or partial response, as assessed per RECIST v1.1 by the investigator.
Database lock	2 March 2023		

Results and Analysis

Analysis description	**Primary endpoint**		
Analysis population and time point description	BLC3001 Cohort 1 ITT Analysis Set (Unstratified Analysis)		
Descriptive statistics and estimate variability	Treatment group	**Erdafitinib**	**Chemotherapy**
	Number of subjects	136	130
	Median OS, months (95% CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)
Effect estimate per comparison	OS	Comparison groups	Erdafitinib vs Chemotherapy
		Hazard ratio	0.64
		95% CI	0.47, 0.88
		P-value	0.0050
Analysis description	**Key Secondary endpoints**		
Descriptive statistics and estimate variability	Treatment group	**Erdafitinib**	**Chemotherapy**
	Number of subjects	136	130
	Median PFS, months (95% CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)
Effect estimate per comparison	PFS	Comparison groups	Erdafitinib vs Chemotherapy
		Hazard ratio	0.58
		95% CI	0.44, 0.78
		P-value	0.0002
	Confirmed ORR	Relative risk	4.16
		95% CI	2.27, 7.64
		P-value	< 0.001
	Confirmed ORR (%)	48 (35.3%)	11 (8.5%)
Notes	CI = confidence interval; NE = not estimable. OS in months is calculated as (date of death – date of randomisation+1)/30.4375. If the subject is alive or the vital status is unknown (for example, lost to follow-up or withdrew consent etc.), OS is censored at the date the subject was last known to be alive. Subjects lacking data beyond randomisation have their OS censored at the date of randomisation. Hazard ratio (HR) and 95% CI are estimated using a Cox proportional hazards regression		

2.8.5.3. Clinical studies in special populations

Table 53: Summary of efficacy for the single pivotal study BLC3001b (Cohort 1 and 2)

	Age 65-74 (Older subjects number /total number)	**Age 75-84** (Older subjects number /total number)	**Age 85+** (Older subjects number /total number)
Controlled Trials	249/617 (40.4%)	119/617 (19.3%)	8/617 (1.3%)
Non Controlled trials	70/172 (40.7%)	30/172 (17.4%)	7/172 (4.1%)

2.8.5.4. In vitro biomarker test for patient selection for efficacy

Scientific rationale for testing of the FGFR alteration status

Mechanism of action:
Erdafitinib is an orally bioavailable pan-FGFR tyrosine kinase inhibitor.

FGFR genetic alterations, particularly mutations and fusions activate the FGFR receptor-signalling pathway by promoting receptor hyperactivation leading to cell proliferation and metastasis. These genetic alterations activate FGFR signalling through a variety of mechanisms including kinase activation, reduced degradation, and aberrant ligand-independent receptor dimerisation.

Biomarker definition / definition of biomarker positivity ("FGFR-positive"):
Tumours must have at least one of the following:

- FGFR fusions / translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1
  or
- FGFR3 gene mutations: R248C, S249C, G370C, Y373C

detected by

- central laboratory screening from tissue with 'Qiagen t*herascreen* FGFR Rotor-Gene Q reverse transcription polymerase chain reaction' ('Qiagen *therascreen* FGFR RGQ RT-PCR') test,
  or
- local (historical) test results from tissue or blood in a CLIA-certified or regional equivalent laboratory using 'next-generation sequencing' (NGS), direct digital counting methods, or 'Qiagen *therascreen* FGFR RGQ RT-PCR'.

Justification / validation of biomarker definition
As to the information applied, the justification for the definition of biomarker-positivity (i.e. "FGFR-positive" as specified above) is following a scientific rationale being based on preclinical data and uncontrolled clinical response data. Regarding clinical validation see below.

Tests used

'Qiagen *therascreen* FGFR RGQ RT-PCR' was used as central confirmation test from tissue samples.

In addition, diverse local tests from tissue or blood using different analytical methods were used for the inclusion of patients.

For further details, please refer to 'definition of biomarker positivity' above and the discussion of clinical validation below.

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method (central confirmation test)

The *therascreen* FGFR RGQ RT-PCR Kit is a real time, reverse transcription PCR test for the qualitative detection of 2 point mutations in exon 7 [p.R248C (c.742C>T) and p.S249C (c.746C>G)], 2 point

mutations in exon 10 [p.G370C (c.1108G>T) and p.Y373C (c.1118A>G)] and 2 fusions [FGFR3-TACC3v1 and FGFR3-TACC3v3] in the FGFR3 gene in RNA samples derived from formalin-fixed paraffin embedded (FFPE) urothelial tumour tissue.

Specimens are processed using the RNeasy DSP FFPE Kit for manual sample preparation followed by reverse transcription and then automated amplification and detection on the Rotor Gene Q MDx 5plex high resolution melt analyser (HRM) instrument.

The *therascreen* FGFR RGQ RT-PCR Kit is also designed to identify FGFR3 fusion, FGFR3-BAIAP2L1 and FGFR2 fusions, FGFR2-BICC1 and FGFR2-CASP7, however, the test is not clinically validated to detect these three fusions due to lack of required clinical samples as the prevalence of these alterations in UC is low.

Allele-specific technology allows accurate and highly reproducible detection of target FGFR alterations, based on the use of specific forward and reverse primer and probe sets; only a perfect match between the primers and probes with the target circular deoxyribonucleic acid (cDNA) allows extension and amplification in the PCR reaction. Result reporting is fully automated. If both the run controls and the sample results are valid and sufficient assay target amplification occurs below the pre-determined cycle number cut-off threshold, the report will display the FGFR alteration(s) detected in each sample.

Pre-clinical tests have been completed by QIAGEN and include limit of blank (LoB), Cut-off setting, limit of detection (LoD) determination, and House Keeping Gene Specifications.

Analytical validation strategy (central confirmation test)

The *therascreen* FGFR RGQ RT-PCR kit is CE Marked under the IVD Directive 98/79/EC, for use with the QIAGEN Rotor Gene Q MDx 5plex HRM Instrument (RGQ) for the identification of certain FGFR genetic alterations in patients with UC.

The **cycle threshold (CT)** is inversely proportional to the amount of target present at the beginning of the reaction, allowing a sensitivity limit to be set for the test. CT values above cut-off can be, when the sample either contain less than the copy number able to be detected by the FGFR Kit (beyond the limit of detection of the Kit), or the sample is negative for an FGFR alteration, both of which are reported as "No Alteration Detected". The false-negative and false-positive rates for each assay were used to determine a **cut-off value for each FGFR** alteration-specific assay, such that a result equal to or less than the cut-off will result in an FGFR Alteration Detected classification.

The RNA quality is checked through the internal control (IC) CT values, which should be within the working range defined in the sample acceptance criteria.

The cut-off for each assay within the *therascreen* FGFR RGQ RT-PCR Kit is shown in the table below:

Table 54: Summary of assay cut-off results

FGFR Assay	Assay cut-off (CT value)
p.R248C (c.742C>T)	36.00
p.S249C (c.746C>G)	39.09
p.G370C (c.1108G>T)	41.00
p.Y373C (c.1118A>G)	43.00
FGFR3-TACC3v1	43.00
FGFR3-TACC3v3	43.00
FGFR3-BAIAP2L1*	43.00
FGFR2-BICC1*	43.00
FGFR2-CASP7*	42.00

* FGFR3 fusion FGFR3-BAIAP2L1 and FGFR2 fusions FGFR2-BICC1 and FGFR2-CASP7 have not been validated with the *therascreen*® FGFR RGQ RT-PCR Kit and clinical specimens.

Limit of blank (LoB) is defined in Clinical and Laboratories Standard's Institute (CLSI) guideline as "the highest result that can reasonably be expected from a blank sample (i.e., a sample with concentration at or near 0) for a given error probability α". For the *therascreen* FGFR RGQ RTPCR Kit, this is the data point that corresponds to the upper 95th percentile in FGFR alteration negative samples. The LoB was determined by measuring the levels of breakthrough for each of the 9 FGFR alteration assays of the *therascreen* FGFR RGQ RT-PCR Kit, where breakthrough is defined as the nonspecific, low-level amplification of an FGFR alteration-negative RNA sample.

High FGFR alteration level samples were tested with the *therascreen* FGFR RGQ RT-PCR Kit and no off-target amplification below the cut-off was observed in any of the assays. Therefore, **no cross-reactivity** was observed between the assays for susceptible FGFR alterations that comprise the *therascreen* FGFR RGQ RT-PCR Kit.

The **limit of detection** (**LoD**, lowest number of FGFR alteration copies/µl that is possible to be detected in 95% of repetitions) was determined by spiking in-vitro transcripts, one for each alteration, into a pool of normalised RNA extracted from wild-type clinical specimens and serially diluted. Sixty replicates of each dilution were tested using three *therascreen* FGFR RGQ RT-PCR Kit lots. The result was reported as the highest RNA copy number/ µl (i.e. worst case) LoD detected across the three kit lots used.

Table 55: Summary of LoD results

FGFR Assay	LoD (copies/µl)
p.R248C (c.742C>T)	75.80
p.S249C (c.746C>G)	289.82
p.G370C (c.1108G>T)	141.57
p.Y373C (c.1118A>G)	274.71
FGFR3-TACC3v1	25.26
FGFR3-TACC3v3	45.75
FGFR3-BAIAP2L1*	9.07
FGFR2-BICC1*	14.34
FGFR2-CASP7*	27.18

* FGFR3 fusion FGFR3-BAIAP2L1 and FGFR2 fusions FGFR2-BICC1 and FGFR2-CASP7 have not been analytically validated with the *therascreen*® FGFR RGQ RT-PCR Kit and clinical specimens.

The LoDs of the p.R248C (c.742C>T), p.S249C (c.746C>G), p.G370C (c.1108G>T), p.Y373C (c.1118A>G), FGFR3-TACC3v1, and FGFR3-TACC3v3 assays were verified using FGFR alteration-positive clinical UC samples.

The **repeatability** (within laboratory) of the *therascreen* FGFR RGQ RT-PCR Kit was assessed by testing contrived samples at 3x LoD, representing the nine alterations detected by the *therascreen* FGFR RGQ RT-PCR Kit and an FGFR alteration-negative sample. Repeatability was assessed by testing these samples at one site across multiple days, Rotor Gene Q instruments, and operators to generate a total of 60 replicates per sample.

Assay **reproducibility** was measured by testing contrived samples at 3x LoD level, clinical samples close to LoD and wild-type samples across the 3 different sites. The contrived samples for all susceptible FGFR alterations at 3× LoD and wild-type samples were tested by 3 operators (per site) over 5 days using three Rotor Gene Q MDx instruments at each external site. In addition, RNA extracted from FFPE UC clinical samples was used to test the device reproducibility.

Table 56: Assay reproducibility: Number of correct callas and two sided 95% confident limits for each FGFR alteration at 3xLoD and wild-type samples tested across one site.

Mutation	Target level	Specimen type	No. correct calls result	Percent correct calls	Lower two-sided 95% confidence limit	Upper two-sided 95% confidence limit
p.R248C (c.742C>T)	3×LoD 1×LoD	Contrived Clinical	120/120 72/72	100% 100%	96.97% 95.01%	100% 100%
p.S249C (c.746C>G)	3×LoD 1×LoD	Contrived Clinical	120/120 72/72	100% 100%	96.97% 95.01%	100% 100%
p.G370C (c.1108G>T)	3×LoD 1×LoD	Contrived Clinical	120/120 71/72	100% 98.61%	96.97% 92.50%	100% 99.96%
p.Y373C (c.1118A>G)	3×LoD 1×LoD	Contrived Clinical	120/120 71/72	100% 98.61%	96.97% 92.50%	100% 99.96%
FGFR3-TACC3v1*	1×LoD 1/3×LoD	Contrived Clinical	119/120 63/72	99.17% 87.50%	95.44% 77.59%	99.98% 94.12%
FGFR3-TACC3v3	3×LoD 1×LoD	Contrived Clinical	119/120 71/72	99.17% 87.50%	95.44% 92.50	99.98% 99.96%
FGFR3-BAIAP2L1	3×LoD 1×LoD	Contrived Clinical	120/120 NA	96.97% NA	96.97% NA	100.00% NA
FGFR2-BICC1	3×LoD 1×LoD	Contrived Clinical	120/120 NA	96.97% NA	96.97% NA	100.00% NA
FGFR2-CASP7	3×LoD 1×LoD	Contrived Clinical	120/120 NA	96.97% NA	96.97% NA	100.00% NA
WT (Mut-1)	NA	Clinical	120/120	100.00%	96.97%	100%
WT (Mut-2)	NA	Clinical	120/120	100.00%	96.97%	100%
WT (Fus-1)	NA	Clinical	120/120	100.00%	96.97%	100%
WT (Fus-2)	NA	Clinical	116/120	96.67%	91.69%	99.08%

The false-negative and false-positive rates for each assay were used to determine a cut-off value for each FGFR alteration-specific assay. Performance Characteristics for the *therascreen* FGFR RGQ RT-PCR Kit have been established, including analytical sensitivity, specificity, repeatability, and reproducibility.

Clinical validation strategy (central confirmation test)

Erdafitinib clinical efficacy against tumours harbouring these susceptible FGFR alterations was evaluated in multiple studies including EDI1001 and BLC2001 prior to BLC3001. Results from BLC3001 study shows erdafitinib activity in most of the alterations enrolled.

A summary of susceptible FGFR alterations with efficacy outcomes for chemo-relapsed/refractory subjects who received the erdafitinib 8 mg daily starting dose in Study BLC2001 is provided in the table below.

Table 57: Susceptible FGFR alteration and efficacy outcomes, chemo-relapsed/refractory subjects (8mg QD), INV assessment (study BLC2001

		Overall Response Rate (CR+PR)	Disease Control Rate (CR+PR+SD)
Any FGFR alterations	87		
Mutations	64 (73.6%)		
FGFR3-S249C	40 (46.0%)	18 (45.0%)	36 (90.0%)
FGFR3-Y373C	11 (12.6%)	6 (54.5%)	8 (72.7%)
FGFR3-R248C	9 (10.3%)	5 (55.6%)	7 (77.8%)
FGFR3-G370C	4 (4.6%)	2 (50.0%)	3 (75.0%)

Fusions	23 (26.4%)	4 (17.4%)	15 (65.2%)
FGFR3-TACC3_V1	10 (11.5%)	4 (40.0%)	7 (70.0%)
FGFR3-TACC3_V3	6 (6.9%)	0	4 (66.7%)
FGFR2-CASP7	3 (3.4%)	0	2 (66.7%)
FGFR2-BICC1	2 (2.3%)	0	2 (100.0%)
FGFR2-CASP7/FGFR3-TACC3_V3	1 (1.1%)	0	0
FGFR3-BAIAP2L1	1 (1.1%)	0	0
FGFR2-CASP7/FGFR3-BAIAP2L1	0	0	0

CR=complete response; PR=partial response, SD=stable disease.

For the pivotal study BLC3001, subjects randomised based on central testing results were molecularly screened using QIAGEN *therascreen* FGFR RGQ RT-PCR diagnostic assay, except for 4 randomised subjects, who were screened using the FGFR test by Almac labs. Local testing was permitted since protocol Amendment 4 dated 29 March 2020. Sixty-seven (25.4%) of 264 subjects randomised were enrolled based on local results. Tissue samples were collected from subjects enrolled by local tests for central test confirmation.

A summary of FGFR genetic alterations by treatment group for Study BLC3001 is provided in the table below.

Table 58: Summary of FGFR Genetic alterations in the pivotal study BLC3001

Gene (Exon) CDS point mutation Amino acid variant	**pathophysiological impact of alteration**	**number of subjects BLC3001 (n = 266)***
FGFR3(7) c.746C>G p.**S249C**	Ligand – independent constitutive phosphorylation and proliferation	124 (46.6%)
FGFR3(7) c.1118A>G p.**Y373C**	Ligand- independent dimerisation and proliferation	45 (16.9%)
FGFR3(10) c.742C>T p.**R248C**	Ligand- independent proliferation	25 (9.4%)
FGFR3 (10) c.1108G>T p.**G370C**	Constitutive activation of FGFR3	13 (4.9%)
Fusion – ID (Exons) Genomic breakpoints		
FGFR3-TACC3v1 (17,11) chr4: 1:1808661 C; G chr4: 1741428	Promotes dimerisation, anchorage - independent proliferation	26 (9.8%)
FGFR3-TACC3		11 (4.1%)
FGFR3-TACC3v3 (17, 10) chr4: 1:1808661 C, G chr4: 1739324	Promotes dimerisation, anchorage - independent proliferation	4 (1.5%)
FGFR3-BAIAP2L1+ (17, 2) chr4: 1:1808661 C A chr7: 97991744	Ligand – independent receptor activation	1 (0.4%)
FGFR2-BICC1+ chr10: 123243211 G; A chr10: 60461834	Anchorage - independent cell - growth	-
FGFR2-CASP7+ chr10:123243211G A chr10:115457252	Anchorage - independent cell - growth	-

\+ *therascreen*® FGFR Kit is clinically not validated to detect these fusions
* subjects with more than one alteration not shown (n=17)

Source: adapted from appendix 2, table 3, 'biomarker report'

Among the 67 subjects who were randomised based on local tests, 45 of them had tumour samples available for central test confirmation, while 22 subjects could not be retested centrally due to a lack of available tissue. Of the 45 tumours retested, 34 (75.6%) subjects were retrospectively confirmed by the central test, while only 11 (24.4%) subjects were not confirmed by the central test and were reported as negative.

Table 59: Efficacy of Erdafitinib vs. chemotherapy as assessed by OS and PFS in subjects enrolled by central and local tests

		Hazard Ratio (95% CI)	
	N	**OS**	**PFS**
Analysis set: ITT	266	0.64 (0.47-0.88)	0.58 (0.44-0.78)
Subgroup			
By Central Test			
Central FGFR +*	231 (86.8%)	0.64 (0.46-0.89)	0.59 (0.44-0.81)
Central FGFR Unknown**	24 (9.0%)	0.49 (0.12-1.99)	0.31 (0.10-0.90)
Central FGFR -	11 (4.1%)	0.63 (0.14-2.87)	1.34 (0.42-5.66)
By Enrolment			
Centrally Enrolled***	199 (74.8%)	0.69 (0.48-0.98)	0.64 (0.46-0.89)
Locally Enrolled	67 (25.2%)	0.47 (0.24-0.94)	0.37 (0.20-0.68)
Centrally Confirmed****	34 (50.7%)	0.41 (0.16-1.07)	0.18 (0.06-0.61)
* Include 197 randomised subjects and 34 subjects enrolled by local and confirmed by central testing ** Include 22 enrolled by local with unknown central test result and 2 false positives enrolled by cent al test *** Include 2 false positives enrolled by central test **** Percentage is within local enrolled, i.e., 34/67=50.7%			

Source: adapted from Table 12, 'biomarker report'

Observed clinical response to erdafitinib in FGFR-selected BLC3001 shows the clinical utility and predictive value of the QIAGEN *therascreen* FGFR RGQ RT-PCR Kit and suggests the selected biomarker panel identifies a subset of UC tumours that are truly FGFR driven and erdafitinib is a potential treatment option for mUC patients harbouring these FGFR alterations who progressed on at least one prior line of anti-PD-(L1) treatment.

Cut-point selection (central confirmation test)

'Qiagen *therascreen* FGFR RGQ RT-PCR' is a qualitative biomarker test delivering a binary result, i.e. 'FGFR alteration detected' or 'FGFR alteration not detected'. The selected cut-off values (PCR – cycle threshold, CT) are analytically driven cut-offs and are intended to optimise the sensitivity of the FGFR assay without compromising the false-positive rate. However, no clinical thresholding was performed.

Table 60: Summary of assay cut-off results within the 'Qiagen therascreen FGFR RGQ RT-PCR' (equal or lower numbers indicate a positive result, i.e. "alteration detected")

FGFR Assay	**Assay cut-off (CT value)**
p.R248C (c.742C>T)	36.00
p.S249C (c.746C>G)	39.09
p.G370C (c.1108G>T)	41.00
p.Y373C (c.1118A>G)	43.00
FGFR3-TACC3v1	43.00
FGFR3-TACC3v3	43.00
FGFR3-BAIAP2L1*	43.00
FGFR2-BICC1*	43.00
FGFR2-CASP7*	42.00
* subjects FGFR3 fusion FGFR3-BAIAP2L1 and FGFR2 fusions FGFR2-BICC1 and FGFR2-CASP7 have not been validated with the *therascreen* Kit and clinical specimens	

Source: adapted from table 3, 'biomarker report'

2.8.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Prior platinum chemotherapy versus No prior platinum chemotherapy (post-hoc defined analysis)

Prior platinum-based chemotherapy was not an eligibility requirement for the pivotal RCT 'BLC3001 – Cohort 1' (details see above in section 'main study') and the supportive SAT BLC2001 (further details see below in section 'supportive studies'). Subjects were required to be cisplatin-ineligible and without prior systemic therapy for mUC to be eligible for supportive SAT BLC2002 (further details see below in section 'supportive studies').

For BLC3001 Cohort 1, notable differences in demographics and baseline characteristics between subjects with prior platinum-based chemotherapy vs no prior platinum-based chemotherapy are as follows: 1 prior systemic therapy line 21.9% vs 81.8%, presence of visceral metastases at baseline 76% vs 63.6%, baseline ECOG 28.2% vs 18.2%, creatinine clearance 30 <60 mL/min 47.6% vs 57.6%, male 70% vs 81.8%. Neither the information on why the 33 (12.4%) subjects were not previously treated with platinum-based chemotherapy, nor the reason for discontinuation of prior therapies, and whether the full planned dose of any component of prior lines of therapy was applied, was collected at screening.

For BLC2001, notable differences in demographics and baseline characteristics between subjects with prior platinum-based chemotherapy vs no prior platinum-based chemotherapy include the following: median age 67 vs 74 years; male 80.2% vs 53.3%; no prior systemic therapy 0% vs 66.7%; median time from initial diagnosis to first dose 27.63 vs 21.91 months; creatinine clearance 30 to <60 mL/min 46.5% vs 80%; and baseline haemoglobin <10 g/dL 16.3% vs 6.7%.

Table 61: Comparison of efficacy by prior anti-cancer therapy (platinum-based or no platinum-based prior therapy) from Studies BLC3001 Cohort 1, BLC2001 and BLC2002

	BLC3001 Cohort 1		**BLC2001**	**BLC2002**
	Erdafitinib	**Chemotherapy**	**Erdafitinib (8 mg QD All)**	**Erdafitinib (8 mg with Upt)**
n				
Platinum	122	111	86	na
No platinum	14	19	15	43*
mOS (95% CI)				
Platinum	11.56 (10.18, 15.74)	7.72 (6.31, 11.30)	11.17 (9.03, 14.85)	na
No platinum	20.53 (6.11, NE)	8.74 (2.37, 19.98)	16.18 (6.08, 42.09)	16.23 (7.36, NE)
mPFS (95% CI)				
Platinum	5.52 (4.37, 5.62)	2.73 (1.54, 3.58)	5.52 (4.04, 5.68)	na
No platinum	5.88 (2.79, 8.31)	2.53 (1.28, 8.41)	9.82 (2.76, 15.90)	5.59 (4.34, 7.36)
ORR (n, confirmed %)				
Platinum	44 (36.1%)	9 (8.1%)	35 (40.7%)	na
No platinum	4 (28.6%)	2 (10.5%)	5 (33.3%)	19 (44.2%)

Key: Chemo=Chemotherapy (docetaxel or vinflunine), mOS=median overall survival, mPFS=median progression-free survival, na=not applicable, NE=not evaluable, ORR=objective response rate, Pembro=pembrolizumab, Upt=uptitration

* cisplatin ineligible study population

2.8.5.6. Supportive studies

Study BLC3001 – Cohort 2

Cohort 2 of Study BLC3001 is an ongoing randomised, controlled, open- label phase III study comparing erdafitinib 8 mg qd monotherapy to pembrolizumab 200 mg q3w in 351 platinum - based pre-treated subjects with FGFR-positive metastatic urothelial cancer. Primary endpoint was overall survival. For further study design details please see above.

The primary endpoint was failed with a median OS of 10.91 months in the erdafitinib treatment-group and 11.07 in the pembrolizumab group (hazard ratio of 1.18, 95% CI 0.92, 1.51, p-value 0.1819).

Study BLC2001

Study BLC2001 was an uncontrolled open-label phase 2 study to evaluate the efficacy and safety of multiple regimens of single-agent erdafitinib in subjects with advanced metastatic or surgically unresectable UC that harbour specific FGFR genomic alterations and had progressed on or after at least 1 prior chemotherapy; or progressed/relapsed within 12 months of last dose of neoadjuvant or adjuvant chemotherapy; or were treatment naïve but determined to be ineligible for cisplatin based upon impaired renal function. Definition of biomarker positivity ("FGFR-positive") was identical to the pivotal study BLC3001.

A subpopulation of 99 patients was treated in the 8 mg daily regimen (with individualised up-titration to 9 mg daily). Results of this subpopulation are presented here.

The median age was 68 years, 96% had metastatic disease, with visceral metastasis reported for 79% of subjects. Mutations in FGFR3 (G370C, R248C, S249C, Y373C) were observed for 75% of subjects, fusions in FGFR2 and FGFR3 were observed for 25% of subjects. No subject had both mutations and fusions. The majority of subjects had chemotherapy relapsed/refractory disease (88%). Of 87 subjects with prior chemotherapy, 84 had received prior platinum-based chemotherapy. Confirmed ORR based on investigator assessment was 40.4% (95% CI: 30.7%, 50.1%).

Study BLC2002

Study BLC2002 was an non-comparative open-label phase 2 study to evaluate the safety and efficacy of erdafitinib monotherapy and erdafitinib in combination with cetrelimab (an anti-PD-1 agent) +/- platinum (cisplatin or carboplatin) chemotherapy in patients with metastatic or locally advanced urothelial carcinoma. The study included 2 parts: Phase 1b (Dose Escalation) followed by Phase 2 (Dose Expansion).

The study included one erdafitinib monotherapy arm in the phase 2 part of the study, including 43 patients who received at least 1 dose of erdafitinib 8-9 mg within study BLC2002. The safety and efficacy of erdafitinib monotherapy was evaluated in subjects with metastatic or locally advanced UC tumours expressing select FGFR gene alterations, who were ineligible for cisplatin-based therapy and had not received prior systemic therapy for metastatic disease. Definition of biomarker positivity ("FGFR-positive") was identical to the pivotal study BLC3001. Results of this subpopulation are presented here.

The median age was 72 years, visceral metastases were present for over half of the patients. Subjects had baseline ECOG Performance Status of 0 (16.3%), or 1 (55.8%), or 2 (27.9%). Per protocol, subjects enrolled in Study BLC2002 were not allowed to have received any prior systemic therapy for metastatic disease. Confirmed ORR based on investigator assessment was 44.2% (95% CI: 29.1%, 60.1%).

2.8.6. Discussion on clinical efficacy

Dose finding and dose recommendation

The recommended starting dose is 8 mg taken orally once daily. This dose should be maintained and serum phosphate level should be assessed between 14 and 21 days after initiating treatment. The dose can then be uptitrated to 9 mg once daily if the serum phosphate level is <9.0 mg/dL and there is no drug-related toxicity. To manage adverse drug reactions, the SmPC recommends stepwise dose reductions to 6, 5, or 4 mg and/or treatment interruptions.

The 8 mg once daily dose was already evaluated in Study BLC2001 as Regimen 3 in participants with urothelial carcinoma. In this study, a serum phosphate concentration threshold of 5.5 mg/dL was used for up-titration of erdafitinib. In the pivotal Phase III Study BLC3001, the threshold for individualised up-titration – based on serum phosphate concentrations measured on Day 14 of Cycle 1 – was increased to 9 mg/dL. Dose interruption and dose reduction guidelines were also provided based on tolerability and AEs. The results of the E/R Analysis indicating correlations of ORR with serum PO4 concentrations up to 6 weeks are acknowledged.

Results of subjects on each dose level at later months for BLC3001 showed that erdafitinib doses are overall fairly distributed between the different daily doses between 4 mg and 9 mg.

In study BLC3001 the subgroup efficacy analyses by number of dose reductions (0, 1 and 2 or more) show higher outcomes in subjects experiencing more dose reductions, i.e. mOS of 9.95 (95% CI: 8.11, 10.94), 10.25 (95% CI: 8.51, 16.76) and 23.33 (95% CI: 18.23, NE) months; mPFS of 4.24 (95% CI: 2.79, 5.39), 5.55 (95% CI: 4.01, 5.88) and 10.84 (95% CI: 5.82, 13.67), confirmed ORR of 19.7%, 48.5% and 52.8% in subjects with no erdafitinib dose reduction, with 1 dose reduction and with 2 or more dose reductions, respectively. However, it remains challenging interpreting those outcomes due to the limited size of subgroup and the likely differences in median duration of treatment across subgroups. At this stage, it is acknowledged that these subgroup data do not suggest reduced efficacy with dose reductions.

Also in study BLC3001, the baseline characteristics for the subgroups by up-titration to 9mg (yes/no) show a higher rate of ECOG PS 2, high PD-L1 expression (CPS≥10), creatinine clearance <60 mL/min and haemoglobin <10 g/dL in subjects with no up-titration compared to subjects with up-titration. In addition, median age was higher in the subgroup with no up-titration than the subgroup with up-titration (70 vs 65 yrs), however, the percentage of visceral metastases was lower (58.1% vs 78.8%). The subgroup efficacy analyses show numerically higher OS outcomes in subjects with up-titration compared to those without up-titration with higher 95% CI lower bound, i.e. mOS (95%CI) of 12.22 (10.28, 16.76) and 11.56 (6.90, NE) months, respectively, and similar PFS and ORR outcomes for both groups, i.e., mPFS (95%CI) of 5.52 [4.40, 5.65] and 5.62 [3.09, 10.84] months and ORR (confirmed) of 36.5% and 32.3% in subjects with and without up-titration, respectively. It is however pointed out that the small number of subjects with no up-titration (n=31), the post-hoc setting of the subgroup analyses and the unbalanced baseline characteristics across subgroups should lead to caution of interpretation.

Based on the submitted clinical data package, the dosing regimen and its individual titrations as proposed in the SmPC are acceptable.

Design and conduct of clinical studies

This application is based on the result from a single pivotal study, namely study BLC3001 Cohort 1**.** Study 'BLC3001 Cohort 1' is a randomised (1:1) controlled open-label phase 3 study. Eligibility criteria

adequately describe a patient population of 'adult patients with advanced urothelial cancer and defined FGFR alterations, who had progressed on or after 1 or 2 prior line(s) of therapy, with at least 1 line including anti-PD-(L)1 as monotherapy or as combination therapy; and no more than 2 prior lines of systemic treatment (ECOG 0-2)'.

According to current scientific guidelines, treatment of patients with metastatic urothelial cancer (mUC), for patients who are ineligible for or have progressed on or after (cis)platin-based chemotherapy and progress on immunotherapy, include enfortumab vedotin or single-agent chemotherapy (including vinflunine and docetaxel) not previously received. However, enfortumab vedotin is approved in the EU since April 2022 only and was therefore not available at study start. Furthermore, the marketing authorisation for enfortumab vedotin is a relevant precedent, as in that procedure in the pivotal study investigator's choice (vinflunine, docetaxel or paclitaxel) was accepted as comparator.

Of note, the applicant received CHMP scientific advice in November 2017 (EMA/CHMP/SAWP/718304/2017) accepting investigator's choice of chemotherapy consisting of vinflunine or docetaxel as comparator arm.

Dosing regimen for vinflunine and docetaxel applied in study BLC3001 follows common standard.

The comparator used in study BLC3001 (i.e. INV choice: vinflunine or docetaxel) is considered acceptable for the 2L+ population studied.

In the intended patient population, OS is the appropriate time-to-event endpoint for evaluation of the direct treatment effect.

The key secondary endpoints PFS and ORR are relevant secondary endpoints and are standard in a situation where OS is the primary endpoint. The hierarchical testing approach with having PFS before ORR in the testing order is agreed.

Patients health-related quality of life was captured using 3 PRO measures: the FACT-BI, PGIS, and the EQ-5D-5L. These are standardised measures appropriate for the target population.

Randomisation / Blinding

Prognosis in metastatic urothelial cancer is impacted by the presence of visceral metastases and the ECOG performance status. Furthermore, treatment guidelines and use of anticancer treatment may differ across different geographical regions. Therefore, stratification with the chosen stratification factors is endorsed.

Open-label design of the pivotal study is agreed due to investigator's choice in the control arm and due to the different routes of administration of erdafitinib (orally once daily), vinflunine (20-minute intravenous infusion once every 3 weeks) and docetaxel (1-hour intravenous infusion every 3 weeks).

Statistical methods / sample size

An estimand was specified in the SAP. To support HR, standard summary measure of the treatment effect for time to event data, the Restricted Mean Survival Time (differences) (+ 95% CIs) were provided after 6,12, and 24 months.

The treatment policy strategy for treatment discontinuation and subsequent anti-cancer therapy is in line with regulatory standards in oncology and acceptable for the primary estimand. Following all patients and using their data irrespective of intercurrent events was appropriately aligned with the targeted estimand.

According to the description of Protocol Amendment 5, the interim analysis was originally planned at an earlier time and included the possibility for sample size re-estimation, which was modified to a group sequential design with the possibility for an early efficacy stop. To provide reassurance that the

study integrity was preserved, the applicant provided details on the firewalls to prevent bias. The measures taken to prevent knowledge of unblinded by-arm data of all study team involved in the study conduct, the data management and data analysis were sufficient to guarantee the trial integrity.

A Cox regression model was pre-specified for estimating the HR, however, details including whether a stratified model was to be used or the covariates to be included were not pre-specified.

Due to the 3 stratification factors resulting in 24 strata, it was planned to pool strata in case of < 10 events per stratum by a pre-specified algorithm. Finally, an unstratified analysis was performed per the pooling algorithm. As sensitivity analyses, an analysis (1) stratified for all 3 factors, and (2) for ECOG status were provided on request. In addition, a Cox regression including the stratification factors as covariates was performed.

The study had two cohorts that were independently analysed. In both cohorts, a 0.05 significance level was used. Although the study-wise type 1 error is not controlled at the 0.05 level, this is acceptable as the two underlying populations were not overlapping.

The study had a group sequential design such that stopping efficacy boundaries corresponding to significance levels <0.05 were defined for interim and final analysis. However, as confidence intervals, still the nominal 95% CI was provided. To ensure consistency of testing and confidence intervals and appropriately reflect the uncertainty, the repeated confidence interval consistent with the testing procedure was requested and is included the SmPC.

The same significance levels as specified for testing the primary endpoint (OS) based on the O'Brien-Fleming alpha-spending function was used for secondary endpoints. This is not appropriate, as these should depend on the information fraction that is not necessarily the same for primary and secondary endpoints. However, considering the size of the p-values for secondary analyses, conclusions would have been the same.

For OS, a treatment policy strategy was to be applied, i.e. patients were to be followed and their data included in the analysis irrespectively of intercurrent events such as refusal or discontinuation of treatment. Still, patients discontinued the study and informative censoring is possible for these patients. The applicant provided several sensitivity analyses (including multiple imputation analyses, tipping point analyses) that are considered sufficient to assess in how far deviations from the non-informative censoring assumption could influence the results.

Censoring rules for PFS were not in line with the recommendations from EMA GL, as patients were censored after new anti-cancer therapy. However, as PFS is only a supportive endpoint this is acceptable.

Study conduct

Most of the study protocol amendments that occurred after the enrolment of the first study patient are not likely to have a major impact on the efficacy outcomes. For the potential impact of the change in timing of the interim analysis in this open-label study see above (section 'statistical methods').

Participant flow

A greater number of subjects who were randomised to the chemotherapy group did not receive study treatment (n=18) compared with the erdafitinib group (n=1), the main reason was 'refused treatment' (n=12; all from control group). This number shows a relevant imbalance; however, demographic and disease characteristics at baseline were sufficiently comparable between those patients 'randomised and treated' and those 'randomised and not treated'. There are no reasonable concerns of informative censoring. Furthermore, the applicant was able to obtain the death date for 8 of the 18 subjects randomised to chemotherapy as well as the subject randomised to erdafitinib.

Baseline data

The demographic characteristics at baseline were sufficiently balanced between the treatment groups.

The disease characteristics at baseline were sufficiently balanced between the treatment groups.

Prior anti-cancer therapy received by subject was generally balanced across treatment groups.

Subjects had at least 1 FGFR3 alteration; no subjects had FGFR2 alterations. FGFR3-S249C was the most prevalent alteration (46.6%) followed by FGFR3-Y373C (16.9%), and FGFR3-TACC3 fusion (9.8%).

Efficacy data and additional analyses

Primary endpoint (OS)

The primary efficacy endpoint of OS showed a statistically and clinically significant improvement in OS for subjects treated with erdafitinib vs chemotherapy (HR=0.64; 95% CI: 0.47, 0.88; p-value=0.0050). The median OS was 12.1 months (95% CI: 10.3, 16.4) in the erdafitinib group versus 7.8 months (95% CI: 6.5, 11.1) in the chemotherapy group, each with approximately 40% of subjects censored. The median survival follow-up was 15.90 months (95% CI: 13.57, 19.22).

Sensitivity and subgroup analyses did not challenge the OS benefit of the primary analysis. Regarding the discussion on the small subpopulation of patients not having received prior platinum-based chemotherapy, please refer to discussion below.

Key secondary endpoints (PFS, ORR, TUSD-3)+

Analysis of key secondary endpoint PFS showed a statistically significant improvement in PFS for subjects treated with erdafitinib vs chemotherapy (HR=0.58; 95% CI: 0.44, 0.78; p value=0.0002).

Best ORR by investigator assessment and per RECIST 1.1 was 45.6% for the erdafitinib treatment group and 11.5% for the chemotherapy treatment group. The difference was statistically significant. 'Confirmed ORR analysis' was consistent with 'best ORR analysis'.

TUSD-3 is not established as a validated PRO endpoint; its clinical relevance is unclear. Furthermore, due to the open-label design of the study and the relevantly imbalanced censoring, no reasonable conclusions can be drawn from the PRO score TUSD-3. Its validation status is not evaluated in this MAA, as no robust benefit claims can be based on this PRO.

Other secondary endpoints

No results were provided for PGIS and only very high-level information was provided for EQ-5D-5L and FACT-Bl ("no meaningful differences") in the clinical study report and its 'supplemental PRO report'. However, due to the open-label design of the pivotal study – no robust benefit claims can be based on PRO data in this MAA.

Companion diagnostic (CDx) / Biomarker "FGFR positive"

CDx used for central confirmation

'Qiagen *therascreen* FGFR RGQ RT-PCR' from tissue was used as central confirmation test. However, 12.5% of patients (33/264) were included into study BLC3001 based on local testing only (tissue or blood) without having a (positive) central confirmation test (for 22 patients no tissue for central confirmation was available, for 11 patients central confirmation test was negative).

Definition of biomarker positivity ("FGFR-positive") and its justification
Regarding definition to declare a patient as "FGFR-positive" in the pivotal study BLC3001 please refer to 'eligibility criteria' above. Despite limitations to the biomarker validation (preclinical data and uncontrolled clinical response data), the definition of biomarker positivity is accepted.

Analytical method (of central confirmation test)
FGFR RGQ-RT-PCR Kit (Qiagen) was chosen as IVD to determine presence of FGFR point mutations. The kit is CE certified according to IVD Directive 98/79/EC, for use with the Qiagen Rotor Gene Q MDx 5plex HRM instrument.

An appropriately detailed description of sample preparation is presented. Run and sample validity is determined based on a no template control (NTC) and a positive control (PC) being within defined specifications. Results are only reported if these criteria are met. The reporting of the results above the established cut-points is fully automated.

Analytical validation strategy (of central confirmation test)
The assay based on *therascreen* FGFR RGQ RT-PCR Kit was validated with respect to mutation specific cut-off values, LoB, cross-reactivity, LoD, repeatability, and reproducibility. The relevant parameters were addressed. The assay is qualitative in nature, hence, it is not possible to draw conclusions on the ratio of mutated vs WT RNA in the samples.

Clinical validation strategy (of central confirmation test)
Patients in BLC3001 were randomised based on central test using *therascreen* FGFR RGQ RT-PCR diagnostic assay (74.6%), or local test (25.4%). Where tumour samples were available, patients with local test were centrally retested. The applicant showed that the treatment effects in patients with central positive test at enrolment, and in patients with central positive test either at enrolment or retesting were consistent with the treatment effect in the ITT population. The applicant claims that the observed clinical response to erdafitinib in FGFR-selected BLC3001 shows the clinical utility and predictive value of the QIAGEN *therascreen*.

While it is agreed that clinical benefit has been demonstrated for the population selected based on the *therascreen* FGFR RGQ RT-PCR, this does not imply clinical validity of the test or its predictive value. A test being clinically valid usually means that it is predictive for an effect on clinical outcomes, i.e., the treatment effect in test positive patients is larger than in negative patients (or can even be observed only in test positive patients). Therefore, while an effect on clinical outcomes such as OS in the central test positive patients is necessary, this is not sufficient for concluding that the test is predictive, as this would require clinical data in test-negative patients. The justification of clinical validity needs to be based on the clinical rationale in this case.

The number of patients enrolled based on a local test with tumour samples available for central test confirmation was limited (n=45), however, 24.4% (n=11) of these were centrally not confirmed (i.e. biomarker-negative in central confirmation test). While this number is too small for any conclusions on clinical effects in these patients, this shows that not all patients who might benefit from erdafitinib may be identified by '*therascreen* FGFR RGQ RT-PCR'.

Initially, only an analysis of activity (objective response rates, ORRs) by genetic alteration was available for study BLC2001. Upon request, an exploratory analysis of clinical benefit (overall survival, OS, and progression-free survival, PFS) supported by ORR was provided for study BLC3001, focusing on genetic alterations. Due to small sample sizes in different subgroups, no definitive conclusions can be drawn. However, trends favouring erdafitinib over chemotherapy were observed across all investigated alterations. Pooled analyses of patients with mutations and fusions also consistently favoured erdafitinib.

Cut-point selection (of central confirmation test)
Cut-points used for the respective genetic alteration defining "FGFR-positivity" were provided for the central confirmation test 'Qiagen *therascreen* FGFR RGQ RT-PCR'. However, no clinical thresholding was performed. Therefore, it remains unclear whether the thresholds / cut-off values applied in study BLC3001 were optimal or whether a lower or higher threshold defining patients as 'FGFR alteration positive' would lead to a better benefit-risk ratio.

Additional analysis - Prior platinum chemotherapy versus No prior platinum chemotherapy (post-hoc defined)
The applicant claims an indication in a second- and later-line setting (2^{nd}+-setting) for a patient population that has received prior treatment with a PD-(L)1 inhibitor. Prior treatment with platinum-based chemotherapy was not required.

However, in-line with the scientific treatment guidelines, the majority of patients included in pivotal study BLC3001 had received prior platinum-containing chemotherapy and only a minority of patients was platinum-naïve. For this ITT study population a statistically and clinically relevant effect on overall survival was shown.

In the platinum-naïve subpopulation the applicant performed a post-hoc defined cross-trial comparison for RCT BLC3001 cohort 1, SAT BLC2001 and SAT BLC2002 showing consistent promising objective responses for the study subpopulations without prior platinum. Results for ORR, OS and PFS are overall comparable to results from the pivotal RCT BLC3001 for the ITT-population. However, the absolute number of patients showing responses is limited (especially in the pivotal RCT) and analyses performed are post-hoc defined, making it difficult to draw robust conclusions from this data.

Patient and healthcare provider engagement

A methodology of engaging with patient organisations at the start of evaluation of new MAAs has been agreed by CHMP (for more details see the dedicated process and FAQs document: https://www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcare-professional-organisations-process-and-faqs_en.pdf). In this context the CHMP invited a healthcare professional society to share their perspectives regarding the assessment of erdafitinib for the applied indications on behalf of its members. The response from one Healthcare Professional Society confirmed the view that there is a substantial need for better treatment options, in particular to meaningfully improve survival and quality of life in patients with advanced bladder cancer following chemotherapy.

2.8.7. Conclusions on the clinical efficacy

Efficacy claims are based on the single pivotal phase 3 study BLC3001 (cohort 1) performed in line with the CHMP scientific advice provided in 2017 (before study start). The RCT met its primary endpoint of OS, showing a statistically and clinically significant improvement in OS in favour of erdafitinib monotherapy. This outcome is supported by analysis of the key secondary endpoints of PFS and ORR showing statistically significant improvement in favour of erdafitinib monotherapy.

The efficacy of erdafitinib has been demonstrated in the second- and later-line setting (2^{nd}+-setting) in patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alteration who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor regardless of prior treatment with platinum-based chemotherapy.

2.8.8. Clinical safety

Clinical Studies providing safety and tolerability data are summarised in **Table 62**.

Key safety data come from BLC3001 Cohort 1 for erdafitinib compared with chemotherapy in the locally advanced or metastatic UC population.

In addition, the following 2 pooled datasets are provided to characterise the overall safety profile of erdafitinib:

• The *BLC3001 erdafitinib pool* (n=308), comprised of safety data from erdafitinib treated subjects in the two cohorts from the *BLC3001 study*. The control arms from Study BLC3001 (chemotherapy group [Cohort 1] and pembrolizumab Group [Cohort 2]) provide context of the safety profile for erdafitinib in the mUC patient population.

• The *mUC Pool* (n=479) integrates data across studies that included subjects with locally advanced or metastatic UC treated with erdafitinib monotherapy 8 mg daily with individualised up-titration to 9 mg daily (8/9 mg daily dose regimen; n=467) or erdafitinib monotherapy 9 mg daily (n=9). Studies included in the pool were: BLC3001 (308/479) *BLC2001* (main study plus mUC subjects in the ongoing DDI sub study), *BLC2002* (erdafitinib monotherapy arm), and *EDI1001*.

Table 62: Overview of Clinical Studies Providing Safety and Tolerability Data

Study	**Phase**	**Study drugs**	**Number of erdafitinib - treated subjects in participating in the mUC Pool** (erdafitinib 8-9 mg qd)
42756493BLC3001 Further termed as BLC3001	Phase III open label, randomised, controlled	*Cohort 1:* Arm 1A: erdafitinib 8mg qd Arm 1B: docetaxel 75mg/m² q3w or vinflunine 320 mg/m² q3w, investigators choice) Anti - PDL1 - agent +/- chemotherapy pretreated FGFR+ mUC patients *Cohort 2:* Arm 2A: erdafitinib 8mg Arm 2B: pembrolizumab 200 mg q3w after 1-2L chemotherapy *Both cohorts:* Up-titration to 9 mg based on c1 d14 phosphate levels	Cohort 1 N=135 Cohort 2 N=173
42756493 BLC2001 (main study)	Phase II two arms, open label, uncontrolled	Different dosing regiments of erdafitinib tablet *Regimen 1:* 10 mg qd intermittent (7d on / 7d off) *Regimen 2:* 6 mg qd *Regiment 3:* 8 mg qd, up-titration to 9 mg (included in mUC pool)	101
42756493 BLC2001 (DDI substudy)	Phase II open label, single sequence	erdafitinib tablet 8 mg qd, up-titration to 9 mg DDI with Metformin and Midazolam	15

42756493 BLC2002	Phase Ib/II open label, dose escalation/ dose expansion	Erdafitinib tablet 8 mg qd, up-titration to 9 mg erdafitinib + cetrelimab erdafitinib + cetrelimab + chemotherapy	43
42756493 EDI1001	Phase I 1st in human, open-label, 4 - part	erdafitinib solution or capsule up to 12 mg continuous or daily	12
			∑ 479

2.8.8.1. Patient exposure

Table 63 provides an overview of the subjects' disposition, whereas Table 64summarises the extent of exposure.

Table 63: Subject Disposition and Treatment Withdrawal Information; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD
Total number of subjects	308	112	173	479
Study treatment ongoing	38 (12.3%)	10 (8.9%)	13 (7.5%)	57 (11.9%)
Discontinued study treatment	270 (87.7%)	102 (91.1%)	160 (92.5%)	422 (88.1%)
Reason for discontinuation				
Adverse event	52 (16.9%)	19 (17.0%)	18 (10.4%)	80 (16.7%)
Death	2 (0.6%)	1 (0.9%)	4 (2.3%)	5 (1.0%)
Non-Compliance with study drug [a]	7 (2.3%)	9 (8.0%)	3 (1.7%)	10 (2.1%)
Progressive disease	206 (66.9%)	62 (55.4%)	130 (75.1%)	322 (67.2%)
Physician decision	2 (0.6%)	6 (5.4%)	3 (1.7%)	3 (0.6%)
Other	1 (0.3%)	5 (4.5%)	2 (1.2%)	2 (0.4%)
Completed study [c]	210 (68.2%)	70 (62.5%)	120 (69.4%)	319 (66.6%)
Ongoing in study	88 (28.6%)	37 (33.0%)	51 (29.5%)	118 (24.6%)
Discontinued study	10 (3.2%)	5 (4.5%)	2 (1.2%)	42 (8.8%)
Reason for discontinuation				
Withdrawal by subject [b]	7 (2.3%)	3 (2.7%)	2 (1.2%)	13 (2.7%)
Lost to follow-up	0	2 (1.8%)	0	1 (0.2%)
Other	3 (1.0%)	0	0	28 (5.8%)

Table 64: Extent of Exposure; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD
Total number of subjects	308	112	173	479
Total treatment duration (months)				
N	308	112	173	479
0 to <3	107 (34.7%)	75 (67.0%)	84 (48.6%)	159 (33.2%)
3 to <6	91 (29.5%)	23 (20.5%)	32 (18.5%)	140 (29.2%)
6 to <9	45 (14.6%)	7 (6.3%)	15 (8.7%)	70 (14.6%)
9 to <12	22 (7.1%)	4 (3.6%)	8 (4.6%)	37 (7.7%)
≥12	43 (14.0%)	3 (2.7%)	34 (19.7%)	73 (15.2%)
Mean (SD)	6.74 (7.081)	2.79 (3.861)	7.10 (9.454)	7.08 (7.340)
Median	4.60	1.40	3.50	4.80
Range	(0.1; 43.4)	(0.0; 26.9)	(0.0; 50.5)	(0.1; 43.4)
Total duration of exposure - excluding dose interruption (months)				
N	308	112	173	479
Mean (SD)	6.7 (7.08)	2.8 (3.86)	7.1 (9.45)	6.7 (6.93)
Median	4.6	1.4	3.5	4.5
Range	(0; 43)	(0; 27)	(0; 51)	(0; 43)
Relative dose intensity (%)*				
N	308	112	173	479
<70%	161 (52.3%)	2 (1.8%)	1 (0.6%)	204 (42.6%)
70% to <90%	91 (29.5%)	1 (0.9%)	0	140 (29.2%)
≥90%	56 (18.2%)	109 (97.3%)	172 (99.4%)	135 (28.2%)
Mean (SD)	69.35 (19.339)	98.76 (10.447)	99.81 (2.534)	74.25 (19.870)
Median	68.24	100.00	100.00	75.13
Range	(12.5; 100.0)	(4.0; 116.7)	(66.7; 100.1)	(12.5; 100.0)

2.8.8.2. Adverse events

The definition of ADRs from the ICH guideline entitled E6 was used as guidance for the ADR medical assessment.

Table 65 provides an overall summary of adverse events reported in study BLC3001, in the complete mUC pool and in the supportive study BLC2001.

Table 65: Overall Summary of Treatment-emergent Adverse Events; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool	BLC2001
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD	
Total number of subjects	308	112	173	479	99
Any TEAEs	306 (99.4%)	109 (97.3%)	167 (96.5%)	477 (99.6%)	99 (100%)
Study treatment related	300 (97.4%)	97 (86.6%)	105 (60.7%)	464 (96.9%)	96 (97%)
Grade 3 or 4 TEAEs	197 (64.0%)	72 (64.3%)	88 (50.9%)	321 (67.0%)	66 (67%)
Study treatment related	137 (44.5%)	52 (46.4%)	21 (12.1%)	220 (45.9%)	45 (46%)
Serious TEAEs	125 (40.6%)	47 (42.0%)	80 (46.2%)	204 (42.6%)	39 (39%)
Study treatment related	41 (13.3%)	27 (24.1%)	18 (10.4%)	62 (12.9%)	9 (9.1%)
Grade 3 or 4 serious TEAEs	108 (35.1%)	41 (36.6%)	68 (39.3%)	177 (37.0%)	33 (33%)
Study treatment related	35 (11.4%)	23 (20.5%)	11 (6.4%)	51 (10.6%)	N/A

	BLC3001			mUC Pool	BLC2001
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD	
TEAE leading to dose reduction	91 (62%)	27 (24.1%)	0	286 (59.7%)	55 (55.6%)
Study treatment related	N/A	N/A	N/A	N/A	55 (55.6%)
TEAE leading to dose interruption	222 (72.1%)	35 (31.3%)	57 (32.9.0%)	345 (72.0%)	70 (70.7%)
Study treatment related	N/A	N/A	N/A	N/A	61 (61.6%)
TEAE leading to study treatment discontinuation	52 (16.9%)	20 (17.9%)	19 (11.0%)	93 (19.4%)	21 (21.2%)
Study treatment related	37 (12.0%)	15 (13.4%)	8 (4.6%)	61 (12.7%)	12 (12.1%)
TEAEs leading to death	11 (3.6%)	7 (6.3%)	12 (6.9%)	29 (6.1%)	7 (7.1%)
Study treatment related	1 (0.3%)	6 (5.4%)	3 (1.7%)	1 (0.2%)	0
Key: QD = once daily, TEAE = treatment-emergent adverse event. BLC3001 CHEMO Cohort 1: vinflunine 320 mg/m ^{2} as a 20-minute intravenous infusion once every 3 weeks or docetaxel 75 mg/m ^{2} as a 1-hour intravenous infusion every 3 weeks. BLC3001 PEMBRO Cohort 2: pembrolizumab 200 mg as a 30-minute intravenous infusion once every 3 weeks. TEAE leading to death: TEAE with outcome death on the AE CRF page or with toxicity grade 5					

Treatment-emergent Adverse Events Related to Study Treatment

Table 66 summarises the incidence of Treatment-emergent Adverse Events Related to Study Treatment by System Organ Class and Preferred Term Occurring in >2%.

Of note, related TEAEs with a worst severity of Grade 3 or 4 were reported for 220 (45.9%) subjects, with stomatitis (49 [10.2%] subjects), PPES (38 [7.9%] subjects) and oncholysis (23 [4.8%] subjects) being the most commonly reported.

Table 66: Incidence of Treatment-emergent Adverse Events Related to Study Treatment by System Organ Class and Preferred Term Occurring in >2% in any Group; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD
Total number of subjects	308	112	173	479
Subjects with TEAEs	300 (97.4%)	97 (86.6%)	105 (60.7%)	464 (96.9%)
System organ class Preferred term				
Gastrointestinal disorders	263 (85.4%)	61 (54.5%)	34 (19.7%)	408 (85.2%)
Stomatitis	140 (45.5%)	13 (11.6%)	5 (2.9%)	242 (50.5%)
Diarrhoea	151 (49.0%)	12 (10.7%)	10 (5.8%)	222 (46.3%)
Dry mouth	113 (36.7%)	3 (2.7%)	5 (2.9%)	186 (38.8%)
Nausea	35 (11.4%)	22 (19.6%)	8 (4.6%)	57 (11.9%)
Constipation	29 (9.4%)	21 (18.8%)	7 (4.0%)	50 (10.4%)
Vomiting	24 (7.8%)	15 (13.4%)	3 (1.7%)	40 (8.4%)
Dyspepsia	13 (4.2%)	2 (1.8%)	0	24 (5.0%)
Abdominal pain	16 (5.2%)	5 (4.5%)	1 (0.6%)	21 (4.4%)
Abdominal pain upper	8 (2.6%)	1 (0.9%)	1 (0.6%)	18 (3.8%)
Gastrooesophageal reflux disease	7 (2.3%)	3 (2.7%)	0	14 (2.9%)
Mouth ulceration	11 (3.6%)	2 (1.8%)	0	12 (2.5%)
Aphthous ulcer	5 (1.6%)	1 (0.9%)	0	10 (2.1%)
Dysphagia	5 (1.6%)	1 (0.9%)	2 (1.2%)	10 (2.1%)
Metabolism and nutrition disorders	248 (80.5%)	24 (21.4%)	11 (6.4%)	392 (81.8%)
Hyperphosphataemia	232 (75.3%)	0	0	361 (75.4%)
Decreased appetite	67 (21.8%)	20 (17.9%)	5 (2.9%)	108 (22.5%)
Hyponatraemia	21 (6.8%)	3 (2.7%)	1 (0.6%)	28 (5.8%)
Hypomagnesaemia	6 (1.9%)	0	0	15 (3.1%)
Cell death	7 (2.3%)	0	1 (0.6%)	7 (1.5%)
Skin and subcutaneous tissue disorders	223 (72.4%)	34 (30.4%)	35 (20.2%)	345 (72.0%)
Dry skin	73 (23.7%)	4 (3.6%)	6 (3.5%)	132 (27.6%)
Palmar-plantar erythrodysaesthesia syndrome	79 (25.6%)	1 (0.9%)	0	120 (25.1%)
Onycholysis	72 (23.4%)	1 (0.9%)	0	101 (21.1%)
Alopecia	58 (18.8%)	24 (21.4%)	1 (0.6%)	100 (20.9%)
Nail discolouration	51 (16.6%)	2 (1.8%)	0	73 (15.2%)
Nail dystrophy	30 (9.7%)	0	0	56 (11.7%)
Onychomadesis	42 (13.6%)	2 (1.8%)	0	54 (11.3%)
Nail disorder	29 (9.4%)	2 (1.8%)	2 (1.2%)	47 (9.8%)
Onychalgia	9 (2.9%)	0	0	18 (3.8%)
Pruritus	9 (2.9%)	2 (1.8%)	21 (12.1%)	18 (3.8%)
Rash	11 (3.6%)	4 (3.6%)	10 (5.8%)	17 (3.5%)
Skin fissures	8 (2.6%)	1 (0.9%)	0	17 (3.5%)
Hyperkeratosis	10 (3.2%)	0	0	16 (3.3%)
Erythema	7 (2.3%)	1 (0.9%)	2 (1.2%)	14 (2.9%)
Nail toxicity	13 (4.2%)	0	0	14 (2.9%)
Nail ridging	7 (2.3%)	1 (0.9%)	0	12 (2.5%)
Skin exfoliation	7 (2.3%)	0	0	12 (2.5%)
Xeroderma	12 (3.9%)	0	0	12 (2.5%)
Eye disorders	143 (46.4%)	7 (6.3%)	3 (1.7%)	234 (48.9%)
Dry eye	42 (13.6%)	2 (1.8%)	2 (1.2%)	75 (15.7%)
Vision blurred	21 (6.8%)	0	0	42 (8.8%)
Lacrimation increased	24 (7.8%)	1 (0.9%)	0	38 (7.9%)
Chorioretinopathy	20 (6.5%)	0	0	30 (6.3%)
Detachment of retinal pigment epithelium	16 (5.2%)	0	0	22 (4.6%)
Visual impairment	11 (3.6%)	1 (0.9%)	0	21 (4.4%)
Xerophthalmia	16 (5.2%)	1 (0.9%)	1 (0.6%)	21 (4.4%)
Keratitis	10 (3.2%)	0	0	19 (4.0%)
Visual acuity reduced	11 (3.6%)	0	0	17 (3.5%)
Blepharitis	8 (2.6%)	0	0	14 (2.9%)
Retinal detachment	4 (1.3%)	0	0	11 (2.3%)
Retinopathy	6 (1.9%)	0	0	10 (2.1%)
Subretinal fluid	7 (2.3%)	0	0	8 (1.7%)

Table 67: Incidence of Treatment-emergent Adverse Events Related to Study Treatment by System Organ Class and Preferred Term Occurring in >2% in any Group; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD
General disorders and administration site conditions	104 (33.8%)	52 (46.4%)	42 (24.3%)	171 (35.7%)
Asthenia	46 (14.9%)	21 (18.8%)	18 (10.4%)	76 (15.9%)
Fatigue	36 (11.7%)	17 (15.2%)	17 (9.8%)	69 (14.4%)
Xerosis	11 (3.6%)	0	1 (0.6%)	16 (3.3%)
Mucosal inflammation	10 (3.2%)	2 (1.8%)	0	10 (2.1%)
Pyrexia	4 (1.3%)	7 (6.3%)	6 (3.5%)	4 (0.8%)
Oedema peripheral	3 (1.0%)	7 (6.3%)	0	3 (0.6%)
Malaise	1 (0.3%)	3 (2.7%)	2 (1.2%)	2 (0.4%)
Nervous system disorders	98 (31.8%)	32 (28.6%)	7 (4.0%)	165 (34.4%)
Dysgeusia	75 (24.4%)	7 (6.3%)	1 (0.6%)	119 (24.8%)
Taste disorder	10 (3.2%)	2 (1.8%)	1 (0.6%)	20 (4.2%)
Peripheral sensory neuropathy	8 (2.6%)	6 (5.4%)	0	13 (2.7%)
Ageusia	6 (1.9%)	0	0	10 (2.1%)
Dizziness	3 (1.0%)	6 (5.4%)	2 (1.2%)	5 (1.0%)
Headache	2 (0.6%)	4 (3.6%)	0	4 (0.8%)
Neuropathy peripheral	0	4 (3.6%)	0	2 (0.4%)
Investigations	97 (31.5%)	11 (9.8%)	22 (12.7%)	148 (30.9%)
Alanine aminotransferase increased	52 (16.9%)	3 (2.7%)	7 (4.0%)	79 (16.5%)
Aspartate aminotransferase increased	44 (14.3%)	1 (0.9%)	8 (4.6%)	63 (13.2%)
Weight decreased	32 (10.4%)	3 (2.7%)	0	51 (10.6%)
Blood alkaline phosphatase increased	18 (5.8%)	1 (0.9%)	3 (1.7%)	20 (4.2%)
Blood creatinine increased	14 (4.5%)	4 (3.6%)	5 (2.9%)	19 (4.0%)
Gamma-glutamyltransferase increased	7 (2.3%)	2 (1.8%)	0	9 (1.9%)
Infections and infestations	74 (24.0%)	12 (10.7%)	12 (6.9%)	125 (26.1%)
Paronychia	27 (8.8%)	0	1 (0.6%)	55 (11.5%)
Conjunctivitis	23 (7.5%)	0	2 (1.2%)	35 (7.3%)
Nail infection	9 (2.9%)	0	0	14 (2.9%)
Respiratory, thoracic and mediastinal disorders	61 (19.8%)	16 (14.3%)	15 (8.7%)	103 (21.5%)
Epistaxis	25 (8.1%)	2 (1.8%)	0	35 (7.3%)
Nasal dryness	14 (4.5%)	0	0	25 (5.2%)
Oropharyngeal pain	4 (1.3%)	0	1 (0.6%)	13 (2.7%)
Dyspnoea	4 (1.3%)	4 (3.6%)	3 (1.7%)	6 (1.3%)
Cough	1 (0.3%)	4 (3.6%)	3 (1.7%)	3 (0.6%)
Pneumonitis	0	2 (1.8%)	5 (2.9%)	0
Musculoskeletal and connective tissue disorders	48 (15.6%)	18 (16.1%)	12 (6.9%)	75 (15.7%)
Pain in extremity	15 (4.9%)	3 (2.7%)	1 (0.6%)	27 (5.6%)
Arthralgia	11 (3.6%)	4 (3.6%)	3 (1.7%)	20 (4.2%)
Muscle spasms	10 (3.2%)	1 (0.9%)	0	18 (3.8%)
Myalgia	5 (1.6%)	8 (7.1%)	1 (0.6%)	12 (2.5%)
Blood and lymphatic system disorders	55 (17.9%)	53 (47.3%)	15 (8.7%)	69 (14.4%)
Anaemia	38 (12.3%)	31 (27.7%)	8 (4.6%)	48 (10.0%)
Thrombocytopenia	14 (4.5%)	6 (5.4%)	5 (2.9%)	16 (3.3%)
Lymphopenia	7 (2.3%)	3 (2.7%)	2 (1.2%)	8 (1.7%)
Neutropenia	2 (0.6%)	21 (18.8%)	0	6 (1.3%)
Leukopenia	3 (1.0%)	13 (11.6%)	0	3 (0.6%)
Febrile bone marrow aplasia	0	3 (2.7%)	0	0
Febrile neutropenia	0	9 (8.0%)	0	0
Renal and urinary disorders	23 (7.5%)	4 (3.6%)	8 (4.6%)	32 (6.7%)
Hepatobiliary disorders	20 (6.5%)	1 (0.9%)	4 (2.3%)	24 (5.0%)
Hepatic function abnormal	7 (2.3%)	0	1 (0.6%)	7 (1.5%)
Vascular disorders	7 (2.3%)	4 (3.6%)	5 (2.9%)	18 (3.8%)
Endocrine disorders	13 (4.2%)	0	26 (15.0%)	17 (3.5%)
Hyperparathyroidism	8 (2.6%)	0	0	11 (2.3%)
Hypothyroidism	1 (0.3%)	0	18 (10.4%)	2 (0.4%)
Hyperthyroidism	0	0	7 (4.0%)	0
Reproductive system and breast disorders	12 (3.9%)	0	5 (2.9%)	17 (3.5%)
Ear and labyrinth disorders	6 (1.9%)	1 (0.9%)	2 (1.2%)	10 (2.1%)
Psychiatric disorders	3 (1.0%)	2 (1.8%)	2 (1.2%)	10 (2.1%)
Injury, poisoning and procedural complications	5 (1.6%)	1 (0.9%)	0	7 (1.5%)
Cardiac disorders	4 (1.3%)	2 (1.8%)	1 (0.6%)	4 (0.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0%)	2 (1.8%)	1 (0.6%)	3 (0.6%)
Congenital, familial and genetic disorders	0	1 (0.9%)	0	0
Immune system disorders	0	1 (0.9%)	0	0

Adverse Events of Special Interest (AESI) and of clinical importance

Central serous retinopathy (CSR) has been identified as an *AESI* for erdafitinib and is a known class effect of FGFR inhibitors. Central serous retinopathy (specifically RPED) is characterised by the separation of the RPE from Bruch's membrane due to the presence of sub-RPE fluid, blood, fibrovascular membrane, or drusenoid material and is attributed to the disruption of the ionic pump of the RPE cells or hyperpermeability of the choroidal vasculature (McCannel 2014).

An overview of Central Serous Retinopathy by worst severity, seriousness, action taken, time to onset and resolution (mUC pool and BLC3001 erdafitinib pool, BLC2001) is provided in **Table 68**. No events of CSR were reported for the chemotherapy and the pembrolizumab arm of study BLC3001.

Table 68: Central Serous Retinopathy by Worst Severity, Seriousness, Action Taken, Time to Onset, and Resolution: mUC Pool and BLC3001 Erdafitinib Pool, BLC2001

	BLC3001 Erdafitinib Pool (n=308)	mUC Pool (n=479)	BLC2001 (n=99)
Overall Incidence	62 (20.1%)	103 (21.5%)	23 (23.2%)
Maximum Severity			
Grade 3 or 4:	5 (1.6%)	11 (2.3%)	3 (3.0%)
Grade 4:	0	0	0
Serious Events	5 (1.6%)	12 (2.5%)	3 (3%)
Dose Modification			
Reduction	40 (13.0%)	58 (12.1%)	13 (13%)
Interruption	25 (8.1%)	41 (8.6%)	8 (8%)
Discontinuation	8 (2.6%)	14 (2.9%)	3 (3%)
Median Time to First Onset (days [range])			
Any grade	44 (5; 274)	45 (5; 554)	53
Grade ³3:	52 (24; 111)	83 (24; 207)	87
Time to First Onset by Treatment Interval[a]			
≤1 month	21 (6.8%)	34 (7.1%)	6 (6.1%)
>1-2 months	16 (5.3%)	27 (5.7%)	8 (8.5%)
>2-3 months	13 (4.6%)	20 (4.5%)	4 (5%)
>3 months	12 (4.9%)	22 (5.7%)	5 (7.6%)
Resolution at Data Cutoff[b]			
Resolved:	40 (64.5%)	65 (63.1%)	
Unresolved	22 (7.1%)	38 (7.9%)	
Grade 1	14 (4.5%)	23 (4.8%)	
Grade 2	6 (1.9%)	12 (2.5%)	
Grade 3	2 (0.6%)	3 (0.6%)	
Grade 4	0	0	

[a] For each interval, only subjects who were treated in corresponding intervals and only AE which occurred in corresponding intervals are counted. AEs beyond last doses are assigned to last intervals in which subjects were treated.

[b] For "Resolved" percentage calculations are based on the "Overall Incidence" as the denominator. For "Unresolved" percentage calculations are based on the total number of subjects as the denominator.

Source: SCS page 52ff

Adverse events of clinical importance include events that are class effects of FGFR inhibitors (*hyperphosphataemia, eye disorders* [other than central serous retinopathy], *nail and skin disorders*), as well as those identified based on clinical findings (e.g., *gastrointestinal disorders*).

Adverse events of clinical importance were observed at a similar frequency across the mUC pool and the BLC3001 erdafitinib pool, and were observed less frequently in the chemotherapy and pembrolizumab groups.

Hyperphosphataemia is an expected and transient laboratory abnormality of FGFR inhibitors due to their mechanism of action (IB Erdafitinib 2023). Hyperphosphataemia was classified as an adverse event of clinical relevance and detailed recommendations for management of elevated phosphate levels in the further course of treatment were provided in the BLC3001, BLC2001, BLC2002, and EDI1001 protocols. The same recommendations are given in SmPC.

An overview of hyperphosphataemia by worst severity, seriousness, action taken, time to onset and resolution (mUC pool and BLC3001 erdafitinib pool, BLC2001) is provided in Table 69.

Table 69: Hyperphosphataemia by Worst Severity, Seriousness, Action Taken, Time to Onset, and Resolution: mUC Pool and BLC3001 Erdafitinib Pools

	BLC3001 Erdafitinib Pool (n=308)	mUC Pool (n=479)	BLC2001 (n=99)
Overall Incidence	242 (78.6%)	376 (78.5%)	76 (76.8%)
Maximum Severity			
Grade 3 or 4:	8 (2.6%)	14 (2.9%)	2 (2%)
Grade 4:	1 (0.3%)	1 (0.2%)	0
Serious Events	0	0	0
Dose Modification			
Reduction	11 (3.6%)	25 (5.2%)	9 (9%)
Interruption	14 (4.5%)	48 (10.0%)	23 (23%)
Discontinuation	0	1 (0.2%)	1 (1%)
Median Time to First Onset (days [range])			
Any grade	15.5 (8; 337)	16 (6; 449)	20
Grade ³3:	35.5 (22; 190)	35.5 (14; 190)	18
Time to First Onset by Treatment Interval[a]			
≤1 month	183 (59.4%)	289 (60.3%)	60 (60.9%)
>1-2 months	42 (13.8%)	56 (11.8%)	8 (8.5%)
>2-3 months	6 (2.1%)	14 (3.2%)	5 (6.3%)
>3 months	11 (4.5%)	17 (4.4%)	3 (4.5%)
Resolution at Data Cutoff[b]			
Resolved:	200 (82.6%)	315 (83.8%)	
Unresolved	42 (13.6%)	60 (12.5%)	
Grade 1	32 (10.4%)	48 (10.0%)	
Grade 2	10 (3.2%)	12 (2.5%)	
Grade 3	0	0	
Grade 4	0	0	

[a] For each interval, only subjects who were treated in corresponding intervals and only AE which occurred in corresponding intervals are counted. AEs beyond last doses are assigned to last intervals in which subjects were treated.

[b] For "Resolved" percentage calculations are based on the "Overall Incidence" as the denominator. For "Unresolved" percentage calculations are based on the total number of subjects as the denominator.

Overall, there was a low incidence of prolonged hyperphosphataemia in both the mUC pool and the BLC3001 erdafitinib pool. The most frequently reported TEAE considered a *potential sequela of prolonged hyperphosphataemia* (i.e., ≥7 mg/dL for >1 month) was hypercalcemia.

Table 70: Treatment-emergent Adverse Events (TEAEs) Considered Potential Sequalae of Prolonged Hyperphosphataemia by Serum Phosphate; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD
Overall				
Total number of subjects	308	112	173	479
Subjects with any TEAEs considered potential sequalae of prolonged hyperphosphataemia	30 (9.7%)	1 (0.9%)	12 (6.9%)	49 (10.2%)
Hypercalcaemia	16 (5.2%)	1 (0.9%)	9 (5.2%)	29 (6.1%)
Hyperparathyroidism	11 (3.6%)	0	0	14 (2.9%)
Hypocalcaemia	5 (1.6%)	0	4 (2.3%)	11 (2.3%)
Hyperparathyroidism secondary	1 (0.3%)	0	0	2 (0.4%)
With phosphate>=7 mg/dl for >1 month				
Total number of subjects	13	-	-	16
Subjects with any TEAEs considered potential sequalae of prolonged hyperphosphataemia[#]	1 (7.7%)	-	-	2 (12.5%)
Hypercalcaemia	0	-	-	1 (6.3%)
Hyperparathyroidism	1 (7.7%)	-	-	1 (6.3%)

Key: QD = once daily.
TEAEs considered potential sequalae of prolonged hyperphosphataemia include Calcium metabolism disorder, Chondrocalcinosis pyrophosphate, Chvostek's sign, Hypercalcaemia, Hypercalcaemic nephropathy, Hypercalcitoninaemia, Hyperparathyroidism, Hyperparathyroidism primary, Hyperparathyroidism secondary, Hyperreflexia, Hypocalcaemia, Hypocalcaemic seizure, Osteomalacia, Tetany, Trousseau's sign.
[#] Only include adverse events which occurred after first assessment of phosphate>=7.0 mg/dL which met the duration criteria of >1 months.
BLC3001 CHEMO Cohort 1: vinflunine 320 mg/m^2 as a 20-minute intravenous infusion once every 3 weeks or docetaxel 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks.
BLC3001 PEMBRO Cohort 2: pembrolizumab 200 mg as a 30-minute intravenous infusion once every 3 weeks.

Table 71 to 74 present the overviews of *eye toxicities*, n*ail and skin disorders* as well as *gastrointestinal disorders* by worst severity, seriousness, action taken, time to onset and resolution (mUC pool and BLC3001 erdafitinib pool, BLC2001).

Table 71: Other Eye Disorders by Worst Severity, Seriousness, Action Taken, Time to Onset, and Resolution: (mUC Pool and BLC3001 Erdafitinib Pool, BLC2001)

	BLC3001 Erdafitinib Pool (n=308)	**mUC Pool (n=479)**	**BLC2001 (N=99)**
Overall Incidence	123 (39.9%)	207 (43.2%)	62 (62.6%)
Maximum Severity			
Grade 3 or 4:	6 (1.9%)	14 (2.9%)	9 (9%)
Grade 4:	0	1 (0.2%)	1 (1%)
Serious Events	3 (1.0%)	9 (1.9%)	9 (9%)
Dose Modification			
Reduction	17 (5.5%)	36 (7.5%)	23 (23%)
Interruption	23 (7.5%)	44 (9.2%)	16 (16%)
Discontinuation	6 (1.9%)	10 (2.1%)	6 (6%)
Median Time to First Onset (days [range])			
Any grade	46 (1; 444)	49 (1; 828)	
Grade ³3:	263.5 (71; 640)	212.5 (60; 640)	

Time to First Onset by Treatment Interval[a]		
≤1 month	33 (10.7%)	60 (12.5%)
>1-2 months	43 (14.1%)	69 (14.6%)
>2-3 months	24 (8.5%)	38 (8.6%)
>3 months	23 (9.4%)	40 (10.4%)
Resolution at Data Cutoff[b]		
Resolved:	53 (43.1%)	102 (49.3%)
Unresolved	70 (22.7%)	105 (21.9%)
Grade 1	53 (17.2%)	76 (15.9%)
Grade 2	15 (4.9%)	26 (5.4%)
Grade 3	2 (0.6%)	2 (0.4%)
Grade 4	0	1 (0.2%)

[a] For each interval, only subjects who were treated in corresponding intervals and only AE which occurred in corresponding intervals are counted. AEs beyond last doses are assigned to last intervals in which subjects were treated.

[b] For "Resolved" percentage calculations are based on the "Overall Incidence" as the denominator. For "Unresolved" percentage calculations are based on the total number of subjects as the denominator.

Source: SCS, page58

Table 72: Nail Disorders by Worst Severity, Seriousness, Action Taken, Time to Onset, and Resolution (mUC Pool and BLC3001 Erdafitinib Pools, BLC2001)

	BLC3001 Erdafitinib Pool (n=308)	mUC Pool (n=479)	BLC2001 (n=99)
Overall Incidence	192 (62.3%)	300 (62.6%)	56 (56.6%)
Maximum Severity			
Grade 3:	39 (12.7%)	60 (12.5%)	14 (14%)
No CTCAE Grade 4			none
Serious Events	2 (0.6%)	2 (0.4%)	none
Dose Modification			
Reduction	70 (22.7%)	105 (21.9%)	20 (20%)
Interruption	66 (21.4%)	98 (20.5%)	17 (17%)
Discontinuation	8 (2.6%)	10 (2.1%)	1 (1%)
Median Time to First Onset (days [range])			
Any grade	59 (2; 617)	63 (2; 617)	68
Grade ³3:	104 (50; 357)	106 (50; 390)	112
Time to First Onset by Treatment Interval[a]			
≤1 month	23 (7.5%)	30 (6.3%)	4 (4%)
>1-2 months	77 (25.3%)	116 (24.5%)	20 (21.3%)
>2-3 months	46 (16.3%)	84 (19.0%)	21 (26.3%)
>3 months	46 (18.9%)	70 (18.3%)	11 (16.7%)
Resolution at Data Cutoff[b]			
Resolved:	44 (22.9%)	83 (27.7%)	
Unresolved	148 (48.1%)	217 (45.3%)	
Grade 1	66 (21.4%)	112 (23.4%)	
Grade 2	67 (21.8%)	87 (18.2%)	
Grade 3	15 (4.9%)	18 (3.8%)	
Grade 4	0	0	

	BLC3001 Erdafitinib Pool (n=308)	mUC Pool (n=479)	BLC2001 (n=99)

[a] For each interval, only subjects who were treated in corresponding intervals and only AE which occurred in corresponding intervals are counted. AEs beyond last doses are assigned to last intervals in which subjects were treated.
[b] For "Resolved" percentage calculations are based on the "Overall Incidence" as the denominator. For "Unresolved" percentage calculations are based on the total number of subjects as the denominator.
Source: SCS page 61

Table 73: Skin Disorders by Worst Severity, Seriousness, Action Taken, Time to Onset, and Resolution (mUC Pool and BLC3001 Erdafitinib Pool, BLC2001)

	BLC3001 Erdafitinib Pool (n=308)	mUC Pool (n=479)	BLC2001 (n=99)
Overall Incidence	168 (54.5%)	261 (54.5%)	50 (50%)I
Maximum Severity			
Grade 3 or 4:	36 (11.7%)	48 (10.0%)	7 (7%)
Grade 4:	0	0	0
Serious Events	2 (0.6%)	3 (0.6%)	1 (1%)
Dose Modification			
Reduction	42 (13.6%)	58 (12.1%)	9 (9%)
Interruption	51 (16.6%)	72 (15.0%)	10 (10%)
Discontinuation	4 (1.3%)	8 (1.7%)	3 (3%)
Median Time to First Onset (days)			
Any grade	43.5 (2; 463)	47 (1; 463)	40
Grade ³3:	135 (27; 463)	116 (27; 463)	94
Time to First Onset by Treatment Interval[a]			
≤1 month	49 (15.9%)	75 (15.7%)	22 (22.2%)
>1-2 months	57 (18.8%)	91 (19.2%)	13 (13.8%)
>2-3 months	27 (9.5%)	44 (10.0%)	9 (11.3%)
>3 months	35 (14.3%)	51 (13.3%)	6 (9.1%)
Resolution at Data Cutoff[b]			
Resolved:	70 (41.7%)	109 (41.8%)	
Unresolved	97 (31.5%)	151 (31.5%)	
Grade 1	58 (18.8%)	91 (19.0%)	
Grade 2	30 (9.7%)	50 (10.4%)	
Grade 3	9 (2.9%)	10 (2.1%)	
Grade 4	0	0	

[a] For each interval, only subjects who were treated in corresponding intervals and only AE which occurred in corresponding intervals are counted. AEs beyond last doses are assigned to last intervals in which subjects were treated.
[b] For "Resolved" percentage calculations are based on the "Overall Incidence" as the denominator. For "Unresolved" percentage calculations are based on the total number of subjects as the denominator.

Table 74: Gastrointestinal Events by Worst Severity, Seriousness, Action Taken, Time to Onset, and Resolution (mUC Pool and BLC3001 Erdafitinib Pool, BLC2001)

	BLC3001 Erdafitinib Pool (n=308)	mUC Pool (n=479)	BLC2001 (n=99)
Overall Incidence	255 (82.8%)	402 (83.9%)	91 (91.9%)
Diarrhea	176 (57.1)	266 (55.5%)	50 (50.5%)
Stomatitis	147 (57.1)	253 (52.8%)	57 (57.6%)
Dry mouth	116 (47.7)	191 (39.9%)	45 (45.5%)
Maximum Severity			
Grade 3 or 4:	38 (12.3%)	68 (14.2%)	
Grade 4:	1 (0.3%)	1 (0.2%)	
Diarrhea	12 (3.9%)	19 (4%)	10 (10.1%)
Stomatitis	4 (1.3%)	5 (1%)	4 (4.0%)
Dry mouth			
Serious Events	6 (1.9%)	7 (1.5%)	
Dose Modification			
Reduction	61 (19.8%)	99 (20.7%)	
Interruption	65 (21.1%)	118 (24.6%)	
Discontinuation	6 (1.9%)	13 (2.7%)	
Median Time to First Onset (days [range])			
Any grade	15 (1; 343)	15 (1; 445)	
Grade ³3:	50.5 (2; 287)	54.5 (2; 585)	
Time to First Onset by Treatment Interval[a]			
≤1 month	187 (60.7%)	298 (62.2%)	
>1-2 months	44 (14.5%)	55 (11.6%)	
>2-3 months	12 (4.2%)	24 (5.4%)	
>3 months	12 (4.9%)	25 (6.5%)	
Resolution at Data Cutoff[b]			
Resolved:	110 (43.1%)	186 (46.3%)	
Unresolved	144 (46.8%)	215 (44.9%)	
Grade 1	99 (32.1%)	148 (30.9%)	
Grade 2	37 (12.0%)	57 (11.9%)	
Grade 3	7 (2.3%)	9 (1.9%)	
Grade 4	1 (0.3%)	1 (0.2%)	

[a] For each interval, only subjects who were treated in corresponding intervals and only AE which occurred in corresponding intervals are counted. AEs beyond last doses are assigned to last intervals in which subjects were treated.

[b] For "Resolved" percentage calculations are based on the "Overall Incidence" as the denominator. For "Unresolved" percentage calculations are based on the total number of subjects as the denominator.

In view of the already approved FGFR inhibitors (pemigatinib and futibatinib), attention should also be paid to *potential renal and hepatic toxicities*.

In the erdafitinib pool, *increase of blood creatinine* was reported as a treatment emergent AE in 14.9% (46 subjects) of subjects, consisting of 8.1% (25 subjects) Grade 1 and 6.8% (21 subjects) Grade 2 elevations (in contrast to 6.3% in the chemotherapy arm and 7.5% in the pembrolizumab arm). Furthermore, acute kidney injury was seen in 5.5% (17 subjects), renal impairment in 3.6% (11 subjects) and renal failure in 3.2% (10 subjects). For 9 subjects (2.9%) a SAE of acute kidney injury was reported, 2 out of 52 patients discontinued the treatment due to acute kidney injury resp. renal failure.

In the erdafitinib pool *increase of transaminases* was reported as a treatment emergent AE in 21.1% (ALT) respectively 18.5% (AST) (in contrast to 3.6% (ALT) resp. 2.7% (AST) in the chemotherapy arm and 7.5% (ALT) resp. 8.1% (AST) in the pembrolizumab arm). In addition, hepatobiliary disorders were reported in 10.4%. Dose modifications due to increased transaminases were reported for 3.9%.

2.8.8.3. Serious adverse event/deaths/other significant events

Serious adverse events were reported in 42.6% of patients in the mUC pool. SAEs were considered treatment-related in 12.9% of patients (n=62).

SAEs occurred at a similar frequency in the BLC3001 erdafitinib pool (125 [40.6%] of 308 subjects), the chemotherapy group (47 [42.0%] of 112 subjects), and the pembrolizumab group (80 [46.2%] of 173 subjects). Of note, in the supportive study BLC2001 in the 8-mg daily regimen, serious TEAEs occurred in 39 subjects (39%).

Overall, 66.2% of 479 subjects on the mUC pool died. The majority of *deaths* (270 of 317) were due to progressive disease, 4.8% were due to adverse events. 12.3% of the 479 subjects died within 30 days of the last dose: 41 of 59 (8.6%) deaths were due to progressive disease and 18 of 59 (3.8%) deaths were due to an AE. Of note, in the BLC3001 erdafitinib pool 12 of 40 (3.9%) deaths were due to an AE.

Grade 5 TEAEs considered by the investigator to be related to treatment were reported by 1 subject in the BLC3001 erdafitinib pool (sudden death), 6 subjects in the chemotherapy group (febrile bone marrow aplasia [n=2], septic shock [n=2], atypical pneumonia, and febrile neutropenia), and 3 subjects in the pembrolizumab group (pulmonary embolism, respiratory failure, and urinary tract infection).

For subjects in the 8-mg daily regimen of the phase 2 study BLC2001, as of the clinical cut-off, 40 subjects (40%) had died. The primary reason for death (39 subjects; 39%) was progression of disease. One subject died due to an adverse event (acute myocardial infarction, considered not related to erdafitinib). Eight subjects (8.1%) died within 30 days of last dose including the 1 subject who died due to the adverse event.

Of note, in the BLC3001 erdafitinib pool 1 patient died due to an adverse event of renal failure within the 30-day safety follow-up period. However, this death was not considered treatment-related.

2.8.8.4. Laboratory findings and vital signs

Table 75 describes haematological laboratory abnormalities observed in ≥10%, or in ≥5% at Grade 3 or 4, of subjects in the BCL3001 erdafitinib pool.

Table 75: Laboratory Abnormalities Reported in ≥10% (All Grade) or ≥5% (Grade 3-4); Erdafitinib Safety Analysis Set (Study 42756493-BLC3001)

	Erdafitinib (N=308)	
	All Grades (%)	Grade 3-4 (%)
Hematology Laboratory Abnormality		
Anemia	47.1	9.1
White Blood Cell Decreased	26.9	0.6
Platelet Count Decreased	15.9	1.0
Neutrophil Count Decreased	15.6	0.6

Table 76 describes chemistry laboratory abnormalities observed in ≥10%, or in ≥5% at Grade 3 or 4, in subjects in the BCL3001 erdafitinib pool. Of note, hyperphosphataemia, hyponatremia, and blood creatinine increased have been identified as ADRs.

Table 76: Laboratory Abnormalities Reported in ≥10% (All Grade) or ≥5% (Grade 3-4); Erdafitinib Safety Analysis Set (Study 42756493-BLC3001)

	Erdafitinib (N=308)	
	All Grades (%)	Grade 3-4 (%)
Chemistry Laboratory Abnormality		
Hyperphosphatemia	68.8	2.6
Alkaline Phosphatase Increased	49.7	4.2
Creatinine Increased	49.7	2.3
Alanine Aminotransferase Increased	46.1	3.2
Aspartate Aminotransferase Increased	43.5	2.3
Hyponatremia	40.9	15.3
Hypophosphatemia	33.1	8.4
Hypomagnesemia	24.0	0.3
Hyperkalemia	21.8	2.3
Hypoalbuminemia	15.6	0
Blood Bilirubin Increased	11.7	1.9
Hypokalemia	10.7	1.6

Electrocardiograms were collected throughout the study EDI1001. No subjects had an average change from baseline in QTcF or QTcB that exceeded 60 msec. 10% had maximum average change in QTcB between 30 and 60 msec. Furthermore, average QTc values exceeded 500 msec post-baseline for 2 subjects, 1 subject with average QTcF and QTcB over 500 msec and 1 subject with average QTcB over 500 msec. 5 subjects had individual recordings that exceeded 500 msec. 10% and 0.5% of subjects had maximum post baseline QTcF values of 450 - ≤480 msec, and 480 - ≤500 msec, respectively.

Four subjects (2%) had electrocardiogram QT prolonged reported as an AE. For 2 subjects, electrocardiogram QT prolonged was considered related to study drug. One subject discontinued treatment due to electrocardiogram QT prolonged of grade3 and considered related to erdafitinib.

In study BLC3001 cohort 1, 12-lead ECGs were performed at screening, cycle 2 day 1, and cycle 4 day 1. 3 (2.5%) subjects in the erdafitinib group had ≥60 msec change in QTcF interval during treatment. 7 (5.8%) subjects in the erdafitinib group had ≥30-60 msec change in QTcF interval during treatment. At cycle 2 day 1, 1 (0.9%) subject in the erdafitinib group had a QTcF value above 500 msec (and ≥60 msec change in QTcF interval). The subject was hospitalised and the investigator considered these events not related to erdafitinib. The subject subsequently died suddenly; no signs or symptoms were reported prior to death. 5 subjects (4.4%) had a QTcF value >450(M) or >470(F). At cycle 4 day 1, 3 (3.4%) subjects in the erdafitinib group had a QTcF value 450(M) or >470(F).

In study BLC3001 cohort 2, at cycle 2 day 1, 9 (6%) subjects in the erdafitinib group had a QTcF value >450(M) or >470(F). At cycle 4 day 1, 4 (3.8%) subjects had a QTcF value >450(M) or >470(F) and 1 subject (1%) had a QTcF value above 500 msec. Three (2.0%) subjects in the erdafitinib group had ≥60 msec change in QTcF interval during treatment, and 8 subjects (5.3%) had ≥30-60 msec change in QTcF interval during treatment.

2.8.8.5. Safety in special populations

Analyses of TEAEs were performed to evaluate potential differences in the safety of erdafitinib in subgroups of subjects defined by age, sex, geographic region, tumour histology, and creatinine clearance. An overview of these results for the mUC pool is presented in **Table 77**.

Table 77: Overall Summary of Treatment-emergent Adverse Events by Demographic Subgroups; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

		N[a]	TEAE	Serious TEAE	Grade 3 or Higher	Grade 3	Grade 4	TEAE Leading to Study Treatment Discontinuation[b]	TEAE Leading to Death[c]
mUC Pool ERDA 8 or 9 mg QD									
Total number of subjects		479	477 (99.6%)	204 (42.6%)	322 (67.2%)	317 (66.2%)	42 (8.8%)	93 (19.4%)	29 (6.1%)
Age (years):	<65 years	191	190 (99.5%)	73 (38.2%)	126 (66.0%)	123 (64.4%)	13 (6.8%)	20 (10.5%)	7 (3.7%)
	>=65 years	288	287 (99.7%)	131 (45.5%)	196 (68.1%)	194 (67.4%)	29 (10.1%)	73 (25.3%)	22 (7.6%)
Sex:	Male	365	363 (99.5%)	154 (42.2%)	237 (64.9%)	232 (63.6%)	32 (8.8%)	70 (19.2%)	21 (5.8%)
	Female	114	114 (100.0%)	50 (43.9%)	85 (74.6%)	85 (74.6%)	10 (8.8%)	23 (20.2%)	8 (7.0%)
Geographic region:	North America	44	44 (100.0%)	22 (50.0%)	32 (72.7%)	32 (72.7%)	5 (11.4%)	9 (20.5%)	2 (4.5%)
	Europe	328	326 (99.4%)	134 (40.9%)	220 (67.1%)	216 (65.9%)	29 (8.8%)	75 (22.9%)	21 (6.4%)
	Rest of the World	107	107 (100.0%)	48 (44.9%)	70 (65.4%)	69 (64.5%)	8 (7.5%)	9 (8.4%)	6 (5.6%)
Baseline creatinine clearance (mL/min):	<30	5	5 (100.0%)	4 (80.0%)	4 (80.0%)	4 (80.0%)	1 (20.0%)	2 (40.0%)	0
	>=30 to <60	217	216 (99.5%)	99 (45.6%)	151 (69.6%)	149 (68.7%)	21 (9.7%)	51 (23.5%)	17 (7.8%)
	>=60	257	256 (99.6%)	101 (39.3%)	167 (65.0%)	164 (63.8%)	20 (7.8%)	40 (15.6%)	12 (4.7%)

Key: QD = once daily, TEAE = treatment-emergent adverse event, CRF = case report form.
[a] Percentages are calculated with the number of subjects in each subgroup as denominator.
[b] Treatment discontinuation due to adverse event on the end of treatment CRF page.
[c] TEAE with outcome death on the AE CRF page or with toxicity grade 5.
BLC3001 CHEMO Cohort 1: vinflunine 320 mg/m^2 as a 20-minute intravenous infusion once every 3 weeks or docetaxel 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks.
BLC3001 PEMBRO Cohort 2: pembrolizumab 200 mg as a 30-minute intravenous infusion once every 3 weeks.
BLC3001 inclusion criterion on renal function: Creatinine clearance (CrCl) >30 mL/min either directly measured via 24-hour urine collection or calculated using the Cockcroft-Gault formula. In this table, Cockcroft-Gault Formula is used for calculating estimated baseline creatinine clearance. That is the reason why there are patients with baseline creatinine clearance <30 (mL/min) in the table.

Table 78: Treatment Emergency Adverse Events by Age group; mUC Safety Analysis

	mUC Pool ERDA 8 or 9 mg QD			
	Age <65	Age 65-74	Age 75-84	Age 85+
Total number of subjects	191	191	85	12
Subjects with 1 or more:				
AEs	190 (99.5%)	191 (100.0%)	84 (98.8%)	12 (100.0%)
Related AEs	187 (97.9%)	185 (96.9%)	80 (94.1%)	12 (100.0%)
AEs leading to discontinuation of study agent	20 (10.5%)	39 (20.4%)	29 (34.1%)	5 (41.7%)
Serious AEs	73 (38.4%)	92 (48.2%)	35 (41.7%)	4 (33.3%)
Fatal	7 (3.7%)	14 (7.3%)	6 (7.1%)	2 (16.7%)
Hospitalization/prolong existing hospitalization	66 (82.5%)	78 (81.3%)	31 (70.5%)	4 (80.0%)
Life-threatening	5 (2.6%)	10 (5.2%)	5 (5.9%)	0
Disability/incapacity	5 (2.6%)	7 (3.7%)	1 (1.2%)	0
Other (medically significant)	7 (3.7%)	13 (6.8%)	5 (5.9%)	0
Infections and infestations	93 (48.7%)	109 (57.1%)	46 (54.1%)	6 (50.0%)
Related AEs	43 (22.5%)	54 (28.3%)	25 (29.4%)	3 (25.0%)
Serious AEs	17 (8.9%)	31 (16.2%)	12 (14.1%)	1 (8.3%)
Nervous system disorders	84 (44.0%)	87 (45.5%)	37 (43.5%)	8 (66.7%)
Related AEs	64 (33.5%)	67 (35.1%)	28 (32.9%)	6 (50.0%)
Serious AEs	2 (1.0%)	3 (1.6%)	1 (1.2%)	0
Central serous retinopathy	30 (15.7%)	50 (26.2%)	21 (24.7%)	2 (16.7%)
Related AEs	28 (14.7%)	47 (24.6%)	20 (23.5%)	2 (16.7%)
Serious AEs	3 (1.6%)	7 (3.7%)	2 (2.4%)	0
Accidents and injuries	26 (13.6%)	26 (13.6%)	16 (18.8%)	3 (25.0%)
Related AEs	10 (5.2%)	15 (7.9%)	11 (12.9%)	0
Serious AEs	4 (2.1%)	1 (0.5%)	1 (1.2%)	1 (8.3%)
Vascular disorders	24 (12.6%)	25 (13.1%)	12 (14.1%)	0
Related AEs	7 (3.7%)	6 (3.1%)	5 (5.9%)	0
Serious AEs	1 (0.5%)	4 (2.1%)	2 (2.4%)	0
Psychiatric disorders	21 (11.0%)	14 (7.3%)	9 (10.6%)	2 (16.7%)
Related AEs	6 (3.1%)	2 (1.0%)	1 (1.2%)	1 (8.3%)
Serious AEs	1 (0.5%)	0	1 (1.2%)	0
Cardiac disorders	8 (4.2%)	12 (6.3%)	6 (7.1%)	0
Related AEs	0	4 (2.1%)	0	0
Serious AEs	1 (0.5%)	3 (1.6%)	4 (4.7%)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	6 (3.1%)	6 (3.1%)	7 (8.2%)	2 (16.7%)
Related AEs	2 (1.0%)	2 (1.0%)	3 (3.5%)	0

	mUC Pool ERDA 8 or 9 mg QD			
	Age <65	Age 65-74	Age 75-84	Age 85+
Serious AEs	0	0	0	0
Cerebrovascular disorders	1 (0.5%)	2 (1.0%)	1 (1.2%)	1 (8.3%)
Related AEs	0	1 (0.5%)	0	0
Serious AEs	1 (0.5%)	0	1 (1.2%)	0
Anticholinergic syndrome	127 (66.5%)	110 (57.6%)	52 (61.2%)	9 (75.0%)
Related AEs	110 (57.6%)	94 (49.2%)	45 (52.9%)	7 (58.3%)
Serious AEs	5 (2.6%)	4 (2.1%)	4 (4.7%)	3 (25.0%)
AEs of clinical importance				
Gastrointestinal toxicity	161 (84.3%)	156 (81.7%)	74 (87.1%)	11 (91.7%)
Related AEs	152 (79.6%)	145 (75.9%)	73 (85.9%)	11 (91.7%)
Serious AEs	1 (0.5%)	5 (2.6%)	1 (1.2%)	0
Hyperphosphatemia	155 (81.2%)	147 (77.0%)	63 (74.1%)	11 (91.7%)
Related AEs	151 (79.1%)	139 (72.8%)	60 (70.6%)	11 (91.7%)
Serious AEs	0	0	0	0
Nail toxicity	121 (63.4%)	115 (60.2%)	54 (63.5%)	10 (83.3%)
Related AEs	120 (62.8%)	111 (58.1%)	51 (60.0%)	9 (75.0%)
Serious AEs	1 (0.5%)	1 (0.5%)	0	0
Skin toxicity	111 (58.1%)	98 (51.3%)	45 (52.9%)	7 (58.3%)
Related AEs	108 (56.5%)	91 (47.6%)	44 (51.8%)	6 (50.0%)
Serious AEs	2 (1.0%)	0	0	1 (8.3%)
Eye toxicity (excluding CSR)	90 (47.1%)	72 (37.7%)	40 (47.1%)	5 (41.7%)
Related AEs	85 (44.5%)	63 (33.0%)	32 (37.6%)	3 (25.0%)
Serious AEs	4 (2.1%)	3 (1.6%)	2 (2.4%)	0

Key: QD = once daily, TEAE = treatment-emergent adverse event
Accidents and injuries are based on the Standardized MedDRA Query (SMQ) per MedDRA Version 24.1.
[TSFAE43A.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_FDA_REQUEST/TSFAE43A.SAS] 07FEB2024, 15:21

2.8.8.6. Immunological events

N/A

2.8.8.7. Safety related to drug-drug interactions and other interactions

Refer to section 2.6.1.

2.8.8.8. Discontinuation due to adverse events

Incidence of treatment-emergent adverse events leading to dose modification by preferred term is summarised in Table 79.

Table 79: Incidence of Treatment-emergent Adverse Events Leading to Dose Modification (which include dose interruption, dose reduction, or both) by Preferred Term; mUC Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	BLC3001			mUC Pool
	ERDA Cohort 1 and Cohort 2 8 or 9 mg QD	CHEMO Cohort 1	PEMBRO Cohort 2	ERDA 8 or 9 mg QD
Total number of subjects	308	112	173	479
Subjects with TEAEs	259 (84.1%)	52 (46.4%)	57 (32.9%)	394 (82.3%)
Preferred term				
Stomatitis	65 (21.1%)	2 (1.8%)	0	121 (25.3%)
Palmar-plantar erythrodysaesthesia syndrome	49 (15.9%)	1 (0.9%)	0	71 (14.8%)
Hyperphosphataemia	23 (7.5%)	0	0	61 (12.7%)
Onycholysis	43 (14.0%)	0	0	58 (12.1%)
Diarrhoea	37 (12.0%)	4 (3.6%)	0	48 (10.0%)
Nail dystrophy	13 (4.2%)	0	0	28 (5.8%)
Onychomadesis	21 (6.8%)	0	0	28 (5.8%)
Chorioretinopathy	17 (5.5%)	0	0	26 (5.4%)
Paronychia	9 (2.9%)	0	0	24 (5.0%)
Asthenia	11 (3.6%)	7 (6.3%)	1 (0.6%)	22 (4.6%)
Decreased appetite	15 (4.9%)	2 (1.8%)	1 (0.6%)	22 (4.6%)
Fatigue	7 (2.3%)	2 (1.8%)	4 (2.3%)	22 (4.6%)
Nail discolouration	17 (5.5%)	0	0	20 (4.2%)
Alanine aminotransferase increased	12 (3.9%)	0	3 (1.7%)	18 (3.8%)
Hyponatraemia	12 (3.9%)	0	0	18 (3.8%)
Vision blurred	7 (2.3%)	0	0	18 (3.8%)
Detachment of retinal pigment epithelium	12 (3.9%)	0	0	17 (3.5%)
Dry mouth	11 (3.6%)	0	0	17 (3.5%)
Aspartate aminotransferase increased	12 (3.9%)	0	3 (1.7%)	16 (3.3%)
Keratitis	8 (2.6%)	0	0	16 (3.3%)
Vomiting	9 (2.9%)	0	1 (0.6%)	16 (3.3%)
Dry skin	12 (3.9%)	0	0	15 (3.1%)
Dysgeusia	7 (2.3%)	0	0	14 (2.9%)
Nail disorder	8 (2.6%)	0	0	14 (2.9%)
Nausea	8 (2.6%)	2 (1.8%)	1 (0.6%)	13 (2.7%)
Pain in extremity	8 (2.6%)	1 (0.9%)	0	11 (2.3%)
Pyrexia	4 (1.3%)	2 (1.8%)	4 (2.3%)	11 (2.3%)
Retinopathy	7 (2.3%)	0	0	11 (2.3%)
Urinary tract infection	7 (2.3%)	2 (1.8%)	5 (2.9%)	11 (2.3%)
Weight decreased	6 (1.9%)	0	0	10 (2.1%)

For the mUC pool, 93 (19.4%) of 479 subjects reported at least one TEAE leading to discontinuation of study treatment. There were 61 (12.7%) subjects who experienced TEAEs leading to discontinuation of study treatment that were considered by the investigator to be related to erdafitinib. Detachment of retinal pigment epithelium (8 [1.7%] subjects) was the most common TEAE considered by the investigator to be related to erdafitinib leading to discontinuation of study treatment.

Results were similar for the mUC pool and the BLC3001 erdafitinib pool.

Adverse events leading to discontinuation of study treatment occurred at a similar frequency in the BLC3001 erdafitinib pool (52 [16.9%] of 308 subjects) and the chemotherapy group (20 [17.9%] of 112 subjects) and at a lower rate in the pembrolizumab group (19 [11.0%] subjects).

2.8.8.9. Post marketing experience

Erdafitinib was approved in the United States under the trade name of BALVERSA® in April 2019. In addition, as of 11 April 2023, erdafitinib was approved in additional countries/territories (Argentina, Canada, Chile, Egypt, Hong Kong, Israel, Jordan, Mexico, Peru, Philippines, Saudi Arabia, Singapore, South Korea, Taiwan, Thailand, and Turkey) under the trade name of BALVERSA® and in Brazil under the name of ERFANDEL® for the treatment of adult patients with locally advanced or mUC. The applicant stated that the surveillance of spontaneous cases of AEs reported with the use of erdafitinib indicates that the safety profile of the drug in the post marketing setting is consistent with what is known about the drug's overall established safety profile from clinical studies.

2.8.9. Discussion on clinical safety

Patient Exposure

In total, 479 subjects were included in the mUC pool. At the time of clinical cutoff, 57 (11.9%) subjects in the mUC pool were still receiving erdafitinib and 422 (88.1%) subjects had discontinued study treatment. The most common reason for study treatment discontinuation was progressive disease (322 [67.2%] subjects). Eighty (16.7%) subjects discontinued study treatment due to an AE. Death was listed as the reason for discontinuation of study treatment for 5 (1.0%) subjects.

For the mUC pool, the median (range) treatment duration was 4.8 months (0.1 to 43.4). 15% in the mUC pool received erdafitinib >12 months. The median relative dose intensity was 75.1%. The median (range) treatment duration for the BLC3001 erdafitinib pool (4.6 [0.1 to 43.4] months) was longer than for the chemotherapy group (1.4 [0.0 to 26.9] months) and for the pembrolizumab group (3.5 [0.0 to 50.5] months).

Adverse events (general)

TEAEs were reported by almost all subjects in the mUC pool and the BLC3001 erdafitinib pool, as well as in the chemotherapy and pembrolizumab groups. TEAEs considered by the investigator to be related to treatment occurred more frequently in BLC3001 erdafitinib pool (300 [97.4%] of 308 subjects) compared with the chemotherapy group (97 [86.6%] of 112 subjects) and the pembrolizumab group (105 [60.7%] of 173 subjects).

Grade 3 or Grade 4 TEAEs considered by the investigator to be related to erdafitinib were reported for 45.9% of subjects in the mUC pool. and at a similar frequently in the BLC3001 erdafitinib pool (44.5%) and the chemotherapy group (46.4%) while at a lower frequency in the pembrolizumab group (12.1%).

Serious TEAEs considered by the investigator to be related to erdafitinib were reported in 12.9% of subjects in the mUC pool. Serious TEAEs considered by the investigator to be related to study treatment occurred at a similar frequency in the BLC3001 erdafitinib pool (13.3%) and the pembrolizumab group (10.4%) and at a higher frequency in the chemotherapy group (24.1%).

TEAEs leading to discontinuation of study drug considered by the investigator to be related to erdafitinib were reported in 12.7% of subjects in the mUC pool. TEAEs leading to discontinuation of

study drug considered by the investigator to be related to study treatment were reported more frequently in the BLC3001 erdafitinib pool (12.0%) and the chemotherapy group (13.4%) compared with the pembrolizumab group (4.6%).

There was 1 death (sudden death) considered by the investigator to be related to erdafitinib in BLC3001 Cohort 1. Six subjects in the chemotherapy group and 3 subjects in the pembrolizumab group experienced a TEAE with an outcome of death considered treatment related.

Overall, the frequencies of TEAEs, Grade 3 or 4 TEAEs, serious TEAEs, dose modifications respectively discontinuations due to TEAEs were similar across the mUC pool and the BLC3001 erdafitinib pool. In addition, the safety profile of study BLC3001 (Erdafitinib pool) was similar to the one of supportive phase 2 study (BLC2001).

Patients treated in the chemotherapy arm (Cohort 1) of study BLC3001 received either vinflunine or docetaxel (investigators choice). A subgroup analyses (comparison vinflunine vs erdafitinib respectively docetaxel vs erdafitinib) showed that more subjects in the erdafitinib group (41.5%) experienced SAEs compared with the docetaxel subgroup (31.9%), but a lower proportion compared with the vinflunine subgroup (58.1%). A similar pattern was noted for TEAEs leading to death (4.4%, 2.9%, and 11.6%, respectively) and Grade 3-4 AEs (63.0%, 55.1%, 79.1%, respectively). Whereas, the proportion of subjects with serious related TEAEs was lower in the erdafitinib group (13.3%) compared with the docetaxel group (18.8%), but notably lower than in the vinflunine group (32.6%); a similar pattern was noted for TEAEs leading to discontinuation of study drug (14.1%, 15.9%, and 20.9%, respectively). In summary, the comparisons of erdafitinib with type of investigator's choice chemotherapy (docetaxel or vinflunine) does not change the safety conclusions for erdafitinib. However, these data should be interpreted with caution, as there was no randomisation between docetaxel and vinflunine.

For the mUC pool, TEAEs considered by the investigator to be related to erdafitinib occurred in 464 (96.9%) of 479 subjects. Hyperphosphataemia was the most frequently reported drug-related TEAE (361 [75.4%] subjects). Other common TEAEs in the mUC pool that occurred with a frequency >40% and were considered by the investigator to be related to erdafitinib were stomatitis (50.5%) and diarrhoea (46.3%).

Related TEAEs with a worst severity of Grade 3 were reported for 45.9% subjects with stomatitis being the most commonly reported (49 [10.2%] subjects). Related TEAEs with a worst severity of Grade 4 were reported for 5 (1.0%) subjects and included events of blood alkaline phosphatase increased (1 [0.2%] subject), duodenal ulcer haemorrhage (1 [0.2%] subject), gastrointestinal haemorrhage (1 [0.2%] subject), hyperphosphataemia (1 [0.2%] subject), and hyponatremia (1 [0.2%] subject).

Adverse events of special interest (AESI) and clinical importance

Central serous retinopathy (CSR) has been identified as an AESI for erdafitinib and is a known class effect of FGFR inhibitors. Chronic CSR can lead to a decline in visual acuity and a lower vision-related quality of life.

Most events of central serous retinopathy in subjects in the mUC pool were Grade 1 or 2, with 2.3% of subjects experiencing Grade 3 events and no subjects experiencing Grade 4 events. The majority of central serous retinopathy events occurred within the first 90 days of treatment. The median time to first onset for any Grade event was 45 days. CSR had resolved for 2/3 of patients, whereas 1/3 had unresolved events. Of note, 8.6% of patients had dose interruptions, 12.1% had dose reductions and 2.9% discontinued Erdafitinib due to an event of CSR. Of the 41 subjects with CSR leading to dose interruption, 16 had recurrence and/or worsening of events after restarting: 15 (3.1) subjects had

recurrent central serious retinopathy events without worsening and 1 subject had recurrent and worsening central serous retinopathy. No central serous retinopathy events of worsening alone were reported. Of the 58 subjects who had CSR events leading to dose reduction, 23 had recurrent CSR without worsening, 7 had recurrent and worsening central serous retinopathy, and 3 had worsening central serous retinopathy alone.

There were no reported events of blindness in clinical studies.

Overall, recurrent events in the same or contralateral eye upon resumption of erdafitinib at the same or lower dose are relatively frequent, while recurrent and worsening events are less common. However, close ophthalmologic surveillance is critically important in subjects who restart erdafitinib after an ocular event.

Central serous retinopathy is included in the SmPC (Section 4.2, 4.4 and 4.8) as well as an important identified risk in the in the list of safety concerns in the RMP.

In the mUC pool, the overall incidence of central serous retinopathy was higher in subjects ≥65 years of age (33.3%) compared with subjects <65 years of age (28.87%). Events of RPED were reported more frequently in subjects ≥65 years of age (6.3%) compared with subjects <65 years of age (2.1%). This was also the trend for grade 3 and higher CSR events, serious CSR events, dose reductions, dose modification and treatment discontinuation. Similarly, in the BLC3001 erdafitinib pool, the overall incidence of central serous retinopathy and RPED was higher in subjects ≥65 years of age compared with subjects <65 years of age. This information about elderly is included in the SmPC.

The frequency of adverse reactions of CSR in the BLC3001 erdafitinib pool was similar to the mUC pool and to the phase 2 study BLC2001 whereas no events of CSR were reported for the chemotherapy and the pembrolizumab arm of study BLC3001.

Adverse events of clinical importance include events that are class effects of FGFR inhibitors (hyperphosphataemia, eye disorders [other than central serous retinopathy], nail and skin disorders), as well as those identified based on clinical findings (gastrointestinal disorders). Adverse events of clinical importance were observed at a similar frequency across the mUC pool and the BLC3001 erdafitinib pool and were observed less frequently in the chemotherapy and pembrolizumab groups.

Hyperphosphataemia is an expected and transient laboratory abnormality of FGFR inhibitors due to their mechanism of action (IB Erdafitinib 2023). This can serve as a pharmacodynamic marker of target engagement in early cycles.

Detailed up-titration guidelines as well as dose modification guidelines are given in SmPC. In the study BLC3001 the majority of patients increased erdafitinib dose to 9 mg (cohort 1 77.0%, cohort 2 82.1%) whereas in the phase 2 study only 41/99 patients (8mg regimen) were up titrated.

In the mUC pool adverse reactions of *hyperphosphataemia* were reported in 78.5% of patients (Grade 3/4 2.9%). The median time to first onset for any Grade event was 15 days. At data cut-off hyperphosphataemia had resolved for approx. most of the patients (83.8%). 10% of patients had dose interruptions, 5.2% had dose reductions and 0.2% discontinued Erdafitinib due to an event of hyperphosphataemia. Similar incidences were reported for the erdafitinib pool and the supportive phase 2 study BLC2001.

Overall, the safety profiles appeared similar between the phase 2 study (BLC2001, up-titration when serum phosphate was less than 5.5 mg/dL) and the phase 3 Study (BLC3001, up-titration when serum phosphate was less than 9 mg/dL) and between patients who were up-titrated vs. those who were not up-titrated in the phase 3 study. Up-titration criteria implemented in study BLC3001 demonstrated a favourable benefit-risk in this subject population when compared with chemotherapy.

There was a low incidence of *prolonged hyperphosphataemia* in the BLC3001 erdafitinib pool. The most frequently reported TEAE considered a potential sequela of prolonged hyperphosphataemia was hypercalcemia, the interpretation of which is difficult as it a very common laboratory abnormality in patients with advanced malignancies (Stewart 2005). TEAEs considered potential sequelae of prolonged hyperphosphataemia were reported in 30 (9.7%) of 308 subjects in the BLC3001 erdafitinib pool and in 1 (7.7%) of 13 subjects in the BLC3001 erdafitinib pool with a phosphate value ≥7 mg/dL for >1 month.

As discussed by the applicant hyperphosphataemia is most commonly seen in the setting of chronic kidney disease. Decreased renal function interferes with the kidneys' ability to maintain fluid and electrolyte homeostasis, which results in decreased ability to excrete excess phosphate, acid, and potassium. Prolonged hyperphosphataemia can lead to sequelae including anaemia, hypotension, hypercalcemia, worsening renal impairment, hypocalcaemia, hyperparathyroidism, and worsening renal failure. Comparison of the incidence of these events between all subjects in the study and those with prolonged hyperphosphataemia showed a lower incidence for subjects with prolonged hyperphosphataemia (25%) versus all subjects (34%). However, there was a slightly higher incidence of anaemia for subjects with prolonged hyperphosphataemia than in all subjects (25% vs 20%), and for renal impairment (10% vs 7.1%).

AEs considered potential sequelae of prolonged hyperphosphataemia and related to erdafitinib (vascular calcification, hypercalcaemia and hyperparathyroidism) are included in the list of ADR of the SmPC In addition, hypocalcaemia, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias were added to the warning of hyperphosphataemia in section 4.4 of the SmPC as potential risks of prolonged hyperphosphataemia.

Thirteen subjects (4.2%) treated with erdafitinib in BLC3001 (Cohorts 1 and 2) experienced hypophosphatemia versus 0% in chemotherapy arm. The majority (84.6%) of subjects with events of hypophosphatemia had experienced a prior event of hyperphosphataemia; most events were of low grade, and all but one resolved with a median duration of 21 days. In summary, reasons for hypophosphataemia in subjects treated with erdafitinib remain unclear. A warning about the risk of potential hypophosphataemia and the need to discontinue phosphate binders and dietary restrictions once a sufficient decline in serum phosphate is attained is included in section 4.4 of the SmPC.

In the mUC pool adverse reactions of *eye disorders* were reported in 43.2% of patients (Grade 3/4 2.9%). The median time to first onset for any Grade event was 50 days. Eye disorders had resolved for 49% of patients, whereas 51% had unresolved events of which the majority were Grade 1. Of note, 9.2% of patients had dose interruptions, 7.5 % had dose reductions and 2.1% discontinued Erdafitinib due to an event of eye disorders. Similar incidences were reported for the erdafitinib pool whereas the frequency of adverse reactions of eye disorders was remarkably lower in the chemotherapy and the pembrolizumab arm. SOC *eye disorders* is included in section 4.8 of the SmPC.

In the mUC pool adverse reactions of *nail disorders* were reported in 62.6% of patients (Grade 3 12.5%). The median time to first onset for any Grade event was 60 days. Nail disorders had resolved for 1/3 of patients, whereas 2/3 had unresolved events. Of note, 20.5% of patients had dose interruptions, 21.9% had dose reductions and 2.1% discontinued Erdafitinib due to an event of nail disorders. In the mUC pool adverse reactions of *skin disorders* were reported in 54.5% of patients (Grade 3/4 10.0%). No severe cutaneous adverse reactions (ie, Stevens-Johnson syndrome/toxic epidermal necrolysis [TENS], drug reaction with eosinophilia and systemic symptoms [DRESS], acute generalised exanthematous pustulosis [AGEP], and generalised bullous fixed drug eruptions [GBFDE]) were observed with erdafitinib. The median time to first onset for any Grade event was 47 days. Skin disorders had resolved for approx. half of patients, whereas 1/2 had unresolved events. Of note, 15% of patients had dose interruptions, 12.1% had dose reductions and 1.7% discontinued Erdafitinib due

to an event of nail disorders. Similar incidences were reported for the *erdafitinib pool and the phase 2 study BLC2001* whereas the frequency of adverse reactions of nail and skin disorders was remarkably lower in the chemotherapy and the pembrolizumab arm.

Recommendations for prophylaxis and symptom managements for nail toxicity, skin disorders, dry mouth and mucositis were applied during treatment with erdafitinib and are included in section 4.4 of the SmPC. Appropriate recommendations and warnings concerning a potential phototoxicity of erdafitinib were added in the relevant sections of the SmPC. In addition, phototoxicity will be subject to routine periodic safety reporting.

In the mUC pool adverse reactions of *gastrointestinal disorders* were reported in 83.9% of patients (Grade 3/4 14.2%). The median time to first onset for any Grade event was 15 days. Gastrointestinal disorders had resolved for approx. half of patients, whereas 1/2 had unresolved events. Of note, 24.6% of patients had dose interruptions, 20.7% had dose reductions and 2.7% discontinued erdafitinib due to an event of gastrointestinal disorders. Similar incidences were reported for the *erdafitinib pool and the phase 2 study BLC2001* whereas the frequency of adverse reactions gastrointestinal disorders was slightly lower in the chemotherapy and the pembrolizumab arm.

SOC *gastrointestinal disorders* is included in 4.8 of the SmPC.

In view of the already approved FGFR inhibitors (Pemigatinib and futibatinib), attention should also be paid to *potential renal and hepatic toxicities*.

In the erdafitinib pool *increase of blood creatinine* was reported as a treatment emergent AE in 14.9% (46 subjects), consisting of 8.1% (25 subjects) Grade 1 and 6.8% (21 subjects) Grade 2 elevation (no >Grade 2 event was observed) in contrast to 6.3% in the chemotherapy arm and 7.5% in the pembrolizumab arm. Furthermore, in the BLC3001 erdafitinib pool, acute kidney injury was seen in 5.5% (17 subjects), renal impairment in 3.6% (11 subjects) and renal failure in 3.2% (10 subjects). Of note for 9 subjects (2.9%) a SAE of acute kidney injury was reported and 2 out of 52 patients discontinued the treatment due to acute kidney injury resp. renal failure.

The potential nephrotoxic effect of erdafitinib, along with further analysis regarding the effect of erdafitinib (exposure and serum phosphate levels) on renal safety was further discussed. In summary, observed incidence of acute renal failure (ARF) events was similar in younger and older subjects, and higher in subjects with history of diabetes, hypertension or kidney impairment at baseline. Of note, neither the exposure to erdafitinib nor the serum phosphate levels were associated with higher incidence of Grade ≥2 serum creatinine increase. Creatinine elevations and renal toxicity are reflected in the SmPC.

It is agreed, that - based on the preclinical and clinical data - OCT2 inhibition is not considered to have contributed significantly to observed increases in serum creatinine among patients receiving erdafitinib.

Increase of transaminases: based on data presented erdafitinib might not have a potential for clinically significant hepatotoxicity. However, *transaminase elevations* and the potential *hepatotoxicit*y are reflected in the SmPC.

Dose modification and discontinuation due to adverse events

Dose interruptions and reductions due to treatment-related adverse events were necessary for 82.3% in the mUC pool, indicating the non-negligible safety profile of erdafitinib. Similar incidences were reported for the erdafitinib pool whereas the frequency of dose modifications was remarkably lower in the chemotherapy (46.4%) and the pembrolizumab arm (33%).

In the mUC pool, ~ 17% patients discontinued treatment due to adverse events and 61 (12.7%) experienced TEAEs leading to discontinuation of study treatment that were considered to be related to erdafitinib. Detachment of retinal pigment epithelium (8 [1.7%] subjects) was the most common TEAE leading to discontinuation of study treatment. Results were similar for the mUC pool and the BLC3001 erdafitinib pool.

The most common TEAEs leading to dose modification of erdafitinib were stomatitis (25.3%), PPES (14.8%), hyperphosphataemia (12.7%), onycholysis (12%), diarrhoea (10%), nail dystrophy (5.8%), onychomadesis (5.8%), chorioretinopathy (5.4%), paronychia, asthenia (4.6%), decreased appetite (4.6%) and fatigue (4.6%), increased ALT (3.8%), and increased AST (3.3%). Similar results were reported, for the BLC3001 erdafitinib pool.

Guidelines on dose modifications for management of specific toxicities (i.e. hyperphosphataemia, nail, skin, eye toxicities and mucosal changes) as well as for other toxicities are included in the SmPC.

Laboratory findings and electrocardiogram QT prolongation

Haematology abnormalities were reported as treatment emergent treatment related adverse events. Particular anaemia occurred frequently with erdafitinib (27%). The incidence of events considered related to erdafitinib was 10%.

Incidence of treatment related anaemia was lower in the erdafitinib arm in comparison to the chemotherapy arm (Cohort 1 of study BLC3001). However, the incidence of treatment related anaemia was remarkably higher in the erdafitinib arm than in the pembrolizumab arm (Cohort 2 of study BLC3001). *Haematology abnormalities* are reported in the SmPC.

Correlation between anaemia and hyperphosphataemia under the treatment with erdafitinib is described in the literature (Kovesdy et al. 2011, Tran et al. 2015 , Wojcicki et al. 2013, Silver et al. 2010) cannot be excluded although rather unlikely.

As already stated above *hyperphosphataemia* is an expected and transient laboratory abnormality of FGFR inhibitors due to their mechanism of action. This can serve as a pharmacodynamic marker of target engagement in early cycles. Mean phosphate values increased immediately after start of dosing, with the observed peak on Cycle 2 Day 1 and Cycle 3 Day 1. Mean values generally decreased from that point forward. However, during treatment most patients had shifts to increased phosphate levels and it is fully supported that hyperphosphataemia is reported as a TEAE and has been identified as an ADR. Mild increases in creatinine laboratory values and mild increases in laboratory values of ALT and AST were observed in the erdafitinib group consistent with the reported TEAEs of ALT increased and AST increased (Cohort 1 and Cohort 2 of BLC3001) and are included as ADR in the SmPC.

In both Cohort 1 and Cohort 2 of BLC3001, *moderate to severe hyponatremia* was identified by clinical laboratory values in the erdafitinib group. The applicant outlined a pathophysiological mechanism for hyponatremia due to FGF23-inhibition by erdafitinib. Risk of hyponatremia was threefold higher in patients with concomitant use of diuretics. These laboratory findings were consistent with hyponatremia reported as a TEA and included in the SmPC.

QT prolongation events of all grades were reported in study BLC3001.

As the potential for hyperphosphataemia leading to QT prolongation cannot be excluded, QT prolongation will be added as an Important Potential Risk in the EU RMP for erdafitinib.

Safety in special populations

More subjects ≥65 years of age experienced serious TEAEs, Grade 4 TEAEs, TEAEs leading to study treatment discontinuation and TEAEs leading to death. As already discussed above, particular central serous retinopathy was reported more frequently in subjects ≥65 years of age.

There was a lower incidence of Grade 3 or 4 events reported for males (236 [64.7%] subjects) compared with females (85 [74.6%] subjects). In all other categories (SAE, death…) women experience slightly higher percentages than men. Further monitoring will be done with routinely collected data.

A small trend to the detriment of patients with poorer creatinine clearance were seen, a possible higher toxicity for subjects with renal impairment will be further monitored with routinely collected data.

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed between subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function.

Post marketing experience

erdafitinib was approved for the first time in the United States in April 2019. Since then, it has been approved in several other countries. The applicant stated that the surveillance of spontaneous cases of AEs reported with the use of erdafitinib indicates that the safety profile of the drug in the post marketing setting is consistent with what is known about the medicine's overall established safety profile from clinical studies.

2.8.10. Conclusions on the clinical safety

The safety profile of erdafitinib as characterised with the current median of exposure in the applied target population is in accordance with what can be expected from the non-clinical studies and known class effects for FGFR inhibition.

Erdafitinib showed high incidence and high level of seriousness of the events reported. The currently identified main safety risks of erdafitinib are hyperphosphataemia, central serous retinopathy, further eye disorders, nail and skin disorders, gastrointestinal disorders and embryofoetal toxicity.

In summary, risks from erdafitinib toxicities in the applied population are clinically relevant, but manageable with treatment interruption and dose modifications, which occurred frequently (82%). Incidence of treatment discontinuation due to AEs were however, lower compared to the chemotherapy group.

2.9. Risk Management Plan

2.9.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 1.4.

Table 80: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Central serous retinopathy • Hyperphosphataemia
Important potential risks	• Reproductive and developmental toxicity • Potential drug toxicity due to accumulation of P-glycoprotein substrates • QT prolongation
Missing information	• None

2.9.2. Pharmacovigilance plan

2.9.2.1. Routine pharmacovigilance activities

No activity beyond routine pharmacovigilance activities is proposed by the MAH.

2.9.3. Risk minimisation measures

Table 81: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risk		
Central serous retinopathy	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, 4.7 and 4.8 • PL Section 2 and 4 • Legal status: medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hyperphosphataemia	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, 4.8, 5.1 and 5.3 • PL Section 2, 3 and 4 • Legal status: medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		
Reproductive and developmental toxicity	**Routine risk minimisation measures:** • SmPC Section 4.4, 4.5, 4.6, 5.3 • PL Section 2 • Legal status: medical prescription **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Potential drug toxicity due to accumulation of P-glycoprotein substrates	**Routine risk minimisation measures:** • SmPC Section 4.5 and 5.2 • Legal status: medical prescription **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
QT prolongation	**Routine risk minimisation measures:** • SmPC Section 4.4 and 5.3 • Legal status: medical prescription **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

2.9.4. Conclusion

The CHMP and PRAC considers that the risk management plan version 1.4 is acceptable.

2.10. Pharmacovigilance

2.10.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

2.10.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 12 April 2019. The new EURD list entry will therefore use the 12 April 2019 to determine the forthcoming Data Lock Points.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Balversa (erdafitinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication endorsed by CHMP is: Balversa as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting (see section 5.1).

3.1.2. Available therapies and unmet medical need

Available systemic therapies in the EU can be broadly categorised as platinum-based chemotherapy regimens, other chemotherapy regimens, antibodies targeting programmed death receptor-1 or programmed death-ligand 1 (anti-PD-(L)1), and antibody-drug conjugates (ADCs). Due to the

significant toxicities and morbidities, in particular kidney dysfunction and peripheral neuropathy, a relevant proportion of patients do not receive any systemic chemotherapy and the number of patients who are eligible for subsequent therapies decreases with every line of treatment. (ESMO; Powles 2022).

No therapies for a biomarker-selected population are approved so far.

There is substantial need for more effective therapies for patients with advanced urothelial cancer having received one or two line(s) of treatment.

3.1.3. Main clinical studies

Efficacy claims of erdafitinib in the proposed indication are based on a single pivotal study, namely study 'BLC3001 Cohort 1'. This is a randomised (1:1) controlled open-label phase 3 study comparing erdafitinib monotherapy versus investigator-choice chemotherapy (docetaxel or vinflunine) in patients with advanced urothelial cancer and susceptible FGFR3 alterations, who had progressed on or after 1 or 2 prior line(s) of therapy, with at least 1 line including anti-PD-(L)1 as monotherapy or as combination therapy; and no more than 2 prior lines of systemic treatment.

3.2. Favourable effects

At the interim analysis data cut-off 15 January 2023 Study 'BLC3001 Cohort 1' was stopped for superiority of erdafitinib (n=136 patients) over chemotherapy (n=130 patients). Patients were allowed to cross-over to erdafitinib treatment. The primary efficacy endpoint of **OS** showed a statistically and clinically significant improvement in OS for subjects treated with erdafitinib vs chemotherapy (HR=0.64; 95% CI: 0.47, 0.88; p-value=0.0050). The median OS was 12.06 months (95% CI: 10.28, 16.36) in the erdafitinib group versus 7.79 months (95% CI: 6.54, 11.07) in the chemotherapy group, each with approximately 40% of subjects censored. Overall, the results of the sensitivity analyses do not challenge the results of the primary analysis. The OS benefit in favour of erdafitinib observed for the primary analysis was consistently reflected in the results of the subgroup analyses. The median survival follow-up was 15.90 months (95% CI: 13.57, 19.22) for the erdafitinib treatment group.

Analysis of key secondary endpoint **PFS** showed a statistically significant improvement for subjects treated with erdafitinib vs chemotherapy (HR=0.58; 95% CI: 0.44, 0.78; p value=0.0002). The median PFS was 5.55 (95% CI: 4.40, 5.65) months in the erdafitinib treatment group and 2.73 (95% CI: 1.81, 3.68) months in the chemotherapy treatment group.

Best **ORR** by investigator assessment and per RECIST 1.1 was 45.6% for the erdafitinib treatment group and 11.5% for the chemotherapy treatment group. The difference was statistically significant. Nine patients in the erdafitinib arm reached CR, while one patient in the chemotherapy arm reached CR. 'Confirmed ORR analysis' was consistent with 'best ORR analysis'.

3.3. Uncertainties and limitations about favourable effects

A greater number of subjects who were randomised to the chemotherapy group did not receive study treatment (n=18) compared with the erdafitinib group (n=1), the main reason was 'refused treatment' (n=12; all from control group). This number shows a relevant imbalance; however, demographic and disease characteristics at baseline were sufficiently comparable between those patients 'randomised and treated' and those 'randomised and not treated'. There are no reasonable concerns of informative censoring. Furthermore, the applicant was able to obtain the death date for 8 of the 18 subjects randomised to chemotherapy as well as the subject randomised to erdafitinib.

A change to the confirmatory testing procedure was introduced in protocol amendment 5 but the applicant provided information that was reassuring regarding the sufficiency of the firewalls to preserve study integrity.

Companion diagnostic (CDx) 'Qiagen *therascreen* FGFR RGQ RT-PCR' / biomarker "FGFR positive":

- 'Qiagen *therascreen* FGFR RGQ RT-PCR' from tissue was used as central confirmation test. However, 12.5% of patients (33/264) were included into study BLC3001 based on local testing only (tissue or blood) without having a (positive) central confirmation test (for 22 patients no tissue for central confirmation was available, for 11 patients central confirmation test was negative).
- While a clear definition to declare a patient as "FGFR-positive" in the pivotal study BLC3001 is provided (see eligibility criteria above) and justification of this definition can be followed, validation of the biomarker definition remains scientifically weak (being based on preclinical data and uncontrolled clinical response data).
- A clinical validation demonstrating the test to be predictive is not possible in the presented trial setting without clinical data in test negative patients. It is acknowledged that including biomarker-negative patients in this study was not ethical/possible but this means that the justification of clinical validity needs to be based on the clinical rationale in this case.
- An exploratory analysis of clinical benefit across the different FGFR alterations included in the biomarker panel was provided. Considering the small sample sizes of subgroups, the analysis is explorative and no definite conclusions are possible but trends in favour of erdafitinib vs chemotherapy were observed for all subgroups.
- Cut-points used for the respective genetic alteration defining "FGFR-positivity" were provided for the central confirmation test 'Qiagen *therascreen* FGFR RGQ RT-PCR'. However, no clinical thresholding was performed. Therefore, it remains unclear whether the thresholds / cut-off values applied in study BLC3001 were optimal or whether a lower or higher threshold defining patients as 'FGFR alteration positive' would lead to a better benefit-risk ratio.

Although the uncertainties, it is agreed that clinical benefit has been demonstrated for the population selected with the test.

3.4. Unfavourable effects

The data presented in this section mainly refers to the mUC pool (n=479) which integrates data across studies that included subjects with locally advanced or metastatic UC treated with erdafitinib monotherapy 8 mg daily with individualised up-titration to 9 mg daily (8/9 mg daily dose regimen; n=467) or erdafitinib monotherapy 9 mg daily (n=9).

The most frequently reported TRAEs included hyperphosphataemia (78.5.%), stomatitis (52.8.%) diarrhoea (55.5%), dry skin (28%), palmar-plantar erythrodysesthesia syndrome (25.5%), dysgeusia (26.3%), decreased appetite (31.7%), onycholysis (21.7%) The most common reported AEs are compatible with the safety profile as is known from other FGFR-inhibitors and the patient population with advanced cancer.

SAEs were reported in 42.6% of patients and were considered treatment-related in 12.9% of patients (n=62). Treatment-related SAEs reported in ≥5 patients included detachment of retinal pigment epithelium (n=5) and stomatitis (n=5).

Overall, 66.2% of 479 subjects died. The majority of deaths (270 of 317) were due to progressive disease, 4.8% were due to adverse events. Grade 5 TEAEs considered by the investigator to be related to treatment were reported by 1 subject (sudden death).

Central serous retinopathy (CSR) has been identified as adverse event of special interest (AESI). Adverse reactions of CSR in any grade were reported in 31.5% of patients (Grade 3/4 2.7%). The most commonly reported events were chorioretinopathy, detachment of RPE, retinal detachment, retinopathy, and subretinal fluid.

Hyperphosphataemia, eye disorders [other than central serous retinopathy], nail and skin disorders, as and gastrointestinal disorders have been classified as adverse events of clinical importance and reported in section 4.4 of the SmPC.

Adverse drug reactions of hyperphosphataemia were reported in 78.5% of patients (Grade 3/4 2.9%).

There was a low incidence of prolonged hyperphosphataemia in the BLC3001 erdafitinib pool. The most frequently reported TEAE considered a potential sequela of prolonged hyperphosphataemia was hypercalcemia, the interpretation of which is difficult as it a very common laboratory abnormality in patients with advanced malignancies (Stewart 2005).

Adverse reactions of eye disorders (other than CSR) were reported in 36.3% of patients (Grade 3/4 2.9%).

Adverse reactions of nail disorders were reported in 62.6% of patients (Grade 3 12.5%).

Adverse reactions of gastrointestinal disorders were reported in 83.9% of patients (Grade 3/4 14.2%).

In the BLC3001 erdafitinib pool, increase of blood creatinine which was reported as a treatment emergent AE in 14.9% (46 subjects). Furthermore, acute kidney injury was seen in 5.5% (17 subjects), renal impairment in 3.6% (11 subjects) and renal failure in 3.2% (10 subjects).

In addition, increase of transaminases was reported as a treatment emergent AE in 21.7% (ALT) respectively 18.0% (AST) of subjects in the erdafitinib pool. Furthermore, hepatobiliary disorders were reported in 10.4%. Of note, dose modifications due to increased transaminases were reported for 3.9%.

In study BLC3001, drug related AEs of hypernatremia in the treatment group were reported for 6.8% of patients.

More subjects ≥65 years of age experienced serious TEAEs, Grade 4 TEAEs, TEAEs leading to study treatment discontinuation and TEAEs leading to death. Central serous retinopathy was reported more frequently in subjects ≥65 years of age.

Dose interruptions and reductions due to treatment-related adverse events were necessary for 82.3% in the mUC pool. In addition, 61 (12.7%) subjects experienced TEAEs leading to discontinuation of study treatment that were considered to be related to erdafitinib. Of note, detachment of retinal pigment epithelium (8 [1.7%] subjects) was the most common TEAE leading to discontinuation of study treatment.

Central serous retinopathy, hyperphosphataemia, potential drug toxicity due to accumulation of P-glycoprotein substrates and QT prolongation are part of the Identified and Potential Risk included in the RMP and will be monitored with routine Pharmacovigilance activities.

3.5. Uncertainties and limitations about unfavourable effects

A relatively large proportion of patients experienced a rise in transaminases, there is a relatively high level of uncertainty as to whether erdafitinib can induce liver damage in certain patient populations. Thus, hepatotoxicity should be monitored in upcoming PSURs.

3.6. Effects Table

Table 82: Effects Table for erdafitinib in the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma, harbouring susceptible FGFR3 genetic alterations with disease progression during or following at least one line of therapy containing a PD-(L)1 inhibitor in the locally advanced unresectable or metastatic treatment setting (data cut-off: 15 January 2023).

Effect	Short Description	Unit	Erdafitinib	Control	Uncertainties/ Strength of evidence	References
Favourable Effects (single pivotal study BLC3001 Cohort 1; erdafitinib arm 136 patients, CTx arm 130 patients)						
OS primary endpoint	Overall Survival	Median in months (95%CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)	RCT data (HR=0.64; 95%CI: 0.47, 0.88; p=0.005)	CSR study BLC3001 Cohort 1
PFS secondary endpoint	Progression Free Survival	Median in months (95%CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)	RCT data HR=0.58; 95%CI: 0.44, 0.78; p=0.0002	CSR study BLC3001 Cohort 1
ORR secondary endpoint	Objective Response Rate, unconfirmed	%	45.6%	11.5%	RCT data	CSR study BLC3001 Cohort 1
Unfavourable Effects based on BLC3001 erdafitinib pool data.						
TEAEs Grade 3 or 4	regardless causality	%	64%			Erdafitinib pool of study BLC3001: CSR of Cohort 1 of study BLC3001 CSR of Cohort 2 of study BLC3001
Serious AEs	regardless causality	%	40.6			
TEAEs leading to discontinuation	regardless causality	%	16.9			
TEAEs leading to death	regardless causality	%	3.6			
Central serous retinopathy	Adverse event of special interest	%	20.1			Erdafitinib pool of study BLC3001: CSR
Hyper-phosphataemia	Adverse event of clinical importance	%	78.6			
Eye disorders (other than Central serous retinopathy)	Adverse event of clinical importance	%	39.9			

Effect	Short Description	Unit	Erdafitinib	Control	Uncertainties/ Strength of evidence	References
Nail disorders	Adverse event of clinical importance	%	62.3			of Cohort 1 of study BLC3001 CSR of Cohort 2 of study BLC3001
skin disorders	Adverse event of clinical importance	%	54.5			
gastrointestinal disorders	Adverse event of clinical importance	%	82.8			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy claims are based on the single pivotal phase 3 study 'BLC3001 cohort 1' being performed in line with CHMP scientific advice from 2017 (before study start).

The study treatment is intended for patients harbouring FGFR3 alterations.

A statistically significant and clinically relevant survival advantage in the experimental arm over the chemotherapy arm has been demonstrated. The RCT met its primary endpoint of OS, showing statistical and clinically significant improvement in favour of erdafitinib monotherapy over single agent chemotherapy (docetaxel or vinflunine). This outcome is supported by analysis of the key secondary endpoints of PFS and ORR.

Clinical benefit in the all-comer population of study BLC3001 (cohort 1) is robustly shown. The vast majority of the patients received prior platinum-based chemotherapy and efficacy data in platinum-naïve patients is limited. However, platinum-naïve subpopulation efficacy data were analysed in a post-hoc defined across trial comparison for RCT BLC3001 cohort 1, SAT BLC2001 and SAT BLC2002 and showed consistent objective responses with the population with prior platinum. Results for ORR, OS and PFS in the post-hoc analysis were overall comparable to the results from the pivotal RCT BLC3001 for the ITT-population.

Due to the open-label design of the study and the imbalanced censoring, no benefit claims can be supported by available PRO data reported in study BLC3001. This includes the key secondary endpoint of TUSD-3, which is not established as a validated PRO measure and its clinical relevance remains unclear.

Erdafitinib showed high incidence and high level of seriousness of the safety events reported. The main safety risks of erdafitinib are hyperphosphataemia, central serous retinopathy, eye disorders (other than CSR), nail and skin disorders, gastrointestinal disorders and embryofoetal toxicity.

Risks from erdafitinib treatment in the intended patient population are clinically relevant, but manageable with treatment interruption and dose modifications, which occurred frequently (82%). Incidence of treatment discontinuation due to AEs were lower compared to the chemotherapy group.

3.7.2. Balance of benefits and risks

Considering the benefit observed with erdafitinib on overall survival compared to single-agent chemotherapy (docetaxel or vinflunine) and the manageable safety profile, it can be concluded that the benefits of treatment with erdafitinib outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Balversa (erdafitinib) is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Balversa is favourable in the following indication:

Balversa as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting (see section 5.1).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that erdafitinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.