swissmedic

Date: 8 April 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

BALVERSA

International non-proprietary name: erdafitinib

Pharmaceutical form:	film-coated tablets
Dosage strength(s):	3 mg, 4 mg, 5 mg,
Route(s) of administration:	oral
Marketing authorisation holder:	Janssen-Cilag AG
Marketing authorisation no.:	67660
Decision and decision date:	approved on 14 January 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CPI	Immune checkpoint inhibitor
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FGFR3	Fibroblast growth factor receptor 3
GLP	Good Laboratory Practice
HDPE	High-density polyethylene
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
mUC	metastatic urothelial carcinoma
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand-1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics

PopPK	Population pharmacokinetics
PP	Polypropylene
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UC	Urothelial carcinoma

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for erdafitinib in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

BALVERSA is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC) with FGFR3 (fibroblast growth factor receptor 3) alteration, with disease progression during or following at least one therapy with a PD-1 or PD-L1 inhibitor (programmed death receptor-1 or programmed death-ligand-1 inhibitor), including within 12 months of neoadjuvant or adjuvant therapy (see Clinical efficacy).

2.2.2 Approved indication

BALVERSA as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC) with FGFR3 (fibroblast growth factor receptor 3) alteration, with disease progression during or following at least one therapy with a PD-1 or PD-L1 inhibitor (programmed death receptor-1 or programmed death-ligand-1 inhibitor), and after platinum-containing chemotherapy, if eligible (see *Clinical efficacy*).

2.2.3 Requested dosage

Summary of the requested standard dosage:

The proposed starting dose is 8 mg orally once daily, with the option to up-titrate to 9 mg once daily if the serum phosphate level is <9.0 mg/dL, and there is no drug-related toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	16 October 2023
Formal control completed	10 November 2023
List of Questions (LoQ)	5 March 2024
Response to LoQ	2 June 2024
Preliminary decision	22 August 2024
Response to preliminary decision	17 October 2024
Final decision	14 January 2025
Decision	approval

3 Medical context

Urothelial carcinoma is the most common cancer of the urinary system, accounting for approx. 90% of all bladder cancers in industrialised nations.[1] For decades, platinum-based chemotherapy was the standard of care for patients with unresectable or metastatic urothelial carcinoma (mUC) who had not previously received systemic treatment. Recently, PD-(L)1 inhibitors have emerged as an additional treatment option. In 2024, the European Association of Urology (EAU) and European Society for Medical Oncology (ESMO) guidelines for the treatment of unresectable urothelial cancer were updated.[2,3] One of the noteworthy changes is the shift from determining platinum eligibility to assessing eligibility for combination therapy (nectin-4 antibody drug conjugate combined with PD-(L)1 inhibitor) as the first step in planning treatment for treatment-naïve mUC. According to updated respective treatment algorithms, platinum-based chemotherapy with immune checkpoint inhibitor (CPI) in the systemic treatment-naïve setting should be considered if the patient is ineligible to receive the combination therapy of nectin-4 antibody drug conjugate combined with PD-(L)1 inhibitor. For patients who had disease progression or are not eligible to receive previously mentioned options and have no targetable tumour alterations, the treatment options include single agent chemotherapy. However, despite these treatment options, the majority of patients will develop disease progression and subsequent fatal disease outcome. There is an unmet medical need to improve the survival outcomes in these patients.

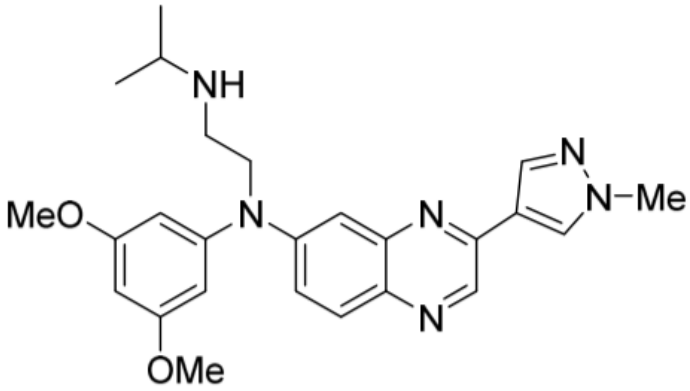
Fibroblast grow factor receptor (FGFR) driver mutations present an actionable target for targeted therapies. These genetic alterations occur in about 20% of patients with relapsed or refractory urothelial cancer.[4] Erdafitinib is a tyrosine kinase inhibitor (TKI) that targets FGFR.

4 Quality aspects

4.1 Drug substance

INN: Erdafitinib
Chemical name: N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine
Molecular formula: $C_{25}H_{30}N_6O_2$
Molecular mass: 446.56
Molecular structure:

[1] Leslie SW, Soon-Sutton TL, Aeddula NR. Bladder Cancer. [Updated 2024 Aug 15]. In: StatPearls Publishing; January 2025.
[2] Witjes JA et al., EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer, EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.
[3] Powles T, Bellmunt J, Comperat E, et al., ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma, Ann Oncol. 2024;35(6):485-490.
[4] Gust KM, McConkey DJ, Awrey S, et al. Fibroblast growth factor receptor 3 is a rational therapeutic target in bladder cancer. Mol Cancer Ther. 2013;12(7):1245-54.



Physicochemical properties: Yellow powder, only slightly soluble in aqueous media

Synthesis: Erdafitinib is produced in a convergent multi-step chemical synthesis. The regulatory starting materials are well defined and justified.

Specification: The specification includes all necessary tests. The limits for potential impurities and residual solvents are in line with the requirements of international guidelines.

Stability: Appropriate stability data to justify the re-test period were presented. The analytical procedure for purity is stability-indicating.

4.2 Drug product

Description and composition: The Balversa film-coated tablet is a round biconvex immediate release tablet. The three dosage strengths of 3 mg, 4 mg and 5 mg can be distinguished by their colour and the debossing.

Pharmaceutical development: The formulation development is sufficiently described. The choice and amounts of excipients are justified. Bioequivalence was shown for the different forms that were used during development and clinical studies.

Manufacture: The drug product is manufactured by direct compression followed by film-coating.

Specification: The release and shelf-life specifications are acceptable. The identification is done by HPLC/UV. All universal tests according to international guidelines are included. Specific tests for solid oral dosage forms are either included in the specification (dissolution, uniformity of dosage units, microbial limits) or performed as in-process controls. Critical in-process controls have been defined and justified.

Container closure system: HDPE bottle and child-resistant PP closure.

Stability: Sufficient stability data to support the shelf-life and the storage conditions are submitted.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Balversa (erdafitinib), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the FDA Assessment report (Multi-Discipline Review, NDA 212018, April 2019) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Balversa in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues were identified in the nonclinical studies, including potential reproductive risks, erdafitinib being embryotoxic and teratogenic in rats, which are of concern for human use. Safety margins were low or non-existent, which is acceptable for the intended indication. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals. The Nonclinical Safety Specifications in the RMP adequately address these nonclinical findings and their relevance for clinical use.

There are no safety concerns regarding impurities and excipients.

Based on the ERA, the risk for the environment is low.

From the nonclinical perspective, approval may be granted in the proposed indication.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption
Erdafitinib was classified as a BCS 1 compound (high solubility, high permeability).

The administration of the proposed commercial tablet with a high-fat, high-calorie meal caused a prolongation of the median tmax from 2.52 h to 3.98 h and a 14% decrease of Cmax. However, the formal bioequivalence criteria were met for both Cmax and AUC. This means erdafitinib can be administered independently of food.

Dose Proportionality
The total erdafitinib Cmax and AUC increased proportionally to the administered dose after administration of single doses and continuous QD dosing between 0.5 mg and 12 mg.

Pharmacokinetics after multiple Dosing
There was an approximately 3- to 5-fold accumulation based on AUC after continuous or intermittent (7 days on, 7 days off) QD dosing. This is in agreement with the half-life of erdafitinib. Steady state after continuous QD dosing is expected to be reached after 15 to 20 days, which is in agreement with the half-life of erdafitinib as well.

Distribution
Erdafitinib *in vitro* plasma protein binding was high. The free fraction ranged from 0.55% at an erdafitinib concentration of 15 ng/mL to 0.74% at 1500 ng/mL erdafitinib, indicating some concentration dependency. Erdafitinib bound mainly to α1-AGP and to a lesser extend to HSA. The *in vitro* blood to plasma ratio was 0.6.

Erdafitinib plasma protein binding determined in clinical studies was high as well. Overall, the mean fu in cancer patients from study EDI1001 was 0.316%. The corresponding value in healthy subjects was 0.510%, i.e. the mean erdafitinib fu was approximately 61% higher in healthy subjects than in cancer patients. Mean α1-AGP concentration in cancer patients was approximately 2.1-fold higher and more

variable than in healthy subjects. These results are due to the decrease of erdafitinib fu with increasing α1-AGP concentrations.

The mean albumin level was 10% lower in cancer patients as compared with healthy subjects. Fu showed a slight increase with increasing serum albumin concentrations.

Pop PK modelling of the erdafitinib plasma protein binding data confirmed that erdafitinib binds mainly to α1-AGP and that the binding to both α1-AGP and albumin is linear within the clinically relevant concentration range.

The *ex vivo* fu increased with decreasing hepatic function. The *ex vivo* fu was comparable in subjects with mild or moderate renal impairment, but it was lower than in subjects with normal renal function. No data were available in subjects with severe renal impairment.

Metabolism & Elimination
In vitro Data
The turnover of erdafitinib in *in vitro* systems was low. The main enzymes involved in erdafitinib metabolism were CYP2C9, CYP3A4 and CYP2D6. CYP2C9 and CYP3A4 were involved in the formation of M6 and CYP3A4 was involved in the formation of M8. Based on PBPK simulations, the contributions of CYP2C9 and 3A4 to the total clearance of erdafitinib were 39% and 20%, respectively.

Clinical Data
The primary metabolic pathway leading to the formation of the major metabolite M6 was an O-demethylation of erdafitinib. N-dealkylation, leading to the formation of M8, and oxidation, leading to the formation of M5, M11 and M27, were minor metabolic pathways.

After oral administration of a ^{14}C-labelled erdafitinib dose, unchanged erdafitinib was the only compound detected in plasma.

The majority of the administered radioactive dose (68.7%) was excreted in faeces, 18.7% was excreted in urine (total recovery 87.4%).

In faeces, unchanged erdafitinib and M6 were the major entities. Erdafitinib represented 20.8% and 14.1% of the dose in CYP2D6 extensive and poor metabolisers, respectively. M6 represented 24.2% and 23.8% of the dose in extensive and poor metabolisers, respectively. Other faecal metabolites, representing between 1.20 % and 3.51 % of the administered dose, were M5 and M11, M8 formed after N-dealkylation of erdafitinib and M27. There was no noticeable difference in the abundance of these minor metabolites between poor and extensive CYP2D6 metabolisers.

In urine, unchanged erdafitinib was the major entity and represented 11.3% of the administered dose. M6 represented on average 2.05% of the dose. Two additional metabolites were identified: M28 (observed as radioactive peak without identification of its MW, 1.15% of the dose) and M8 (1.01% of the dose). The identification of radioactivity in faeces and urine was almost complete.

The half-life of erdafitinib was 66.3 h.

Special populations

Erdafitinib exposures were up to 31% lower in CYP2D6 poor metabolisers compared to extensive metabolisers, i.e. CYP2D6 does not play a major role in erdafitinib metabolism.

The CYP2C9 genotype (*1/*2 plus *1/*3 versus wild type *1/*1) had no major impact on erdafitinib PK. However, the respective study included only 2 subjects with genotype *1/*3. Based on PBPK

simulations, a 1.5-fold increase of erdafitinib AUC would be expected in cancer patients with genotype *3/*3 compared to genotype *1/*1.

Mild hepatic impairment (Child Pugh A) had no clinically relevant impact on the total or free erdafitinib exposures. In subjects with moderate hepatic impairment (Child Pugh B), the total erdafitinib AUC was approximately 40% lower compared to subjects with normal hepatic function. However, there were no clinically relevant changes of the free erdafitinib exposures.

Only 2 subjects with severe hepatic impairment (Child Pugh C) were included in the respective study. In these two subjects, total erdafitinib exposures were lower compared to subjects with normal hepatic function, the half-life was longer, Fu was larger and AUClast,free was 1.5- and 2.3-fold higher, respectively.

The pharmacokinetics of erdafitinib in healthy subjects and cancer patients and the potential impact of covariates was further investigated in a pop PK analysis.

The dataset included 1142 subjects, of whom 28 (2.5%) were healthy subjects (same as in the first analysis) and the remaining 97.5% were cancer patients. Of the subjects, 600 (52.5%) had urothelial cancer. The mean age of the subjects was 61 years (range 21-92 years). The mean body weight was 72 kg (range 36.2 – 166 kg). The dataset included more men than women (63% versus 37%). The majority (54.2%) of the subjects was White, followed by 25.6% patients of Asian origin. Most of them (80 %) had normal hepatic function based on NCI criteria. The dataset included 220 (19.3%) subjects with mild hepatic impairment, 3 subjects with moderate hepatic impairment and one subject with severe hepatic impairment. The dataset included 36.1%, 36.9%, 26.4% and 0.7% (n=8) of subjects, respectively, with normal renal function, mild, moderate or severe renal impairment. The CYP2C9 genotype was missing in 70% of the subjects. The dataset included 257 (22.5%) extensive (EM), 75 (6.6%) intermediate (IM) and 11 (1%) poor metabolisers (PM).

Covariates to be investigated included weight, age, sex, race, CYP2C9 polymorphism and markers of hepatic and renal function.

The final pop PK model was an open, linear, 3-compartment disposition model with free erdafitinib distributing to peripheral compartments and binding to AGP in the central compartment. It included the following covariate relationships:

- Different absorption rate constants and lag times for different formulations (already included in the base model)
- Fu on V2total and F1
- Spiking on Fu
- Weight on volume terms and CLfree
- Age on CL
- Sex and health status on F1

CLtotal, F1, V2total increased with increasing free fraction. CLfree, V2total, V3, and V4 increased with body weight. CLfree decreased with increasing age, and F1 was higher in women than in men, and higher in healthy subjects than in patients. The impact of these covariates on free erdafitinib exposures was low.
The final model predicted the total erdafitinib concentrations reasonably well. It slightly under-predicted the free concentrations, especially at later time points.

The data obtained in special populations support the dosing recommendations in the information for healthcare professionals (Appendix).

Interactions

IMPACT OF OTHER DRUGS ON ERDAFITINIB

In vitro Data
As mentioned above, erdafitinib was metabolised by CYP2C9, CYP3A4 and CYP2D6. The role of CYP2D6 is most likely minor.
Erdafitinib is a substrate for P-gp. However, the *in vitro* data indicated saturation of P-gp transport at concentrations above 0.3 µM (134 ng/mL. Considering the dose-proportional increase of erdafitinib over the investigated dose range, inhibition of P-gp is unlikely to affect erdafitinib PK after therapeutic dosing.
Erdafitinib is not a substrate for BCRP, OATP1B1 and OATP1B3.

Clinical Data

Perpetrator	**Geometric Mean Ratio (90% CI)**
Fluconazole (moderate CYP2C9 and moderate CYP3A4 Inhibitor)	**Erdafitinib (CYP2C9 genotype *1/*1 + *1/*2):** Cmax: 121.10 (99.88, 146.84) AUCinf: 147.85 (119.95, 182.24)
	Erdafitinib (CYP2C9 genotype *1/*1): Cmax: 120.37 (95.30, 152.04) AUCinf: 152.09 (118.77, 194.76)
	Erdafitinib (CYP2C9 genotype *1/*1 + *1/*2 + *1/*3): Cmax: 120.68 (98.92, 147.21) AUCinf: 143.82 (116.89, 176.96)
Itraconazole (strong CYP3A4 and P-gp Inhibitor)	**Erdafitinib (CYP2C9 genotype *1/*1 + *1/*2):** Cmax: 104.79 (86.66, 126.70) AUCinf: 133.86 (109.05, 164.33)
	Erdafitinib (CYP2C9 genotype *1/*1): Cmax: 102.13 (81.22, 128.41) AUCinf: 122.85 (95.94, 157.32)
Carbamazepine (weak CYP2C9 and strong CYP3A4 Inducer)	**Total Erdafitinib** Cmax: 65.44 (60.77, 70.46) AUCinf: 37.72 (35.35, 40.25)
	Free Erdafitinib Cmax: 77.76 (72.76, 83.12) AUCinf: 45.28 (39.74, 51.59)

The mean erdafitinib half-life was prolonged from 59.1 h after administration of erdafitinib alone to 68.3 h and 77.5 h after co-administration with fluconazole and itraconazole, respectively.
After co-administration with carbamazepine, the erdafitinib half-life was shortened from 56.6 h to 36.8 h.
The co-administration of sevelamer had no major impact on erdafitinib exposures.

Recommendations for the co-administration of erdafitinib and moderate CYP2C9 or strong CYP3A4 inhibitors as well as strong or moderate CYP3A4 inducers are given in the information for healthcare professionals (see Appendix).

IMPACT OF ERDAFITINIB ON OTHER DRUGS

In vitro Data
Based on mRNA levels, erdafitinib induced CYP1A2, 2B6 and 3A4. Taking the mean percent induction of the positive control into consideration as well, erdafitinib induced CYP3A4 only.

At concentrations up to 15 µM, erdafitinib did not directly inhibit CYP1A2, 2C8, 2C19, 2D6 and 3A4. At concentrations up to 30 µM, erdafitinib did not show direct or time-dependent inhibition of CYP2B6 or CYP2C8.

Erdafitinib showed time-dependent inhibition of CYP3A4, but not of CYP1A2, 2C9, 2C19 or 2D6. The time-dependent inhibition of CYP3A4 by erdafitinib was comparable to the corresponding effect of erythromycin.

Erdafitinib inhibited P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K *in vitro,* with IC50 values ranging from 0.0434 µM for OCT2 to > 68.6 µM for OAT3. Based on the static DDI risk assessment, the inhibition of intestinal P-gp and of OCT2 *in vivo* cannot be excluded. In the calculations, a free fraction of 0.003 was assumed. The current ICH M12 guideline recommends the use of a free fraction of 0.01 for highly bound drugs if the reliability of the measurements cannot be demonstrated. With a free fraction of 0.01, there was a signal for the inhibition of renal and intestinal P-gp, OCT1, OCT2 and MATE2-K. As depicted below, erdafitinib had no clinically relevant impact on metformin exposures.

Clinical Data

Victim	**Geometric Mean Ratio (90% CI)**
Midazolam (CYP3A4 substrate)	**Midazolam** Cmax: 86.29 (73.52, 101.28) AUCinf: 82.11 (70.83, 95.18)
	1-OH-Midazolam Cmax: 99.77 (81.09, 122.75) AUCinf: 101.46 (70.08, 146.89)
Metformin (OCT2 and MATE substrate)	Cmax: 108.66 (90.31, 130.75) AUCinf: 113.92 (93.22, 139.23)

The DDI signal for the inhibition of intestinal P-gp was further investigated in a PBPK analysis. The simulations indicated that an interaction with digoxin was attenuated if erdafitinib and digoxin dosing were staggered by at least 6 hours. However, as there were no clinical data available to qualify the model and considering the uncertainties associated with PBPK simulations of transporter-based interactions, neither dosing recommendations based on these simulations nor the simulation results were included in the information for healthcare professionals. Instead, a cautionary statement and a reference to the respective information for healthcare professionals was added for P-gp substrates with a narrow therapeutic index. Apart from that, the interaction potential of erdafitinib as a perpetrator appeared to be low.

Pharmacodynamics

MECHANISM OF ACTION AND PRIMARY PHARMACOLOGY

The relationship between total and free erdafitinib concentrations and serum phosphate concentrations (biomarker for FGFR inhibition) was investigated in a pop PKPD analysis.

The dataset included 1132 subjects, all cancer patients. Of the subjects, 546 (48.2%) had urothelial cancer. The mean age of the subjects was 61.3 years (range 12-92 years – the 3 paediatric subjects were excluded from the analysis). The majority (60.5%) of the patients was ≤ 65 years old. The dataset included more men than women (62.8% versus 37.2%). The majority (53.3%) of the subjects was White, followed by 25.8% patients of Asian origin. The dataset included 34.7% patients with normal renal function and 37.5%, 27.1% and 8 (0.7%) patients with mild, moderate or severe renal impairment, respectively.
Covariates to be investigated included age, sex, race, renal function and disease-related factors.

The final PKPD model to describe the relationship between free erdafitinib plasma concentrations included an Emax model, an effect compartment to account for the delay between erdafitinib PK and PD effect, and a rate constant describing the attenuation of the drug effect on serum phosphate over time. The effect compartment equilibration half-life was 53 hours, indicating that pseudo-steady state in the effect compartment would be reached after approximately 9 to 11 days. The attenuation of PO_4 effect developed slowly, with a half-life of 44 weeks.

It included the following covariate relationships:

- Sex on baseline
- Age, Japanese origin and coadministration of PO_4-lowering drugs on Emax.

The PO4 baseline value was estimated to be 6.5% higher in women. Emax was 26.9% higher in subjects who received PO_4-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. Overall, the impact of the covariates on serum PO4 was small.
The final model underestimated the serum phosphate levels at earlier time points.

SECONDARY PHARMACOLOGY (SAFETY)

The relationship between total and free erdafitinib plasma concentrations and QTc was investigated in Part 1 of study EDI1001 after single and multiple dosing. QTcI provided the best QT correction for heart rate. The relationship between total and free erdafitinib plasma concentrations and QTcI was described by a linear model. The slope was statistically significant, but negative, i.e. QTcI decreased with increasing erdafitinib concentrations. Erdafitinib had no impact on heart rate.

The total and free erdafitinib concentrations included in the ER analysis just covered the exposures after 8 mg QD, but no supratherapeutic exposures.

ER ANALYSES OF EFFICACY

The relationship between serum phosphate or erdafitinib plasma concentrations and efficacy and safety endpoints was investigated for the phase 2 (study BLC2001) and the phase 3 (study BLC3001) data separately due to the different dose titration schemes used in both studies.

Phase 2
The analysis included both continuous dosing regimens of study BLC2001 (Regimen 2: Continuous 6 mg once daily with possible up-titration to 8 mg once daily at Day 28 and Regimen 3: Continuous 8 mg once daily with possible up-titration to 9 mg once daily at Day 14). The intermittent dosing regimen was not included.

The serum phosphate level cut-off for up-titration was 5.5 mg/dL. At phosphate levels ≥ 7 mg/dL, erdafitinib treatment was interrupted. This target range of serum phosphate was selected based on data from the FIH study EDI1001. However, the choice was not fully comprehensible, as a phosphate target range between 7 and < 9 mg/dL seemed more appropriate.

The efficacy endpoints investigated were objective response rate (ORR, primary endpoint), disease control rate (DCR) and progression-free survival (PFS, both secondary endpoints). The covariates assessed were ECOG performance status, haemoglobin level, presence of liver metastasis, FGFR alteration type (fusion versus mutation) and pre-treatment status (chemotherapy-relapsed/refractory versus chemotherapy-naïve).

The dataset included 177 patients on the continuous dosing regimen with a mean age of 65.4 years (range 36-88 years) and a mean body weight of 74.7 kg (range 37.5-159.7 kg). The majority of the

patients were male (73.4%) and White (70.6%), had moderate renal impairment (50.8%), visceral metastasis (79.5%) and FGFR mutations (80.8%.

The results of the ER analyses are summarised below:

Endpoint	**Exposure measure (OR (95% CI) p-value)**	**Covariates**	**Comments**
ORR Evaluated by Investigator	Phosphate up to ~6 weeks 1.38 (1.02-1.86), 0.04	FGFR alteration (fusion vs mutation) 0.26 (0.10-0.70), 0.01	The probability of response was lower in patients with FGFR fusion
ORR Evaluated By Independent Radiologic Review Committee	Phosphate up to ~6 weeks 1.30 (0.83-2.06), 0.25	FGFR alteration (fusion vs mutation) 0.06 (0.007-0.49), 0.01	The probability of response was lower in patients with FGFR fusion
DCR By Investigator	Average daily phosphate up to Day 14 (p=0.005) Average daily phosphate up to 6 weeks (p<0.001)	Not investigated	
DCR By IRRC	Average daily phosphate up to Day 14 (p=0.09) Average daily phosphate up to 6 weeks (p=0.05)	Not investigated	
PFS by Investigator	Phosphate up to 6 weeks 0.80 (0.67-0.94), 0.01	None	None of the covariates reached statistical significance in the Cox regression analysis, but PFS decreased with ECOG status of 2 relative to ECOG status of 0 or 1 and the presence of visceral metastases
PFS by Independent Radiologic Review Committee	Phosphate up to 6 weeks 0.85 (0.69-1.06), 0.15	FGFR alteration (fusion vs mutation) 2.03 (1.18-3.50), 0.01	PFS was shorter in patients with FGFR fusion

Erdafitinib plasma exposures were not evaluated as potential predictors of efficacy in this analysis.

Phase 3
The analysis included only the data from Cohort 1 of study BLC3001 (subjects following 1 or 2 prior line[s] of systemic therapy, with at least 1 line containing anti-PD-[L]1, who were 1:1 randomly assigned to receive erdafitinib or chemotherapy). The data from Cohort 2 (subjects following 1 prior line of systemic chemotherapy without anti-PD-[L]1, who were 1:1 randomly assigned to receive erdafitinib or pembrolizumab) were not included.

Based on the results of study BLC2001, the serum phosphate cut-offs for up- or down-titration were adjusted to a target range of 7 to < 9 mg/dL in study BLC3001. However, down-titrations were mainly guided by the occurrence of AEs rather than by the serum phosphate levels.

The efficacy endpoints investigated were overall survival (OS, primary endpoint) and the secondary endpoints of progression-free survival (PFS), overall response rate (ORR) and duration of response (DOR).

The covariates assessed were ECOG performance status (0 or 1 vs 2), disease distribution (presence vs absence of visceral metastases: lung, liver, or bone), and region (North America vs Europe vs rest of world), race and haemoglobin.

The dataset included 266 patients (136 on erdafitinib and 130 on chemotherapy) with a mean age of 66.3 years (range 32.0 - 86.0 years) and a mean body weight of 73.1 kg (range 41.0 - 166 kg). The majority of the patients were male (71.4%) and White (49.6%), had moderate renal impairment (44.7%), visceral metastasis (76.7%) and FGFR mutations (80.8%.

The results of the ER analyses are summarised below:

Endpoint	**Exposure measure (OR (95% CI) p-value)**	**Covariates**	**Comments**
OS	PO4-Time-dependent 0.53 (0.44-0.65), <0.001	Baseline ECOG >1 (vs 0-1) 1.84 (1.09-3.11), 0.023 Haemoglobin ≥10 g/dL vs <10 g/dL) 0.53 (0.35-0.78), 0.001 Race: white (vs non-white) 1.58 (1.14-2.20), 0.007	OS was longer in patients with ECOG 0-1, Hb ≥ 10 g/dL and in non-White patients
PFS	Time-Dependent Weekly average of Daily Serum PO4 0.69 (0.60-0.79), <0.001	None	
ORR	PO4avg, 6weeks 1.84 (1.43-2.37), <0.001	None	
DOR	No ER relationship		

Erdafitinib plasma exposures were statistically significant predictors of OS, PFS and ORR as well. For OS, Cavg appeared to be the better predictor based on AIC. For PFS and ORR, AIC was comparable for Cavg and PO4.

ER ANALYSES OF SAFETY

Phase 2

The dataset was the same as for the ER analysis efficacy. Safety endpoints included AEs related to the eyes, including central serous retinopathy (CSR), nails, palmar-plantar erythrodysaesthesia syndrome (PPES) and the skin. No covariates were investigated.

The results of the analyses are summarised below:

Endpoint	Exposure measure	(OR (95% CI) p-value)
Eye	Average daily phosphate up to day of event	2.44 (1.65-3.62), <0.001
CSR	Average daily phosphate up to day of event	1.97 (1.30-3.00), 0.002
Nail	Average daily phosphate up to day of event	2.84 (1.87-4.31), <0.001
PPES	Average daily phosphate up to day of event	1.72 (1.15-2.59), 0.009
Skin	Average daily phosphate up to day of event	1.61 (1.14-2.27), 0.007

In contrast to serum phosphate, erdafitinib free AUC was not a predictor of the probability to experience the AEs listed above.

Phase 3
The safety dataset included erdafitinib monotherapy data from studies BLC2001 (continuous treatments only) and BLC2002 and all cohorts of study BLC3001.

The dataset included 814 patients (529 on erdafitinib, 112 on chemotherapy and 173 on immunotherapy) with a mean age of 66.4 years (range (31.0 - 92.0 years) and a mean body weight of 72.3 kg (range 37.5 -166 kg). The majority of the patients were male (75.1%) and White (57.4%) and had moderate renal impairment (46.4%).

Safety endpoints included AEs related to the eyes, including central serous retinopathy (CSR), nails, GI tract and the skin. No covariates were investigated.

Endpoint	Exposure measure/predictor	(OR (95% CI) p-value)
Eye	PO4avg, event	1.903 (1.426 - 2.54), <0.001
	Erdafitinib (vs Chemotherapy/Pembrolizumab)	4.198 (1.506 - 11.704), 0.006
CSR	Erdafitinib treatment	0.046 (0.01 - 0.212), <0.001
Nail	PO4avg, event	2.387 (1.863 - 3.056), <0.001
	Erdafitinib (vs Chemotherapy/Pembrolizumab)	20.646 (4.825 - 88.355), <0.001
Skin	PO4avg, event	1.849 (1.456 - 2.348), <0.001
	Erdafitinib (vs Chemotherapy/Pembrolizumab)	5.172 (2.273 - 11.766), <0.001
GI	Erdafitinib (vs Chemotherapy/Pembrolizumab)	9.097 (5.909 - 14.006), <0.001

In contrast to the Phase 2 data analysis, erdafitinib plasma exposures were statistically significant predictors of AEs of the eyes, nails, and skin. For the safety endpoints, PO4 was the better predictor based on AIC (.

COMPARISON OF PHASE 2 AND PHASE 3 DOSING REGIMENS
As already said, the phosphate-based dose adjustments were changed between Phase 2 and 3:
Phase 2: The serum phosphate level cut-off for up-titration was 5.5 mg/dL. At phosphate levels ≥ 7 mg/dL, erdafitinib treatment was interrupted.
Phase 3: The serum phosphate cut-offs for up- or down-titration were adjusted to a target range of 7 to < 9 mg/dL in study BLC3001. Down-titrations were mainly guided by the occurrence of AEs.

For the 8 mg dose, OS and PFS were comparable for the Phase 2 and 3 titration schemes.

The incidence of CSR, eye disorders and GI AEs was lower in study BLC3001, while the incidence of nail AEs was higher than in study BLC2001. The incidence of skin disorders was similar in both studies.

The dose intensity was higher in study BLC3001 during the first 2 to 5 months due to the increased number of subjects up-titrated to 9 mg at Week 2. The number of dose interruptions was similar in both studies over 6 months and longer and slightly lower in study BLC3001. However, starting from month 4, the duration of dose interruptions was longer in study BLC3001.

The median serum phosphate concentrations were comparable for both studies – and mostly below 5.5 mg/dL. However, the fraction of patients with serum phosphate levels > 5.5 mg/dL was higher in study BLC3001 for the first 5 months of treatment. As indicated above, this did not result in significantly better OS or PFS.
The investigation of covariates on the serum phosphate levels in Cohorts 1 and 2 of study BLC3001 indicated that:

- The average PO4 concentrations were higher in women, the average dose intensity was lower.
- The average PO4 concentrations at later time points, as well as the average dose intensity, decreased with increasing age.
- The a1AGP concentrations appeared to have no major impact on both PO4 concentrations or dose intensity.
- Body weight had no apparent impact on serum PO4. The dose intensity was highest in the heaviest patients, but there was no trend of decreasing dose intensity with decreasing weight.
- The PO4 concentrations were higher in patients on PO4-lowering medications (=> despite taking them), and the dose intensity was more variable in these patients.
- PO4 concentrations and dose intensity were lower in Japanese patients.

The changes in dose intensity and serum phosphate levels due to these covariates were small.

In summary, the main benefit of the BLC3001 titration scheme was a lower incidence of some AEs at comparable efficacy.

6.2 Dose finding and dose recommendation

Pharmacometrics aspects: The dose selection for Phase 2 was based on the serum phosphate levels in the FIH study EDI1001 evaluated by PKPD modelling and limited efficacy data. Of note, hyperphosphataemia is an expected and transient laboratory abnormality of FGFR inhibitors due to their mechanism of action. MTD was not determined in EDI1001. The selected target serum phosphate range for Phase 2 was conservative. It was adjusted accordingly for Phase 3 to higher serum phosphate levels based on acceptable Phase 2 safety data. Furthermore, the down-titration in

Phase 3 was mainly based on the occurrence of AEs rather than just the phosphate levels, resulting in a lower incidence of AEs at comparable efficacy to Phase 2.

The median serum phosphate levels were mostly below the minimum target of 5.5 mg/dL in studies BLC2001 and BLC3001. Even with the higher target range/dose in study BLC3001, less than 60% of the patients included in the ER analysis efficacy achieved serum phosphate levels > 5.5 mg/dL. Erdafitinib plasma exposures were not evaluated in the ER analysis for efficacy of the Phase 2 data. The ER analysis of the Phase 3 data indicated that they are a significant predictor of efficacy.

In summary, from a pharmacometrics point of view, higher erdafitinib doses in combination with down-titration due to AEs might have been possible.

Clinical aspects: The available preliminary efficacy and safety data from the Phase 2 study support the initial continuous dose of erdafitinib 8 mg daily with phosphate-guided up-titration to 9 mg daily, which was therefore selected for further evaluation in the Phase 3 study.

6.3 Efficacy

BLC3001 is a Phase 3, open-label, randomised study in pre-treated mUC patients with FGFR-alterations. The study consisted of two cohorts with distinct populations. The pivotal data for the requested indication are from Cohort 1 of this study (THOR trial). This cohort evaluated erdafitinib (136 subjects) versus investigator's choice of either docetaxel or vinflunine (130 subjects) in patients who progressed after one or two lines of therapy, at least one of which included an anti-PD-(L)1 agent. The primary endpoint was overall survival (OS). The study was also designed to formally test progression-free survival (PFS), overall response rate (ORR) by investigator assessment and the time to urinary cancer symptom deterioration. The majority of THOR trial patients received prior chemotherapy (89.1%). Of these patients, the majority received platinum-based chemotherapy (89.7% in the erdafitinib arm and 85.4% in the chemotherapy arm).

The applicant submitted the results from the final analysis (data cut-off date 15 January 2023). The study demonstrated statistically significant OS benefit in the intent-to-treat population: hazard-ratio (HR) of 0.64 with 95% confidence interval (CI95%) 0.47 to 0.88, OS event rate was 56.6% in the erdafitinib arm and 60.0% in the chemotherapy arm, median OS was 12.06 versus 7.79 months, respectively. The results were also statistically significant for secondary endpoints of PFS (HR 0.58 CI95% 0.44, 0.78, median PFS 5.55 vs 2.73 months, respectively) and unconfirmed ORR. The confirmed ORR was 35.3% in the erdafitinib arm and 8.5% in the chemotherapy arm. Further details on clinical efficacy can be found in the attached information for healthcare professionals.

6.4 Safety

The overall pooled erdafitinib database of safety regardless of underlying disease or dose consists of 1081 patients. The most frequently reported treatment emergent adverse events (TEAEs) of any grade in the erdafitinib safety pool were: hyperphosphataemia, diarrhoea, stomatitis, dry mouth, decreased appetite, anaemia, dry skin, constipation, dysgeusia, and palmar-plantar erythrodysaesthesia. The following toxicities were identified as adverse events of special interest: eye (including central serous retinopathy), skin, gastrointestinal and nail disorders as well as hyperphosphataemia. Further details on undesirable effects can be found in the attached information for healthcare professionals.

In the pivotal BLC3001 trial, the incidence of grade 3–4 TEAEs was 64.0% in the erdafitinib group (n=308, all treated patients across cohorts) compared with 64.3% in the investigator's choice

chemotherapy arm (n=112). The rates of serious adverse events were 41.5% and 42.0%, respectively, and TEAEs leading to death occurred in 3.6% versus 6.3% of patients, respectively.

6.5 Final clinical benefit risk assessment

Despite the available treatment options, most patients with mUC will experience disease progression under the available treatment options. There is an unmet medical need for additional treatment options that improve the survival outcome in these patients. Fibroblast growth factor (FGF) receptor pathway alterations are common in patients with relapsed urothelial cancer and present an actionable target for targetable therapies. Erdafitinib is a tyrosine kinase inhibitor with activity against fibroblast growth factor receptor (FGFR).

Erdafitinib exhibits linear pharmacokinetics in the therapeutic dose range and can be administered independently of food. Dose adjustments in special populations are not required from a pharmacokinetic point of view. However, there are no data available in subjects with severe hepatic or renal impairment or with CYP2C9 *3/*3 genotype. The interaction potential of erdafitinib as a perpetrator is low. Erdafitinib did not cause QTc prolongations. However, the total and free erdafitinib concentrations included in the respective ER analysis just covered the exposures after 8 mg once daily, but no supratherapeutic exposures.

Erdafitinib has a relatively narrow therapeutic index. The co-administration of moderate CYP2C9 or strong CYP3A4 inhibitors should be avoided or requires erdafitinib dose adjustments. Similarly, the co-administration of strong inducers of CYP2C9 or CYP3A4 should be avoided. Due to its mechanism of action, erdafitinib increases serum phosphate concentrations. Increasing serum phosphate levels were associated with both better efficacy and a higher incidence of AEs. For the Phase 3 data, this was also the case for erdafitinib plasma exposures. For OS, Cavg appeared to be the better predictor based on AIC. For PFS and ORR, AIC was comparable for Cavg and PO4. For the safety endpoints, AIC was consistently lower for PO4, i.e. it was the better predictor. From a pharmacometrics point of view, the derivation of the final erdafitinib dose adjustments is not fully comprehensible, as they are based on both serum phosphate levels and toxicity. Although ER models for efficacy and safety were available after Phase 2, they were apparently not used to define a target range of serum phosphate or erdafitinib plasma concentrations to derive the altered adjustments for Phase 3.

Erdafitinib PK and PD were appropriately characterised. Its interaction potential as a victim was handled by appropriate labelling. However, the use of the available ER models for the selection of the Phase 3 dose adjustments was suboptimal.

Nonetheless, the proposed continuous dose of 8 mg daily with phosphate-guided up-titration to 9 mg daily is acceptable. Phosphate-guided dose up-titration is a practically implementable measure to reduce the risk of severe hyperphosphataemia in the first weeks of treatment.

In the Cohort 1 of the Phase 3 study BLC3001, erdafitinib demonstrated statistically significant and clinically meaningful improvements in overall survival, progression-free survival and overall response rates response rates in mUC patients with FGFR3 alterations patients who received prior systemic treatment including a PD-(L)1 inhibitor. The majority of study patients received prior platinum-based chemotherapy. There was insufficient data for a conclusive assessment of benefit-risk in a platinum-naïve population eligible to receive platinum-based chemotherapy.

The reported adverse events are manageable in daily clinical practice, and the relevant safety aspects are adequately described in the information for healthcare professionals.

The benefit-risk assessment is positive for erdafitinib in the approved indication.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for BALVERSA was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

BALVERSA®

Composition

Active substances

Erdafitinib

Excipients

Tablet Core: Croscarmellose sodium, Magnesium stearate, Mannitol, Meglumine, and Microcrystalline cellulose.
Film coating: Glycerol monocaprylocaprate Type I, Polyvinyl alcohol-partially hydrolyzed, Sodium lauryl sulfate, Talc, Titanium dioxide (E 171), Iron oxide yellow (E 172), Iron oxide red (E 172) (for the orange and brown film-coated tablets only), iron oxide black (E 172) (for the brown film-coated tablets only).

Sodium content

3 mg film-coated tablets: 0.33 mg sodium
4 mg film-coated tablets: 0.44 mg sodium
5 mg film-coated tablets: 0.55 mg sodium

Pharmaceutical form and active substance quantity per unit

For oral use.
3 mg film-coated tablets: Each film-coated tablet contains 3 mg of erdafitinib. Yellow, round film coated, debossed with “3” on one side; and “EF” on the other side.
4 mg film-coated tablets: Each film-coated tablet contains 4 mg of erdafitinib. Orange, round film coated, debossed with “4” on one side; and “EF” on the other side.
5 mg film-coated tablets: Each film-coated tablet contains 5 mg of erdafitinib. Brown, round film coated, debossed with “5” on one side; and “EF” on the other side.

Indications/Uses

BALVERSA as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC) with FGFR3 (fibroblast growth factor receptor 3) alteration, with disease progression during or following at least one therapy with a PD-1- or PD-L1-inhibitor (programmed death receptor-1- resp. programmed death-ligand-1-inhibitor), and after platinum-containing chemotherapy, if eligible (see *Clinical efficacy*).

Dosage/Administration

BALVERSA should be used only under the guidance of medical personnel experienced in the treatment of urothelial carcinoma.
Before taking BALVERSA, patients must have confirmation of certain FGFR3 gene alterations as confirmed by a validated test (see Properties/Effects - Clinical efficacy).

Usual dosage (adults ≥ 18 years)

The recommended starting dose of BALVERSA is 8 mg orally once daily; with individualized up-titration, based on serum phosphate concentrations and drug-related toxicity, to 9 mg daily if criteria are met (see *Dosage/Administration - Dose Modifications*).

Administration

The film-coated tablets should be swallowed whole with or without food. If vomiting occurs any time after taking BALVERSA, the next dose should be taken the next day.
Grapefruit or bitter oranges (Seville oranges) should be avoided while taking BALVERSA due to strong CYP3A4 inhibition.
Treatment should continue until disease progression or unacceptable toxicity occurs.

Missed dose

If a dose of BALVERSA is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for BALVERSA the next day. Extra film-coated tablets should not be taken to make up for the missed dose.

Dose adjustments

Individualized up-titration based on serum phosphate concentrations and drug-related toxicity

Serum phosphate (PO_4) concentrations should be assessed between 14 and 21 days after initiating treatment. Up-titrate the dose to 9 mg daily as soon as possible if that serum phosphate (PO_4) concentration is <9.0 mg/dL, and there is no drug-related toxicity (see Table 2). After day 21 the serum phosphate level should not be used to guide up-titration decision.

Dose adjustment following undesirable effects/interactions

For possible dose reductions and management of undesirable effects see Tables 1 to 4.

Table 1: BALVERSA dose reduction schedule

Dose	**1st dose reduction**	**2nd dose reduction**	**3rd dose reduction**	**4th dose reduction**	**5th dose reduction**
9 mg (three 3 mg film-coated tablets)	8 mg (two 4 mg film-coated tablets)	6 mg (two 3 mg film-coated tablets)	5 mg (one 5 mg film-coated tablet)	4 mg (one 4 mg film-coated tablet)	Stop

8 mg (two 4 mg film-coated tablets)	6 mg (two 3 mg film-coated tablets)	5 mg (one 5 mg film-coated tablet)	4 mg (one 4 mg film-coated tablet)	Stop	---

Hyperphosphatemia management

Hyperphosphatemia is an expected, transient laboratory abnormality of FGFR inhibitors (see *Pharmacodynamics*). Phosphate concentrations should be monitored monthly. For elevated phosphate concentrations in patients treated with BALVERSA follow dose modification guidelines in Table 2. For persistently elevated phosphate concentrations, adding a non-calcium containing phosphate binder (e.g., sevelamer carbonate) may be considered.

Table 2: Recommended dose modifications based on serum phosphate concentrations with the use of BALVERSA after up-titration

Serum Phosphate Concentration	**BALVERSA Management[a]**
<6.99 mg/dL (<2.24 mmol/L)	Continue BALVERSA at current dose.
7.00-8.99 mg/dL (2.25-2.90 mmol/L)	Continue BALVERSA treatment. Start phosphate binder with food until phosphate level is <7.00 mg/dL. A dose reduction should be implemented for a sustained serum phosphate level of ≥7.00 mg/dL for a period of 2 months or if clinically necessary.
9.00-10.00 mg/dL (2.91-3.20 mmol/L)	Withhold BALVERSA treatment until serum phosphate level returns to ≤7.00 mg/dL (weekly testing recommended). Start phosphate binder with food until serum phosphate level returns to <7.00 mg/dL. Re-start treatment at the same dose level. A dose reduction should be implemented for sustained serum phosphate level of ≥9.00 mg/dL for a period of 1 month or if clinically necessary.
>10.00 mg/dL (>3.20 mmol/L)	Withhold BALVERSA treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Re-start treatment at the first reduced dose level. If serum phosphate level of ≥10.00 mg/dL is sustained for >2 weeks, erdafitinib should be discontinued permanently. Medical management of symptoms as clinically appropriate.
Significant alteration from baseline renal function or Grade 3 hypocalcemia due to hyperphosphatemia.	BALVERSA should be discontinued permanently.

[a] For phosphate concentrations ≥5.5 mg/dL (1,75 mmol/l), restrict phosphate intake to 600-800 mg/day.

Eye disorder management

Prior to initiating BALVERSA, perform a baseline ophthalmological exam including an Amsler grid test, fundoscopy, visual acuity and, if available, an optical coherence tomography (OCT). Treatment with BALVERSA should be discontinued or modified based on erdafitinib-related toxicity as described in Table 3.

Table 3: Guideline for management of eye disorders with use of BALVERSA

Severity Grading	BALVERSA Dose Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only, or abnormal Amsler grid test.	Refer for an ophthalmologic examination (OE). If an OE cannot be performed within 7 days, withhold BALVERSA until an OE can be performed. If no evidence of eye toxicity on OE, continue BALVERSA at same dose level. If diagnosis from OE is keratitis or retinal abnormality (i.e., CSR[a]), withhold BALVERSA until resolution. If reversible in 4 weeks on OE, resume at next lower dose. Upon restarting BALVERSA continue to monitor for recurrence every 1-2 weeks for a month. Consider dose re-escalation if no recurrence.
Grade 2: Moderate; limiting age appropriate instrumental activities of daily living (ADL).	Immediately withhold BALVERSA and refer for an OE. Resume BALVERSA at the next lower dose level. If diagnosis from OE is keratitis or retinal abnormality (i.e., CSR), withhold BALVERSA until resolution. If resolved (complete resolution and asymptomatic) within 4 weeks on OE, resume BALVERSA at the next lower dose level. Upon restarting BALVERSA monitor for recurrence every 1-2 weeks for a month.
Grade 3: Severe or medically significant but not immediate sight-threatening; limiting self-care ADL.	Immediately withhold BALVERSA and refer for an OE. If resolved (complete resolution and asymptomatic) within 4 weeks, then BALVERSA may be resumed at 2 dose levels lower. Monitor for recurrence every 1 to 2 weeks for a month. Consider permanent discontinuation of BALVERSA for recurrence.
Grade 4: Sight-threatening consequences; blindness (20/200 or worse).	Permanently discontinue BALVERSA. Monitor until complete resolution or stabilization.

[a] CSR-central serous retinopathy

Dose modification for other adverse reactions

Nail, skin and mucosal changes have been observed with BALVERSA. Follow dose modification guidelines in Table 4.

Table 4: Recommended dose modifications for nail, skin and mucosal adverse reactions with use of BALVERSA

Severity of Adverse Reaction	**BALVERSA**
Nail Disorder	***BALVERSA Dose Management***
Grade 1:	Continue at current dose.
Grade 2:	Consider holding BALVERSA with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below.
Grade 3:	Hold BALVERSA, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below.
Grade 4:	Discontinue BALVERSA.
Dry Skin and Skin Toxicity	
Grade 1:	Continue at current dose.
Grade 2:	Continue at current dose.
Grade 3:	Hold BALVERSA (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below.
Grade 4:	Discontinue BALVERSA.
Oral Mucositis	
Grade 1:	Continue at current dose.
Grade 2:	Consider holding BALVERSA if the subject has other drug related concomitant Grade 2 AEs. Hold BALVERSA if the subject was already on symptom management for more than a week. If the BALVERSA is withheld, reassess in 1-2 weeks. If this is the first occurrence of toxicity and resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below.
Grade 3:	Hold BALVERSA, with reassessments of clinical condition in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below.

Grade 4:	Discontinue BALVERSA.
Dry Mouth	
Grade 1:	Continue BALVERSA at current dose.
Grade 2:	Continue BALVERSA at current dose.
Grade 3:	Hold BALVERSA (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤Grade 1 or baseline, restart at 1 dose level below.

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is required for patients with mild or moderate hepatic impairment (see *Pharmacokinetics*). Limited data are available in patients with severe hepatic impairment.

Patients with renal disorders

Based on population pharmacokinetic (PK) analyses, no dose adjustment is required for patients with mild or moderate renal impairment (see *Pharmacokinetics*). Limited data are available in patients with severe renal impairment.

Elderly patients (65 years of age and older)

No overall differences in safety and effectiveness were observed between elderly and younger adult patients. No specific dose adjustments are considered necessary for elderly patients (see Clinical Efficacy and *Undesirable effects*).

Pediatrics (< 18 years)

The safety and efficacy of erdafitinib in children have not been established. No data are available.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Ocular disorders

BALVERSA can cause ocular disorders, including central serous retinopathy (CSR) (a grouped term including retinal pigment epithelial detachment (RPED) resulting in visual field defect.
CSR was reported in 165 patients treated with BALVERSA, with a median time to first onset of 50.0 days. Grade 3 or 4 CSR, was reported in 1.3 of patients. Based on the overall safety pool of 1081 patients, central serous retinopathy had resolved for 104 of 165 patients, 61 of 165 patients had unresolved events. In patients with CSR, 69 had dose interruptions and 88 had dose reductions. There were 18 patients who discontinued erdafitinib due to: detachment of RPE (9), chorioretinopathy

(3), maculopathy (3), retinal detachment (1), retinopathy (1), subretinal fluid (1) and serous retinal detachment (1).
Dry eye symptoms occurred in 197 patients during treatment with BALVERSA and were Grade 3 or 4 in 4 patients. All patients should receive dry eye prophylaxis or treatment with ocular demulcents (for example artificial tear substitutes, hydrating or lubricating eye gels or ointment) at least every 2 hours during waking hours. Severe treatment-related dry eye should be evaluated by an ophthalmologist.
Perform monthly ophthalmological examinations including Amsler grid test, during the first 4 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms. If any abnormality is observed, follow the management guidelines in Table 3 (see *Dosage/Administration*).
Ophthalmological examination should include assessment of visual acuity, slit lamp examination, fundoscopy, and if available optical coherence tomography.
Withhold BALVERSA when CSR occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity. For ocular adverse reactions, follow the dose modification guidelines (see *Dosage/Administration*).

Hyperphosphatemia and soft tissue mineralization

BALVERSA can cause hyperphosphataemia. Prolonged hyperphosphatemia can lead to soft tissue mineralisation, cutaneous calcinosis, non-uraemic calciphylaxis, hypocalcaemia, anaemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation and arrhythmias.
Hyperphosphatemia was reported early during BALVERSA treatment, with most events occurring within the first 3-4 months and Grade 3 events occurring within the first month.
Monitor for hyperphosphatemia throughout treatment. Restrict dietary phosphate intake (600-800 mg daily) and avoid concomitant use of agents that may increase serum phosphate levels for serum phosphate levels >5.5 mg/dl. Supplementation with vitamin D in patients receiving erdafitinib is not recommended due to potential contribution to increased serum phosphate and calcium levels.
If serum phosphate is above 7.0 mg/dL, consider adding an oral phosphate binder until serum phosphate level returns to <7.0 mg/dL. Withhold, dose reduce, or permanently discontinue BALVERSA based on duration and severity of hyperphosphatemia according to Table 2 (see *Dosage/Administration*).

Use with medicinal products known to prolong QT interval

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 or class III (e.g., amiodarone, sotalol,) antiarrhythmic medicinal products, macrolide antibiotics, SSRIs (e.g., citalopram, escitalopram), methadone, moxifloxacin, and antipsychotics (e.g., haloperidol).

Reproductive and developmental toxicity

Based on findings in animal reproduction studies, erdafitinib can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic

at exposures less than the human exposures at all doses studied (see *Preclinical data*). Pregnancy testing with a highly sensitive assay is recommended for females of reproductive potential prior to initiating BALVERSA. Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use highly effective contraception prior to and during treatment, and for 1 month after the last dose (see *Pregnancy, lactation*).

Central nervous system (CNS) metastases

As subjects with symptomatic central nervous system metastases were excluded from the study, efficacy in this population was not investigated and no dose recommendations can be made, but penetration of the blood-brain barrier by erdafitinib is expected to be low (see *Preclinical data*).

Combination with strong or moderate CYP2C9 or CYP3A4 inhibitors

Concomitant use of BALVERSA with moderate CYP2C9 or strong CYP3A4 inhibitors requires dose adjustment (see *Interactions*).

Combination with strong or moderate CYP3A4 inducers

Concomitant use of BALVERSA with strong CYP3A4 inducers is not recommended. Concomitant use of BALVERSA with moderate CYP3A4 inducers requires dose adjustment (see *Interactions*).

Combination with hormonal contraceptives

Concomitant administration of BALVERSA may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative contraceptive not affected by enzyme inducers (e.g., non-hormonal intrauterine device) or an additional nonhormonal contraception (e.g., condom) during treatment with and until 1 month after the last dose of BALVERSA (see *Interactions* and *Pregnancy, lactation*).

Excipients

This medicine contains less than 1 mmol (23 mg) of sodium per film-coated tablet, i.e. it is almost «sodium-free».

Interactions

Pharmacokinetic interactions

Effect of other agents on the pharmacokinetics of Erdafitinib

Moderate CYP2C9 or strong CYP3A4 inhibitors

Co-administration with a moderate CYP2C9 or strong CYP3A4 inhibitor increased erdafitinib exposure and may lead to increased drug-related toxicity. Erdafitinib mean ratios (90% CI) for C_{max} and AUC_{∞} were 121% (99.9, 147) and 148% (120, 182), respectively, when co-administered with fluconazole, a moderate CYP2C9 and CYP3A4 inhibitor, relative to erdafitinib alone. C_{max} of erdafitinib was 105% (90% CI: 86.7, 127) and AUC_{∞} was 134% (90% CI: 109, 164) when co-

administered with itraconazole, a strong CYP3A4 inhibitor and P-gp inhibitor, relative to erdafitinib alone. Consider alternative agents with no or minimal enzyme inhibition potential. If BALVERSA is co-administered with a moderate CYP2C9 or strong CYP3A4 inhibitor (such as itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, miconazole, ceritinib, clarithromycin, elvitegravir, ritonavir, lopinavir, amiodarone, piperine), reduce the BALVERSA dose based on tolerability (see *Dosage/Administration*). If the moderate CYP2C9 or strong CYP3A4 inhibitor is discontinued, the BALVERSA dose may be adjusted as tolerated.
Grapefruit or bitter oranges (Seville oranges) should be avoided while taking BALVERSA due to strong CYP3A4 inhibition.

Strong or moderate CYP3A4 inducers

Co-administration with carbamazepine, a strong CYP3A4 and weak CYP2C9 inducer leads to decreased erdafitinib exposure. Mean ratios of C_{max} and AUC_{inf} for free erdafitinib was 78% (90% CI: 72.8, 83.1) and 45% (90% CI: 39.7, 51.6), respectively, when co-administered with carbamazepine, a strong CYP3A4 and weak CYP2C9 inducer, relative to erdafitinib alone. Avoid co-administration of strong CYP3A4 inducers (such as apalutamide, enzalutamide, lumacaftor, ivosidenib, mitotane, rifampicin, carbamazepine, phenytoin, and St. John's wort) with BALVERSA. If a moderate CYP3A4 inducer (such as dabrafenib, bosentan, cenobamate, efavirenz, etravirine, lorlatinib, modafinil, phenobarbital, primidone, rifabutin, sotorasib, telotristat ethyl), must be co-administered at the start of BALVERSA treatment, the dose should be cautiously increased by 1 to 2 mg and adjusted gradually every two to three weeks based on clinical monitoring for adverse reactions, not to exceed 9 mg. If the moderate CYP3A4 inducer is discontinued, the BALVERSA dose may be adjusted as tolerated.

Acid lowering medicinal products

Erdafitinib is a BCS Class I compound with adequate solubility across the pH range of 1 to 7.4. Acid lowering medicinal products (e.g., antacids, H_2-antagonists, or proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib.

Drugs affecting transporters

Erdafitinib is a substrate for P-gp but not for BCRP, OATP1B1, and OATP1B3. P-gp inhibitors are not expected to affect the PK of erdafitinib in a clinically relevant manner.

Sevelamer

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed in patients taking sevelamer.

Effect of Erdafitinib on the pharmacokinetics of other agents

Major CYP isoform substrates

Erdafitinib is not an inhibitor of major CYP isozymes at clinically relevant concentrations; however, it was shown *in vitro* to be a weak time dependent inhibitor towards CYP3A4 activity as well as a weak inducer of CYP3A4. Mean ratios of C_{max} and AUC_{∞} for midazolam (a sensitive CYP3A4 substrate) were 86.3% (90% CI: 73.5, 101) and 82.1% (90% CI: 70.8, 95.2), respectively, when co-administered with erdafitinib relative to midazolam alone. Erdafitinib does not have a clinically meaningful effect on midazolam PK.
However, it cannot be excluded that CYP3A4 induction after administration of BALVERSA alone or concomitant administration of other CYP3A4 inducers together with BALVERSA may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative contraceptive not affected by enzyme inducers (e.g., non-hormonal intrauterine device) or an additional nonhormonal contraception (e.g., condom) during treatment with and until 1 month after the last dose of BALVERSA.

P-Glycoprotein (P-gp) substrates

Concomitant administration of BALVERSA with P-gp substrates may increase their systemic exposure if administered concurrently. The concomitant administration of BALVERSA and oral P-gp substrates with a narrow therapeutic index should therefore be avoided. If this is not possible, an oral narrow therapeutic index P gp substrates such as digoxin, colchicine, dabigatran, and apixaban should be taken at least 6 hours before or after erdafitinib. Furthermore, the details in the information for professionals of the respective P-gp substrate must be considered.

Other transporters

Erdafitinib is not an *in vitro* inhibitor of OATP1B3, OAT1, and OAT3. At clinically relevant concentrations, erdafitinib is not considered to be an inhibitor of BCRP, OATP1B, OCT1, MATE-1, and MATE-2K transporters. Erdafitinib is an OCT2 inhibitor *in vitro*. However, mean ratios of C_{max} and AUC_{∞} for metformin (a sensitive OCT2 substrate) were 109% (90% CI: 90.3, 131) and 114% (90% CI: 93.2, 139), respectively, when co-administered with erdafitinib relative to metformin alone. Erdafitinib does not have a clinically meaningful effect on metformin PK.

Pharmacodynamic interactions

Serum phosphate level-altering medicinal products

In patients receiving BALVERSA, medicinal products that can alter serum phosphate levels should be avoided until assessment of serum phosphate level between 14 and 21 days after initiating treatment due to potential impact on up-titration decision.

Pregnancy, lactation

Pregnancy testing

Pregnancy testing with a highly sensitive assay is recommended for females of reproductive potential prior to initiating BALVERSA.

Contraception

BALVERSA can cause fetal harm when administered to pregnant women. Advise female patients of reproductive potential to use highly effective contraception prior to and during treatment, and for 1 month after the last dose of BALVERSA. Male patients must use effective contraception (e.g., condom) and not donate or store semen during treatment and for 1 month after the last dose of BALVERSA.
Concomitant administration of BALVERSA may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative contraceptive not affected by enzyme inducers (e.g., non-hormonal intrauterine device) or an additional nonhormonal contraception (e.g., condom) during treatment with and for 1 month after the last dose of BALVERSA (see *Interactions*).

Pregnancy

There are no available human data informing the erdafitinib-associated risk. Animal studies have shown reproductive toxicity (embryotoxic and teratogenic) (see *Preclinical data*). The potential risk for humans is not known. BALVERSA must not be used during pregnancy unless treatment with erdafinitib is clearly necessary due to the clinical condition of the woman. Pregnant women and women of childbearing potential should be informed about the potential risk to the fetus.

Lactation

There are no data on the transfer of erdafitinib into human milk, or the effects of BALVERSA on the breast-fed infant, or on milk production. A risk for the breastfed child cannot be excluded. Due to the potential for serious adverse reactions in breast-fed infants, women are to be advised not to breast-feed during treatment and for 1 month following the last dose of BALVERSA.

Fertility

No data are available to determine potential effects of BALVERSA on fertility in males or females. Animal experimental studies with erdafitinib indicate that female fertility may be affected (see *Preclinical Data*).

Effects on ability to drive and use machines

No studies to establish the effects of erdafitinib on the ability to drive and use machines have been conducted. However, eye disorders such as central serous retinopathy or keratitis have been noted with FGFR inhibitors and with BALVERSA treatment. If patients experience treatment related

symptoms affecting their vision, it is recommended that they do not drive or use machines until the symptomes subsides (see *Warnings and Precautions*).

Undesirable effects

Adverse reactions are adverse events (AEs) that were considered to be reasonably associated with the use of erdafitinib based on the comprehensive assessment of the available adverse event information. A causal relationship with erdafitinib cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of the safety profile

The safety profile is based on pooled data from 1081 patients that were treated with BALVERSA at the recommended 8 mg starting dose or higher regardless of tumor entity. Median duration of treatment was 4.01months (range: 0.1 to 49.4 months).
1049 (97%) patients reported ARs. The most common AR was hyperphosphatemia (76%). ARs reported at ≥10% were stomatitis (51%), diarrhea (50%), dry mouth (43%), decreased appetite (30%), dry skin (28.0%), palmar-plantar erythrodysesthesia syndrome (PPES) (23%), alanine aminotransferase (ALT) increased (23%), dysgeusia (23%), aspartate aminotransferase (AST) increased (21%), alopecia (20%), onycholysis (19%), dry eye (18%), weight decreased (15%), paronychia (15%), nail discoloration (14%), epistaxis (13%), central-serous retinopathy (12%), nail disorder (11%), nail dystrophy (10%), and blood creatinine increased (10%),.
Grade 3 or higher ARs reported for ≥3% were stomatitis (10%), palmar-plantar erythrodysesthesia syndrome (6%),hyponatremia (5%), onycholysis (5%), alanine aminotransferase (ALT) increased (4%), diarrhea (3%), decreased appetite (3%), hyperphosphatemia (3%) and aspartate aminotransferase (AST) increased (3%).
Adverse reactions leading to dose reduction occurred in 51.4% of patients. Stomatitis (13.1%) was the most common adverse event leading to dose reduction.
Adverse reactions leading to treatment discontinuation occurred in 6.1% of patients. Detachment of retinal pigment epithelium (0.6%) was the most common adverse event leading to treatment discontinuations.

List of adverse reactions

Table 5 presents ARs reported in patients treated with BALVERSA at the recommended 8 mg starting dose or higher regardless of tumor entity. ARs are listed by system organ class and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, ARs are presented in order of decreasing frequency.

Table 5: Adverse reactions reported in patients treated with BALVERSA

SOC		Overall Erdafitinib safety pool (8 mg or higher regardless of tumor entity) (N=1081)		
MedDRA Preferred Term	**Frequency Category[a]**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Metabolism and nutrition disorders				
Hyperphosphataemia	very common	76	3	<1
Decreased appetite	very common	30	3	0
Hyponatraemia	very common	11	5	1
Gastrointestinal disorders				
Stomatitis	very common	51	10	0
Diarrhoea	very common	50	3	<1
Dry mouth	very common	43	<1	0
Skin and subcutaneous tissue disorders				
Dry skin	very common	28	1	0
Palmar-plantar erythrodysaesthesia syndrome	very common	23	6	0
Alopecia	very common	20	<1	0
Onycholysis	very common	19	5	0
Paronychia	very common	15	2	0
Nail discolouration	very common	14	1	0
Nail disorder	very common	11	1	0
Nail dystrophy	very common	10	2	0
Onychomadesis	common	8	1	0
Pruritus	common	5	0	0
Nail ridging	common	3	<1	0
Onychalgia	common	3	1	0
Skin fissures	common	3	<1	0
Onychoclasis	common	2	<1	0
Skin exfoliation	common	2	0	0
Xeroderma	common	2	0	0
Hyperkeratosis	common	2	<1	0
Eczema	common	1	0	0
Nail bed bleeding	uncommon	1	0	0
Skin lesion	uncommon	1	<1	0
Palmar erythema	uncommon	1	0	0
Skin toxicity	uncommon	1	<1	0
Nail discomfort	uncommon	<1	0	0
Skin atrophy	uncommon	<1	0	0
Investigations				

Alanine aminotransferase (ALT) increased	very common	23	4	<1
Aspartate aminotransferase (AST) increased	very common	21	3	<1
Weight decreased	very common	15	1	0
Blood creatinine increased	common	10	<1	0
Eye disorders				
Dry eye	very common	18	<1	0
Central serous retinopathy (CSR)[b]	very common	12	1	0
Conjunctivitis	common	8	0	0
Keratitis	common	5	1	<1
Xerophthalmia	common	3	<1	0
Ulcerative keratitis	common	1	<1	0
Nervous system disorders				
Dysgeusia	very common	23	1	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	very common	13	0	0
Nasal dryness	common	6	0	0
Renal and urinary disorders				
Acute kidney injury	common	4	2	<1
General disorders and administration site conditions				
Mucosal dryness	common	1	0	0

[a] Frequency categories are based on the frequency of the All Grades (%); very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100).
[b] Central serous retinopathy (CSR) includes Retinal detachment, Vitreous detachment, Retinal edema, Retinopathy, Chorioretinopathy, Detachment of retinal pigment epithelium, Detachment of macular retinal pigment epithelium.

Description of specific adverse reactions and additional information

The following ARs were reported with the administration of BALVERSA and are considered to be class effects with FGFR Tyrosine kinase inhibitors occurring at highest frequency:

Central serous retinopathy (CSR)

CSR has been reported with the use of BALVERSA as well as with other FGFR inhibitors. Adverse reactions of CSR were reported in 15.3% of patients. The most commonly reported events were chorioretinopathy, detachment of RPE, retinal detachment, retinopathy, and subretinal fluid. 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 50 days (see *Warnings and Precautions*).

Other eye disorders

Eye disorders (other than central serous retinopathy) were reported in 41.9% of patients. The most commonly reported events were dry eye (18.2%), vision blurred (10.5% subjects) and conjunctivitis (7,9%). Of patients with events, 6.7% had dose reductions and 9.2% had dose interruptions. There were 1.7% who discontinued erdafitinib due to eye disorders. The median time to first onset for eye disorders was 45 days (see *Warnings and Precautions*).

Nail disorders

Nail disorders were reported in 58.1% of patients. The most commonly reported events included onycholysis (18.8%), paronychia (14.6%), nail discolouration (13.6%), nail disorder (11.2%), nail dystrophy (10.2%) and onychomadesis (7.9%). The incidence of nail disorders increased after the first month of exposure. The median time to first onset for any grade nail disorder was 57 days.

Skin disorders

Skin disorders were reported in 51.9% of patients. The most commonly reported events were dry skin (28.2%), and palmar-plantar erythrodysesthesia syndrome (23.2%). The median time to first onset for any grade skin disorder was 43 days.

Gastrointestinal disorders

Gastrointestinal disorders were reported in 80.6% of patients. The most commonly reported events were stomatitis (50.9%) diarrhea (50.4%), and dry mouth (43.5%). The median time to first onset for any grade gastrointestinal disorder was 14 days.

Hyperphosphatemia and soft tissue mineralization

BALVERSA can cause hyperphosphataemia. Prolonged hyperphosphatemia can lead to soft tissue mineralisation, cutaneous calcinosis, non-uraemic calciphylaxis, hypocalcaemia, anaemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation and arrhythmias. Hyperphosphatemia was reported as an adverse event in 75.9 % of patients treated with BALVERSA.

No event of hyperphosphatemia was reported as serious. Hyperphosphatemia was reported early during erdafitinib treatment, with Grade 1-2 events generally occurring within the first 3 months and Grade 3 events occurring within the first month. The median onset time for any grade event of hyperphosphatemia was 15 days. Vascular calcification has been observed in 0.1% of patients treated with BALVERSA.

Of the 1081 patients treated with BALVERSA in clinical studies at the 8 mg or higher dose, 56.2% of patients were less than 65 years old, 31.7% of patients were 65 years to 74 years old, and 12% were 75 years old and over. Patients 65 years of age and older treated with BALVERSA experienced a higher incidence of adverse reactions requiring treatment discontinuation than younger patients. In clinical trials, the incidence of treatment discontinuations of BALVERSA due to adverse reactions was 10% in patients younger than 65 years, 16.9% in patients ages 65-74 years, and 32.3% in patients 75 years or older.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is no information on overdosage with BALVERSA.

Treatment

There is no known specific antidote for BALVERSA overdose. In the event of an overdose, stop BALVERSA, undertake general supportive measures until clinical toxicity has diminished or resolved.

Properties/Effects

ATC code

L01EN01

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% tumor growth inhibition (IC50) is in the low nanomolar range 0.1 to 129.2 nM.
Erdafitinib demonstrated antitumor activity in FGFR-driven cell lines and xenograft models derived from multiple tumor types, including bladder cancer.

Pharmacodynamics

Cardiac electrophysiology

Based on evaluation of QTc interval in an open-label, dose escalation and dose expansion study in 187 patients with cancer, erdafitinib had no large effect (i.e., > 20 ms) on the QTc interval.

Serum phosphate

Erdafitinib increased serum phosphate concentration, a pharmacodynamic biomarker of FGFR inhibition. Achieving serum phosphate concentrations ≥ 5.5 mg/dL in early cycles with continuous daily dosing is associated with an improved clinical response (see *Dosage/Administration*).

Clinical efficacy

Urothelial carcinoma tumors with select FGFR genetic alterations

Study BLC3001(THOR) was a phase 3, randomized, open-label, multicenter study to evaluate the overall survival (OS) of erdafitinib versus chemotherapy (docetaxel or vinflunine) or pembrolizumab in patients with advanced urothelial cancer harboring selected FGFR alterations, who have progressed after 1 or 2 prior treatments, at least 1 of which includes a PD-1 or PD-L1 inhibitor (anti-PD-(L)-1) (Cohort 1) or 1 prior treatment not containing an anti-PD-(L)1 agent (Cohort 2). Patients who received neoadjuvant or adjuvant chemotherapy or immunotherapy and showed disease progression within 12 months of the last dose were considered to have received systemic therapy in the metastatic setting.

Study BLC3001 (THOR) – Cohort 1

A total of 266 patients previously treated with an anti-PD-(L)1 agent were randomized to erdafitinib (8 mg with individualized up-titration to 9 mg) versus chemotherapy (Docetaxel 75 mg/m^2 once every 3 weeks or Vinflunine 320 mg/m^2 once every 3 weeks). Of 136 subjects randomized in the erdafitinib treatment arm, 135 received the assigned treatment, and of 130 subjects randomized in the chemotherapy treatment arm, 112 received the assigned treatment.
Tumors must have at least 1 of the following FGFR fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or one of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C. In Cohort 1, molecular eligibility was determined using central (74.6%) or local (25.4%) FGFR results. Tumor samples were tested for FGFR genetic alterations by a Polymerase Chain Reaction (PCR) test at the central laboratory. Local historical test on tumor or blood samples were based on local next generation sequencing (NGS) tests.
In Cohort 1, 99.2% of patients had FGFR genetic alterations (2 subjects did not have FGFR alterations: 80.8% of patients had FGFR3 mutations, 16.5% of patients had FGFR3 fusions, and 1.9% of patients had both FGFR3 mutations and fusions). No patients had FGFR2 alterations. All patients in Cohort 1 with FGFR alterations had at least 1 FGFR3 alteration. FGFR3-S249C was the most prevalent alteration (46.6%) followed by FGFR3-Y373C (16.9%), and FGFR3-TACC3 fusion (9.8%).

The demographic characteristics for Cohort 1 were balanced across the erdafitinib and chemotherapy treatment groups. The median age at full-study screening was 67 years (range: 32 to 86 years). The majority of patients were 65 years or older: 19.9% 65 to 69 years; 19.9% 70 to 74 years; 21.1% 75 years or older. The majority of patients were male (71.4%) and white (54.1%). In Cohort 1, 60.9% of subjects were in Europe, 4.9% in North America, and 34.2% in the rest of the world. Only 1 patient was Black or African-American. Although ethnicity was not reported for 18.8% of the patients, only 2.3% patients were Hispanic or Latino.

All patients had transitional cell carcinoma, with a small percentage (5.3%) of patients having minor components (<50% overall) of variant histology. The primary tumor location was the lower tract for 66.5% and upper tract for 33.5% of patients. Patients had baseline ECOG scores of 0 (42.9%), 1 (47.7%), or 2 (9.4%).

Patients with symptomatic central nervous system metastases were excluded from the study.

All patients received at least 1 prior line of anti-cancer therapy and must have included an anti-PD-(L)-1. The most frequently received anti-PD-(L)1 therapies, included pembrolizumab (35.3%), avelumab (22.2%) and atezolizumab (19.5%). Prior treatment with chemotherapy was not required, however, the majority of patients (89.1%) received at least one line of prior chemotherapy. Almost all patients received platinum-based chemotherapy (89.7% erdafitinib, 85.4% chemotherapy): most frequently cisplatin (55.9% erdafitinib, 45.4% chemotherapy) followed by carboplatin (27.2% erdafitinib, 31.5% chemotherapy).

The primary efficacy endpoint was Overall Survival. Assessment of radiographic response was performed by investigators according to RECIST (Response Evaluation Criteria in Solid Tumours Version 1.1) until disease progression, intolerable toxicity, withdrawal of consent, or decision by the investigator to discontinue treatment, or the end of the study, whichever occurred first. Progression-Free Survival (PFS), Objective Response Rate (ORR) and Duration of Response were included as secondary efficacy endpoints.

The key efficacy is based on data from 136 patients who were treated in the erdafitinib 8 mg resp. 9 mg daily regimen in Study BLC3001. The primary efficacy endpoint of OS showed a statistically significant improvement in OS for patients treated with erdafitinib vs chemotherapy, with erdafitinib significantly prolonging OS compared to treatment with chemotherapy (median OS of 12.1 vs 7.8 months (HR=0.64; 95% CI: 0.47, 0.88; p value=0.0050). This represents a 36.0% reduction in the risk of death for patients in the erdafitinib treatment group vs the chemotherapy treatment group. The estimated 6-month survival rate was 0.85 (95% CI: 0.77, 0.90) and the 12 month survival rate was 0.51 (95% CI: 0.41, 0.60). In the chemotherapy group, the median OS was 7.8 (95% CI: 6.5, 11.1) months; the estimated 6-month survival rate was 0.66 (95% CI: 0.56, 0.74) and the 12-month survival rate was 0.38 (95% CI: 0.28, 0.47). Median PFS was 5.55 months for the erdafitinib group and 2.73 months for the chemotherapy group. Treatment with erdafitinib led to an improved response, with an ORR (CR+PR) of 35.3% in the erdafitinib group compared with 8.5% in the chemotherapy group.

Efficacy results are summarized in Table 6.

Table 6: Overview of Efficacy Results for Study BLC3001, Cohort 1

	Erdafitinib (N=136)	**Chemotherapy (N=130)**
Overall Survival (OS)		
Number of events (%)	77 (56.6%)	78 (60.0%)
Median, months (95% CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)
HR (95% CI)	0.64 (0.47, 0.88)	
P-value	0.0050	
Progression-free survival (PFS)		
Number of events (%)	101 (74.3%)	90 (69.2%)
Median, months (95% CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)
HR (95% CI)	0.58 (0.44, 0.78)	
P-value	0.0002	
Objective response rate (ORR), confirmed		
Complete response, CR (%)	7 (5.1%)	1 (0.8%)
Partial response, PR (%)	41 (30.1%)	10 (7.7%)
ORR (CR + PR)	48 (35.3%)	11 (8.5%)
Relative Risk (RR), (95% CI)	4.16 (2.27, 7.64)	
P-value	< 0.001	

All p-values reported are 2-sided.
Note: The Statistical Analysis Plan (SAP) pre-specified stratified analyses of OS, PFS and ORR as determined by a strata pooling algorithm. Due to a limited number of events by treatment arm (ie, <10 events) per strata for OS and PFS, the stratification factors were dropped based on the algorithm and the analyses were unstratified for OS and PFS. ORR analysis was stratified by ECOG performance status per the pooling algorithm.

Pharmacokinetics

Following single and repeat once daily dosing, erdafitinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration time curve [AUC]) increased in a dose-proportional manner across the dose range of 0.5 to 12 mg. Steady state was achieved after 2 weeks with once daily dosing and the mean accumulation ratio was 4-fold. Following administration of 8 mg once daily, the proposed starting dose, mean (coefficient of variation [CV%]) erdafitinib steady-state C_{max}, AUC_T, and minimum observed plasma concentration (C_{min}) 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.

Absorption

After single dose oral administration, median time to achieve peak plasma concentration (t_{max}) was 2.5 hours (range: 2 to 6 hours) and oral absorption is near complete.

Effect of food

Administration of erdafitinib to healthy subjects under fasting conditions and with a high-fat meal did not result in clinically relevant changes in C_{max} and AUC. Median time to reach t_{max} was delayed about 1.5 hours with food (see *Dosage/Administration*).

Distribution

The mean apparent volume of distribution of erdafitinib in subjects with cancer was 28.8 L.
In patients with cancer, erdafitinib was 99.7 % bound to human plasma proteins, preferentially to α1-acid glycoprotein AGP.

Metabolism

Metabolism is the main route of elimination for erdafitinib. Erdafitinib is primarily metabolized in human by CYP2C9 and CYP3A4 to form the O-demethylated major metabolite. The contribution of CYP2C9 and CYP3A4 in the total clearance of erdafitinib is estimated to be 39% and 20% respectively. Unchanged erdafitinib was the major drug-related moiety in plasma, there were no circulating metabolites.

Elimination

Mean total apparent clearance (CL/F) of erdafitinib was 0.362 L/h in patients.
The mean effective half-life of erdafitinib in patients was 58.9 hours.

Excretion

Up to 16 days following a single oral administration of radiolabeled [^{14}C]-erdafitinib, 69% of the dose was recovered in feces (14-21% as unchanged erdafitinib) and 19% in urine (13% as unchanged erdafitinib).

Kinetics in specific patient groups

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed based on age (21-92 years), sex, race (White, Hispanic or Asian) or body weight (36-166 kg).

Hepatic impairment

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function based on PK analysis.

Renal impairment

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed between subjects with normal renal function (eGFR-MDRD [estimated glomerular filtration rate modification of diet in renal disease] ≥90 mL/min/1.73 m^2), and subjects with mild (eGFR-MDRD 60 to 89 mL/min/1.73 m^2) and moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m^2).

Pediatric

Pharmacokinetics of erdafitinib has not been studied in pediatric patients.

CYP2C9 poor metabolizer

Erdafitinib exposure was comparable in subjects with CYP2C9 *1/*2 and *1/*3 genotypes relative to subjects with wild type and similar results were obtained in simulations. No data are available in subjects characterized by other genotypes (e.g., *2/*2, *2/*3, and *3/*3). Simulation suggested no clinically meaningful changes of erdafitinib exposure in CYP2C9 *2/*2 and *2/*3 subjects. The exposure of erdafitinib is predicted to increase by 50% in subjects of CYP2C9 *3/*3 genotype, estimated to be 0.4% to 3% of the population among various ethnic groups and representing the worst-case scenario among the various heterogenous CYP2C9 poor metabolizer populations.

Preclinical data

Safety pharmacology and Repeated dose toxicity

Erdafitinib is an intrinsic hERG blocker (human ether-à-go-go-related gene) with a proarrhythmic liability which translated into a prolonged repolarisation (corrected QT interval) after intravenous dosing in the anaesthetised dog and guinea pig, and after oral dosing in the conscious dog. The no effect level represents a safety margin of 2.4 relative to the clinical steady-state free maximum plasma concentration ($C_{max,u}$) for a 9 mg once daily dose.

In repeated dose toxicity studies in rats and dogs up to 90 days, cartilage dysplasia and soft tissue mineralization were observed as primary drug-related toxicities at exposures less than the human exposures at all doses studied. When rats were given a diet supplemented with the phosphate scavenger sevelamer, the soft tissue mineralizations were reduced. Atrophy of gland and epithelial structures (dental changes, thinning of the corneal epithelium lacrimal gland atrophy changes to haircoat and nails) were seen.
Soft tissue mineralizations (except for the aorta mineralization in dogs) and chondroid dysplasia in rats and dogs and mammary gland atrophy in rats were partially to fully recovered at the end of a 4-week drug-free recovery period.

Genotoxicity

Erdafitinib did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either *in vitro* micronucleus or the *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of erdafitinib.

Reproductive Toxicology

No animal fertility studies have been conducted with erdafitinib. In the 3-month general toxicity study in rats, effects on female reproductive organs (necrosis of the *corpora lutea*) were observed at an exposure approximating highest recommended dose of 9 mg.
Erdafitinib was teratogenic and embryotoxic in rats at ≥ 4 mg/kg/day and exposures less than the human exposures at all doses studied. Fetal toxicity was characterized by hand/foot defects and malformations of some major blood vessels, such as the aorta.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging.
Keep out of the reach of children.

Instructions for handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67660 (Swissmedic)

Packs

BALVERSA 3 mg: Bottles containing 56 and 84 film-coated tablets [A].
BALVERSA 4 mg: Bottles containing 28 and 56 film-coated tablets [A].
BALVERSA 5 mg: Bottles containing 28 film-coated tablets [A].

Marketing authorisation holder

Janssen-Cilag AG, Zug

Date of revision of the text

August 2024