swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Orpathys

International non-proprietary name:	savolitinib
Pharmaceutical form:	**Film coated tablets**
Dosage strength(s):	Orpathys 100 mg
Route(s) of administration:	**oral**
Marketing authorisation holder:	AstraZeneca AG
Marketing authorisation no.:	70151
Decision and decision date:	temporary authorisation in accordance with Art. 9a TPA approved on 13 February 2026

Note:

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

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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
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HGF	Hepatocyte growth factor
HPLC	High-performance liquid chromatography
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
MET	Mesenchymal-epithelial transition factor
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung cancer
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
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
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)
UGT	UDP-glucuronosyltransferase

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

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

Temporary authorisation for human medicinal products
The applicant requested temporary authorisation in accordance with Article 9*a* TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Orpathys in combination with osimertinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have MET overexpression or amplification, and who had disease progression on or after osimertinib.

2.2.2 Approved indication

Orpathys in combination with osimertinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have an EGFR mutation as well as MET overexpression and/or amplification, and who had disease progression on or after osimertinib (see "*Dosage/Administration*").

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose of Orpathys is 300 mg twice daily (approximately 12 hours apart). The two doses of Orpathys should be taken at approximately the same time each day. Orpathys should be taken immediately after a meal.
Orpathys is used in combination with osimertinib, and the recommended dose of osimertinib is 80 mg taken orally once daily. The dose of osimertinib should be taken at the same time each day, either with the morning or evening dose of Orpathys. See also the product information for osimertinib.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	04 March 2025
Formal control completed	07 March 2025
List of Questions (LoQ)	08 May 2025
Response to LoQ	09 September 2025

Preliminary decision	28 October 2025
Response to preliminary decision	28 December 2025
Final decision	13 February 2026
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

The prognosis and treatment of non-small lung cell cancer (NSCLC) depend on histology, molecular characteristics, tumour stage, and the patient's overall condition. Advances in understanding molecular pathways have led to the development of targeted therapies. However, the prognosis remains poor, with a 5-year overall survival rate of less than 5% (12,13).

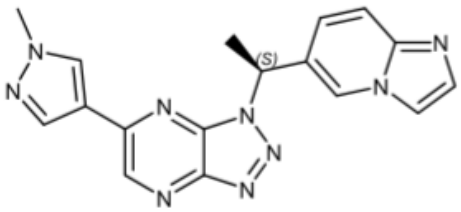
Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is one of the preferred first-line treatments for EGFR-mutant NSCLC. However, resistance to osimertinib is a challenge, the most common resistance mechanism being mesenchymal-epithelial transition factor (MET) amplification/overexpression, which occurs in approximately 25% of patients treated with third-generation TKIs. The prognosis for cases of disease progression on osimertinib due to acquired resistance mutations is unfavourable and there are no clearly defined treatment recommendations. According to the 2025 guidelines of the European Society for Medical Oncology (ESMO), enrolment in clinical trials is recommended. (6)

The combination of amivantamab with carboplatin and pemetrexed is approved for the treatment of patients with EGFR-mutated (mEGFR) NSCLC, who have progressed after prior treatment with osimertinib regardless of MET mutation status. However, this combination is associated with relevant haematological toxicities and the separate components must be administered intravenously. There is an unmet medical need for a therapy option with a different safety profile, a more convenient route of administration and an improvement of survival outcome in this patient group. The investigated therapeutic strategy adds a MET inhibitor to osimertinib to overcome the acquired resistance mutation.

4 Quality aspects

4.1 Drug substance

INN: Savolitinib
Chemical name: 1-[(1S)-1-(imidazo[1,2-a]pyridin-6-yl)ethyl]-6- (1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine
Molecular formula: $C_{17}H_{15}N_9$
Molecular mass: 345.3 g/mol
Molecular structure:



Physicochemical properties: Savolitinib is a crystalline, white to off-white to yellow powder. It is a single enantiomer with S configuration. Savolitinib exhibits a pH-dependent solubility profile across the physiological pH range with lower solubility at neutral pH.

Synthesis: The synthesis of savolitinib consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps and intermediates.

Specification: The drug substance specification includes tests for description, identification, assay, organic impurities, residue on ignition and particle size distribution. The applied limits are justified and in line with the relevant guidelines and the European Pharmacopoeia, if applicable. The analytical methods are adequately described and validated in accordance with ICH guidelines.

Stability: Savolitinib drug substance is stored in low-density polyethylene (LDPE) bags within a rigid outer container. Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Description and composition: The drug product is presented as a yellow film-coated tablet containing 100 mg of savolitinib drug substance. The tablets are debossed with ‘SAV100’ on one side and are plain on the reverse.

Manufacture: Savolitinib tablets have been developed as conventional immediate release film-coated tablets and are manufactured using a standard granulation process. The core tablets are composed of the well known excipients mannitol, microcrystalline cellulose, hydroxypropyl cellulose and magnesium stearate. The film coating consists of hypromellose, titanium dioxide, macrogol, iron oxide yellow, iron oxide red and iron oxide black.

Specification: The drug product specifications include tests for description, identification, assay, degradation products, dissolution, uniformity of dosage units and microbial purity. The proposed acceptance criteria and analytical methods are considered appropriate for quality control of the drug product.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use (HDPE bottles) and according to the relevant international guidelines. The product should not be stored above 30°C.

4.3 Quality conclusions

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

5 Nonclinical aspects

5.1 Pharmacology

Savolitinib inhibited MET kinase with an IC_{50} of 4 nM. Apart from wild-type MET, it also inhibited mutant M1268T and, to a lesser extent, Y1248C and Y1248H. All other tested kinases were either not or less sensitive to savolitinib, except for PAK3 (51% inhibition at 1 µM). The relevance of this observation is unknown.

In various cancer cell lines where MET is constitutively activated (NSCLC NCI-H441 and NCI-H1993; gastric cancer MKN-45), savolitinib inhibited MET autophosphorylation with IC_{50} values in the range of 2 to 6 nM. It also inhibited hepatocyte growth factor (HGF)-stimulated MET activation in NCI-H69 (small cell lung cancer) and U87MG (glioblastoma) cells with IC_{50} values in the range of 1 to 2 nM. Inhibition of HGF-mediated cell functions such as migration, invasion, and scattering, as well as angiogenesis, were also shown.

The applicant assessed the antiproliferative effect of savolitinib in various tumour cells as well as the correlation of tumour cell sensitivity to savolitinib and MET status. Cell lines with MET gene amplification, such as MKN-45 or NCI-H1993, were highly sensitive to savolitinib, with IC_{50} values ≤10 nM. Cell lines without MET amplification but with high MET expression, such as NCI-H441 or NCI-H69, were insensitive to savolitinib (IC_{50} values >30 µM), whereas HGF-dependent cell proliferation was inhibited with IC_{50} values of 6 and 16 nM in NCI-H441 and H69 cells, respectively. Tumour cells with low MET expression were insensitive to savolitinib (IC_{50} values >30 µM).

MET amplification/overexpression is a well-known resistance mechanism to EGFR tyrosine kinase inhibitors in NSCLC. In tumour cells where both MET and EGFR pathways are activated, the applicant showed a superior effect of savolitinib in combination with erlotinib on both cell signalling pathways (inhibition of MET and EGFR phosphorylation, and downstream p-AKT) and inhibition of tumour cell survival.

Of the Phase I metabolites that were tested – M2, M3 and M4 – only M2 was pharmacologically active *in vitro* but was less potent than savolitinib. M8, the glucuronide of M2, was less active than M2.

The applicant confirmed inhibition of MET phosphorylation in tumour-bearing mice (NSCLC cell line NCI-H441 and gastric cancer cell line Hs746T). Savolitinib showed anti-tumour activity in xenograft mouse models harbouring tumours with MET gene amplification, including gastric cancer (Hs746T) and NSCLC (EBC-1), and in a MET-dependent intra-cranial tumour model (U87MG glioblastoma).

The applicant also confirmed the superior effect of savolitinib in combination with EGFR tyrosine kinase inhibitors in mice bearing tumours in which both the MET and EGFR pathways are activated. In particular, the combination of savolitinib with osimertinib elicited greater anti-tumour activity in an osimertinib-resistant, MET-amplified NSCLC patient-derived xenograft model than either savolitinib or osimertinib alone.

An off-target screen identified savolitinib as an agonist at the melatonin MT2 receptor, with an EC_{50} of 1.8 µM. This concentration is close to human unbound C_{max} at therapeutic dose, but the observation is not considered to be a clinical safety concern.

Savolitinib inhibited the hERG current with an IC_{50} of 25.8 µM (21-fold human unbound C_{max} at therapeutic dose). There were no effects on other major cardiac ion channels *in vitro* at concentrations exceeding 28- or 83-fold human unbound C_{max}. In telemetered dogs, a single dose of savolitinib did not induce any changes in blood pressure, heart rate, or ECG parameters at exposures of 7-fold human unbound C_{max}. Whilst these safety pharmacology study findings were unremarkable, a thorough QT study in humans did reveal a potential for QTc prolongation. Except for a transient

slight decrease in body temperature, the safety pharmacology studies in rats did not reveal any effects of savolitinib on the central nervous or respiratory system at plasma concentrations of approximately 17-fold human unbound C_{max}.

5.2 Pharmacokinetics

After oral administration, savolitinib was rapidly absorbed (T_{max} 0.3-2.2 h) and oral bioavailability was 27%, 43%, 87%, and 69% in mice, rats, dogs, and humans, respectively. The low oral bioavailability (<2%) in monkeys possibly results from a high first-pass metabolism. Elimination half-life was 2.6 h in rats, 5.5 h in dogs, and 4 h in humans. After repeated oral doses to rats or dogs, exposure increased with dose in a generally proportional manner. No clear accumulation was noted. There were no sex-related differences in exposure.

Plasma protein binding of savolitinib in mouse, rat, dog, monkey, and human plasma was 41.8%, 70.6%, 63.3%, 81.9%, and 71.3%, respectively. Savolitinib-derived radioactivity distributed into tissues, including the brain, and showed affinity for melanin.

Many enzymes are involved in the metabolism of savolitinib, including CYP3A4/5, CYP1A2, CYP2D6, CYP2C19, aldehyde oxidase, UGT1A4, and UGT2B15. Metabolic pathways include hydroxylation, demethylation, dealkylation, and hydrolysis, followed by conjugation with sulphate, glucuronide, or N-acetylcysteine. M8 (glucuronide of M2) and M44 (glucuronide of M3) are major circulating human metabolites. Although none of them is sufficiently covered in the toxicity studies, this is acceptable for a product intended for treatment of advanced cancer, in accordance with ICH S9.

In rats, savolitinib-derived radioactivity was mainly excreted via the faeces, where unchanged savolitinib was a major component.

5.3 Toxicology

The applicant conducted a toxicology programme in line with ICH S9. The repeat-dose toxicity studies (up to 13 weeks) were conducted in rats and dogs, both of which are pharmacologically relevant animal species. Savolitinib was administered orally, in line with the intended clinical route of administration.

Single oral doses of up to 2000 mg/kg to rats and up to 1000 mg/kg/day to dogs were without any significant toxicity, but repeated administration of lower doses led to mortalities/premature terminations in rats and dogs. Target organs in the 13-week studies were the lymphoreticular system (hypocellularity in lymphoid tissues; decreased RBC (red blood cells), WBC (white blood cells) and platelets), gastro-intestinal tract (ulcerative effects), heart (minimal/slight myocardial degeneration and epicardial inflammation; chronic progressive cardiomyopathy in male rats only), kidney and urinary tract (rats only; various microscopic changes with increased urea and creatinine as well as increased urinary protein and NAG), liver (rats only; hepatocellular hypertrophy), thyroid (rats only; hypertrophy), adrenals (rats only; cortical hypertrophy), and reproductive system (in dogs, tubular degeneration in the testis and cellular debris in the epididymis; in rats, atrophy of the prostate, uterus, cervix, and vaginal epithelium, and follicular atresia in the ovaries). Recovery was not assessed in the pivotal 13-week studies, but data from other studies suggest that findings in most of the target organs were reversible or at least partially reversible. However, it remains unclear whether the findings in dog testis and epididymis are reversible. No NOAEL could be established in the pivotal 13-week studies. At the LOAEL of 50 mg/kg/day in rats and 7.5 mg/kg/day in dogs, exposure was 3-fold human AUC at therapeutic dose, suggesting that there is no or only a very small safety margin. This could be accepted for a product intended for the treatment of advanced cancer. Several of the above findings

were confirmed to be of clinical relevance (decreased blood cell counts, stomatitis, increased creatinine, and increased liver enzymes including DILI were reported in clinical studies).

Savolitinib was not genotoxic. In accordance with ICH S9, no carcinogenicity studies were conducted.

The 13-week repeat-dose toxicity study in dogs revealed findings in the testes and epididymides (see above). The fertility and early embryonic development study, in which both male and female rats were dosed, indicated an increase in the number of days for mating and a decrease in the number of pregnant females and number of live fetuses. At the NOAEL, exposure was 11-fold human AUC at therapeutic dose. In an additional rat study, where only males where dosed, savolitinib did not impair fertility at exposures up to 17-fold human AUC at therapeutic dose. Maternal and embryofetal toxicity were noted in pregnant rats and rabbits. The NOAEL for embryofetal toxicity was below 7.5 mg/kg/day in rats (exposure of 0.7-fold human AUC at therapeutic dose) and equal to 1 mg/kg/day in rabbits (exposure of 0.2-fold human AUC at therapeutic dose). In accordance with ICH S9, the applicant did not conduct any pre- and postnatal development toxicity studies. Due to the reproductive toxicity at clinically relevant exposure, savolitinib is not recommended during pregnancy and in women of childbearing potential not using contraception.

Savolitinib showed a weak phototoxicity potential *in vitro* that could not be confirmed *in vivo*.

There were no safety concerns with impurities.

All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. The PIP does not include any nonclinical measures. Based on the ERA, use of savolitinib is unlikely to result in any significant risk to the environment.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support the approval of savolitinib in the proposed indication. All safety-relevant nonclinical data are included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

Biopharmaceutical development

The final to-be-marketed drug product is supplied as 100 mg strength immediate-release film-coated tablets.

The impact of food was investigated in a biopharmaceutic study. Following the administration of a single dose of 600 mg (6 x 100 mg) savolitinib in healthy Chinese male subjects, C_{max} and AUC_{0-t} were increased by 3% (85% – 124%) and 17% (104% – 133%), respectively, when co-administered with a high-fat, high-calorie breakfast meal. A significant food effect for T_{max} was observed. T_{max} was longer under fed conditions. Although the food effect can be considered not clinically relevant, it is recommended that savolitinib be administered with food for reasons of better tolerability. The proposed dosing recommendation was also applied in the pivotal Phase 2 study.

In healthy subjects, co-administration with a gastric pH-altering agent (famotidine) decreased C_{max} and AUC_{0-t} by 21% (68%–92%) and 12% (82%–94%), respectively, under fasting conditions. Furthermore, PPI was identified as a statistically significant covariate in the population PK analysis. Overall, however, these effects were not considered to be clinically significant.

Pharmacokinetics

The PK profiles of savolitinib and its major Phase 1 metabolites M2 and M3 were evaluated in healthy subjects and oncology patients following single (100 mg to 1000 mg) and multiple (100 mg to 1000 mg QD and 300 mg to 600 mg BID) doses. Savolitinib was investigated as monotherapy or in combination with osimertinib.

Absorption

Following the administration of tablets and solution formulation in healthy subjects, the peak plasma concentrations were rapidly reached with a mean T_{max} of between 0.95 h and 4 h. Similar T_{max} were observed in oncology patients after single and multiple dosing.
Based on the PO/IV ratio of AUC, the absolute bioavailability of a single oral dose of savolitinib was estimated to be 69%.
Following multiple doses of savolitinib, no significant accumulation in the dose ranges up to 1000 mg QD and up to 500 mg BID was observed, with accumulation ratios of up to 1.4. Accumulation ratios of up to 2.2 were observed for the 600 mg BID dosing regimen. No indications of time-dependant PK were discerned. Steady state was generally reached by day 2.

Exposures were shown to increase dose-proportionally after a single dose within the QD dosing regimen of 100 mg to 1000 mg and the BID dosing regimen of 300 mg to 500 mg. After multiple doses, dose proportionality was demonstrated for the QD dosing regimen, whereas greater than dose-proportional increases were observed between 300 mg and 500 mg BID.

No differences in PK between healthy subjects and oncology patients were observed.

Distribution

Based on *in vitro* findings, protein binding of savolitinib in humans was determined at 71.3% over the concentration range of 1 µM to 20 µM. A B/P ratio of 0.977 suggests approximately equal distribution between red blood cells and plasma.
In healthy subjects, the Vd/F following a single IV dose of 100 µg [^{14}C]savolitinib was calculated to be 139 L. Based on the population PK analysis, the Vd/F at steady state was estimated at 173 L in oncology patients.

In healthy subjects, savolitinib crossed the intact BBB based on PET imaging. Following IV administration, savolitinib was detected in the brain with a maximum injected dose of 0.80%.

Metabolism and elimination
The primary human *in vitro* Phase 1 metabolites of savolitinib are M2, M3, and M4. It was shown *in vitro* that M2 was formed by CYP1A2 (mean contribution to savolitinib clearance 32.3%), CYP2D6 (13.5%), and CYP2C19 (7.6%), whereas M3 formation is catalysed by aldehyde oxidase (AO; 18.4%). The third Phase 1 metabolite M4 is predominantly formed by CYP3A4/5 (9.1%). It is noteworthy that M4 was not measured in human plasma, urine or faeces. M8 and M44 are the glucuronide conjugates of M2 and M3, respectively. Glucuronidation was mainly mediated through UGT1A4 and UGT2B15. Savolitinib was excreted via urine and faeces, which accounted for 55.7% and 38.4% of the total radioactivity. The predominant circulating entity was M8 (35.7%), followed by savolitinib (22.0%), and M44 (13.0%). All other metabolites accounted for <10% of the total radioactivity in plasma. The major metabolite in urine was M8, which accounted for 20.3% of the administered radioactive dose, whereas only small amounts of the savolitinib were present in urine (3.4%). The major metabolite in faces was M2, which accounted for 14.6% of the administered radioactive dose. Only 0.8% savolitinib was present in faeces. The low amounts of parent drug in urine and faeces suggest that savolitinib is primarily eliminated by metabolism.

Across the different studies, the apparent oral CL/F of savolitinib was between 23 and 58 L/h. Based on the population PK analysis, the apparent oral CL/F was estimated at 31.7 L/h. The half-life of around 4 h remained relatively constant across the studied dose range.

Special populations / Intrinsic factors
No dedicated renal and hepatic impairment studies were conducted.
In the population PK analysis, mild hepatic impairment (n = 113) did not have an impact on the PK of savolitinib. Only four subjects with moderate hepatic impairment were included in the dataset. No exposure changes or safety signals were observed in the limited number of patients with moderate hepatic impairment. No dose adjustment is required for patients with mild or moderate hepatic impairment. Caution is recommended when administering savolitinib to patients with moderate hepatic impairment. Administration to patients with severe hepatic impairment is not recommended. Furthermore, an updated analysis on the impact of hepatic impairment, including data from the SAFFRON confirmatory phase 3 study, will be submitted as a post-approval requirement.

In the population PK analysis, mild and moderate renal impairment (n = 437 and 223, respectively) did not have an impact on the PK of savolitinib. Only seven subjects with severe renal impairment were included in the dataset. Considering that only 3.4% of unchanged drug is renally eliminated, no dose adjustment is required for patients with mild, moderate, and severe hepatic impairment.

Using data from 10 clinical studies, a population PK analysis was conducted to identify factors that account for variability in the savolitinib PK. The dataset included a total of 9,706 concentration time points from 998 oncology patients treated with savolitinib, with and without osimertinib. A first-order absorption model with two transit compartments and one central compartment for distribution with first-order elimination was used to describe the PK of savolitinib. After stepwise forward selection and backward elimination, the following statistically significant covariates were retained in the final model: (1) Baseline alkaline phosphatase, baseline total bilirubin, race, osimertinib combination treatment, and gender on CL/F; (2) baseline body weight, baseline alkaline phosphatase, gender, race, and the use of a proton pump inhibitor (PPI) on Vd/F; and (3) race and the use of a proton pump inhibitor (PPI) on absorption rate constant (KA). Overall, no dose adjustments are required based on any of the evaluated covariates, including gender, age, body weight, and race.

Interactions
The *in vitro* DDI interaction potential of savolitinib, M8, and M44 was investigated at clinically relevant concentrations.

The primary human *in vitro* Phase 1 metabolites of savolitinib are M2, M3, and M4.
Savolitinib was shown to be a substrate of P-gp as well as BCRP *in vitro*, but not of the hepatic uptake transporters OATP1B1 or OATP1B3. Renal uptake and efflux transporters were not investigated, which is acceptable considering that only 3.4% of the administered dose are excreted in urine as unchanged parent drug.
In vitro, savolitinib reversibly inhibited all investigated CYPs, i.e., CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Whereas inhibition of CYP1A2, CYP1A6, CYP2B6, CYP2CB19, and CYP2E1 are unlikely at clinically relevant concentrations, there is a significant inhibition potential for CYP2C8 ($K_{i,u}$ = 4.5 µM), CYP2C9 ($K_{i,u}$ = 2.3 µM), CYP2D6 ($K_{i,u}$ = 12.0 µM), and CYP3A4 ($K_{i,u}$ = 22.7 µM). No relevant time-dependent inhibition was observed for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.
M8 weakly inhibited CYP2C8 ($K_{i,u}$ = 128 µM) and CYP2D6 ($K_{i,u}$ = 95 µM) *in vitro*, whereas time-dependent inhibition was only observed for CYP2C8. There is no risk of inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 by M44.
The induction potential of savolitinib on CYP1A2, CYP2B6, and CYP3A4 was investigated *in vitro*. Based on mRNA fold-change, induction of CYP1A2, CYP2B6, and CYP3A4 cannot be excluded. The induction potential of the metabolites was not investigated (post-approval requirement).
In vitro, savolitinib was shown to be an inhibitor of UGT1A1 and UGT2B15, but not of UGT1A4, UGT2B7, or UGT1A9. M8 did not inhibit UGT1A1 and UGT2B7. The induction potential of M44 was not investigated.
In vitro, savolitinib was shown to be an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BSEP and MATE1 and MATE2-K. At clinically relevant savolitinib concentrations, inhibition of P-gp ($IC_{50,u}$ = 17.7 µM), BCRP ($IC_{50,u}$ = 29.7 µM), OATP1B1 ($IC_{50,u}$ = 29.7 µM), OATP1B3 ($IC_{50,u}$ = 24.8 µM), MATE1 ($IC_{50,u}$ = 2.8 µM), and MATE2-K ($IC_{50,u}$ = 0.68 µM) cannot be ruled out. M8 only showed relevant inhibition of MATE1 ($IC_{50,u}$ = 52.5 µM) and OCT2 ($IC_{50,u}$ = 8.8 µM). There is no risk of inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2-K, and OCT2 by M44.

Overall, savolitinib and its metabolite showed a significant DDI risk *in vitro*. Based on these *in vitro* findings, five clinical DDI studies as well as PBPK modelling/simulation were conducted to investigate savolitinib as a potential object and precipitant drug.

Co-administration with itraconazole, a strong CYP3A inhibitor, caused an increase of savolitinib C_{max} and $AUC_{(0-t)}$ by 5% and 8%, respectively.
Co-administration with rifampicin, a strong inducer of CYP3A and CYP2C19, led to a decrease of savolitinib C_{max} and $AUC_{(0-t)}$ by 55% and 61%, respectively. M3 C_{max} increased by 40%, whereas $AUC_{(0-t)}$ decreased by 10% when savolitinib was dosed in combination with rifampicin. Furthermore, the metabolite-to-parent AUC ratios for M2 and M3 increased by 42% and 181%, while the C_{max} ratios increased by approximately 39% and 208%, respectively. Based on PBPK modelling, interpolation to moderate inducers indicated less induction, which is not considered clinically relevant. Co-administration with strong CYP3A4 inducers should be avoided. When co-administered with fluvoxamine, a strong CYP1A2 inhibitor, savolitinib C_{max} and $AUC_{(0-t)}$ were increased by 95% and 223%, respectively. The metabolite-to-parent ratios for M2 were lower when savolitinib was dosed in combination with fluvoxamine, which was not the case for M3. These findings suggest that CYP1A2 is not involved in M3 formation. Based on PBPK modelling, it was demonstrated that a dose reduction of savolitinib from 300 mg BID to 100 mg BID when co-administered with a strong CYP1A2 inhibitor (fluvoxamine), and 200 mg BID when co-administered with moderate CYP1A2 inhibitor (ciprofloxacin), results in exposures comparable to those for 300 mg BID savolitinib alone. The dose reductions are appropriate to mitigate DDI risks. Based on the population PK analysis, smoking status did not have a significant impact on savolitinib PK, suggesting no effects of moderate CYP1A2 inducers on savolitinib exposure.

Co-administration with savolitinib resulted in a decrease in midazolam, a sensitive substrate for CYP3A4, C_{max} and $AUC_{(0-t)}$, by 16% and 4%, which is not considered clinically relevant. In a clinical

cocktail study, the impact of savolitinib on the PK of sensitive substrates of the human transporters digoxin (P-gp), rosuvastatin (OATP1B1/3 and BCRP), metformin (OCT2, MATE1/2K), and furosemide (OAT1/3) was investigated. Whereas the AUC of digoxin remained comparable, C_{max} was 23% (107%–141%) higher when co-administered with savolitinib. Co-administration with savolitinib led to increased rosuvastatin AUC_{last} and C_{max} by 26% (117%–137%) and 30% (118%–143%), respectively. Metformin AUC_{last} and C_{max} were increased by 43% (136%, 152%) and 58% (149%–168%) when co-administered with savolitinib. Urinary excretion of metformin was decreased following co-administration with savolitinib. Furosemide exposures were comparable. Overall, these findings suggest that savolitinib may be a weak inhibitor of renal MATE1/2K and/or OCT2.
No clinical data on savolitinib-mediated inhibition of CYP2C8, CYP2C9, and CYP2D6 are available. Co-administration with substrates for these enzymes should be avoided (post-approval requirement). The DDI risk with oral contraceptives was not investigated. A non-hormonal contraceptive method should be used during treatment.

Based on the population PK analysis, combination therapy with osimertinib did not have a significant impact on savolitinib exposure.

Pharmacodynamics
Mechanism of action and primary pharmacology
Savolitinib is a potent and highly selective MET kinase inhibitor. M2 is approximately 3- to 6-fold less potent than savolitinib for pMET inhibition and tumour cell growth inhibition, whereas M3 is not pharmacologically active. M8 is at least 60-fold less potent than savolitinib in cellular assays for pMET inhibition and tumour cell growth inhibition. The pharmacological activity of M44 has not been evaluated, but it is likely to be inactive considering that it is a glucuronide of M3. M2 is approximately 3- to 6-fold less potent than savolitinib and accounts for 6.6% of the administered dose in plasma.
The population PK analysis showed that in contrast to the QD dosing regimen, the 300 mg BID dosing regimen resulted in $C_{min,ss}$ above the pMET IC95 of 17.3 ng/mL. See the “Dose finding / Dose recommendation” section for the dose finding evaluation.

Secondary pharmacology (safety)
A thorough QT/QTc study was conducted in healthy subjects. Following a single dose of 600 mg savolitinib, the upper bounds of the 2-sided 90% CI for ΔΔQTcF was above the regulatory threshold of 10 ms at 3 to 6 hours post-dose. 600 mg is not considered a supratherapeutic dose.

Exposure efficacy/safety relationship
The exposure-efficacy relationship was investigated using individual PK exposure metrics ($AUC_{24,ss}$, $C_{max,ss}$, and $C_{min,ss}$) obtained as part of the population PK analysis from a total 360 patients who had been assigned to 300 mg BID, 300 mg QD, or 600 mg QD in combination with osimertinib 80 mg QD in the SAVANNAH study.
Boxplots indicated that the percentage of responders was highest among the patients who received 300 mg BID across all subpopulations, especially the all-comers. The significantly higher $C_{min,ss}$ in the BID dosing regimen is likely to be contributing to greater target engagement and therefore better efficacy.
Using logistic regression analysis (LRA), no significant exposure-efficacy relationship was observed for ORR in the target population analysis set (TPAS; n = 79). However, there was a trend towards higher probability of ORR with higher $C_{min,ss}$ and $AUC_{24,ss}$. Based on Kaplan-Meier plots, no exposure-efficacy relationship was observed for PFS and DoR in the TPAS.

The exposure-safety relationship was investigated using pooled data from 10 clinical studies where savolitinib was administered either as monotherapy or in combination with osimertinib. Furthermore, the exposure-safety relationship in the TPAS of the SAVANNAH study was specifically assessed. Boxplots only showed statistically significant positive exposure-safety relationships ($p < 0.001$) for $C_{max,ss}$ and the occurrence of dose discontinuations of savolitinib and $AUC_{24,ss}$ and Grade ≥1 hepatotoxicity. These relationships were not statistically significant in the TPAS. Using LRA, a

statistically significant correlation ($p < 0.001$) was observed for hepatoxicity. However, it appears that the probabilities of dose discontinuations of savolitinib or developing hepatotoxicity are comparable between the 300 mg BID and 300 mg QD dosing regimens.

6.2 Dose finding and dose recommendation

The osimertinib dose of 80 mg once daily (QD) was adopted from the approved monotherapy dose for EGFRm NSCLC. A review of savolitinib dosing in the SAVANNAH study indicated consistent target engagement with 300 mg twice daily (BID), supporting the selection of osimertinib 80 mg QD plus savolitinib 300 mg BID as the recommended regimen.

6.3 Efficacy

Efficacy was evaluated in the pivotal Phase II SAVANNAH study in adult patients with locally advanced or metastatic EGFR-mutated NSCLC who had radiologically documented disease progression on prior osimertinib and had centrally confirmed MET overexpression, assessed by immunohistochemistry (IHC; score 3+ in ≥ 90% of tumour cells), and/or MET amplification, assessed by fluorescence in situ hybridisation (FISH; ≥ 10 gene copies). The efficacy population consisted of 80 patients who received savolitinib 300 mg BID in combination with osimertinib 80 mg QD until progression or unacceptable toxicity; prior systemic anticancer therapy in the metastatic setting other than osimertinib was not allowed.

The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST 1.1**Fehler! Textmarke nicht definiert.**. Key secondary endpoints included ORR assessed by blinded independent central review (BICR) and duration of response (DoR). Investigator-assessed ORR was 56.3% (95% CI 44.7–67.3) and BICR-assessed ORR was 55.0% (43.5–66.2), with a median DoR of 7.1 and 9.9 months, respectively. Results were consistent across predefined subgroups. Among 14 patients with baseline central nervous system (CNS) metastases, the BICR-assessed CNS ORR was 43% (6/14; 95% CI 17.7–71.1).

6.4 Safety

The safety assessment of savolitinib in combination with osimertinib is primarily based on the SAVANNAH study, supplemented by the overall safety database. The most frequently reported treatment emergent adverse reactions (≥ 20%) included peripheral oedema, nausea, fatigue, rash, vomiting, diarrhoea, decreased appetite, and paronychia. Relevant serious adverse events encompassed venous thromboembolic events (VTE), pyrexia, and interstitial lung disease (ILD) /pneumonitis. Relevant treatment emergent adverse events of Grade ≥ 3 included peripheral oedema, elevated liver enzymes, pneumonia, dyspnoea and gastrointestinal events. Warnings and precautions include VTE, ILD/pneumonitis, hepatotoxicity, QTc prolongation and cardiac events. Please refer to the Information for healthcare professionals for further details.

6.5 Final clinical benefit risk assessment

Patients with EGFR-mutated, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC that progresses after osimertinib have an unmet medical need, as no authorised chemotherapy-free options are available.

Savolitinib 300 mg BID in combination with osimertinib provides a treatment option with an oral administration route and demonstrated promising efficacy in patients with MET-overexpression and/or amplification (defined as IHC90+ and/or FISH10+) in the Phase II SAVANNAH study.

The safety profile is distinct and may offer advantages for selected patients due to a lower incidence of haematological grade 3–5 toxicities than would be expected with platinum-based chemotherapy. Identified risks include venous thromboembolic events (VTE), ILD/pneumonitis, cardiac toxicity and QTc prolongation and are appropriately addressed through the warnings and precautionary statements in the Information for healthcare professionals, alongside existing guidance on managing hepatotoxicity, hypersensitivity reactions and QTc prolongation.

To confirm a clinical benefit and to allow for a conclusive assessment of the benefit-risk ratio of Orpathys when used as per the above indication, the applicant agreed to submit data from the ongoing SAFFRON study (a Phase III randomised controlled trial of savolitinib combined with osimertinib versus platinum-based doublet in locally advanced or metastatic NSCLC patients with EGFR-mutated and MET-overexpression and/or amplification who have progressed on treatment with osimertinib) as a prerequisite for converting the temporary authorisation into a marketing authorisation without special conditions.

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 Orpathys 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.
ORPATHYS has been authorised temporarily, see “Indications/Uses” section.

ORPATHYS® 100 mg film-coated tablet

Composition

Active substances

Savolitinib

Excipients

Tablet core: Mannitol (E 421), microcrystalline cellulose (E460), low-substituted hydroxypropyl cellulose, magnesium stearate.
Tablet coating: Hypromellose, titanium dioxide (E 171), macrogol 400, iron oxide yellow (E 172), iron oxide red (E 172), iron oxide black (E 172).

Pharmaceutical form and active substance quantity per unit

ORPATHYS 100 mg tablets are oval, biconvex, yellow film-coated tablets measuring approximately 12 x 6 mm. The tablets are debossed with ‘SAV 100’ on one side and are plain on the reverse.
Each 100 mg film-coated tablet contains a dose of 100 mg savolitinib.

Indications/Uses

ORPATHYS in combination with osimertinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have an EGFR-mutation as well as MET overexpression and/or amplification, and who had disease progression on or after osimertinib (see “*Dosage/Administration*”).

This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Dosage/Administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer. Patients with MET-overexpression and/or MET-amplification in locally advanced or metastatic NSCLC should be selected for treatment with ORPATHYS based on the presence of MET-overexpression and/or MET-amplification using validated tests. MET overexpression is defined as ≥ 90% of tumour

cells immunohistochemically stained at 3+ intensity. MET amplification is defined as ≥ 10 copies of the MET gene in tumour cells.
A positive EGFR mutation status (exon 19 deletions or L858R substitution mutations in exon 21) must have been proven. For initiating treatment with ORPATHYS, the EGFR mutation status does not need to be retested.

Usual dosage

The recommended dose of ORPATHYS is 300 mg taken orally twice a day (approximately 12 hours apart). The twice-daily doses of ORPATHYS should be taken at similar times each day. ORPATHYS should be taken immediately after a meal.
ORPATHYS is used in combination with osimertinib, and the recommended dose of osimertinib is 80 mg orally once a day. The once-daily dose of osimertinib should be taken at the same time each day with either the morning dose or the evening dose of ORPATHYS. Refer also to the prescribing information for osimertinib.
ORPATHYS is for oral use. The tablets should be swallowed whole to ensure that the full dose is administered, with water and not chewed, crushed, dissolved, or divided. ORPATHYS should not be ingested if it is broken, cracked, or otherwise not intact.

Treatment duration

Patients should receive treatment until disease progression or unacceptable toxicity.

Missed dose

If the patient vomits after taking ORPATHYS or in the event of a missed dose they should take the next dose at the next scheduled time.
If a dose of osimertinib is missed when taken in combination with ORPATHYS, make up the dose unless the next dose is due within 12 hours.

Dose adjustment

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. The dose of ORPATHYS can be reduced up to two times. The recommended ORPATHYS dose modifications for adverse reactions are presented in Table 1.

Table 1: ORPATHYS recommended dose reductions for adverse reactions

Starting dose	300 mg twice a day
First dose reduction	200 mg twice a day
Second dose reduction	100 mg twice a day

The recommended dosage modifications of ORPATHYS for specific adverse reactions are presented in Table 2. Refer to the osimertinib prescribing information for information about dosage modifications for osimertinib.

Table 2: ORPATHYS recommended dose reductions for specific adverse reactions

Adverse drug reaction	Dose modification
Drug-induced liver injury	
– ALT or AST > 8 × ULN and combined TBL elevation exceeds baseline level or ULN – ALT or AST > 5 × ULN for >2 weeks combined with TBL elevation above baseline level or ULN – ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5 without anticoagulants that increase INR) – AST or ALT > 3 × ULN with obvious fatigue, nausea, vomiting, upper abdominal pain or distension, fever, rash, and/or new onset of eosinophilia above the normal reference range, or significant change in pre-existing eosinophilia – Recurrence of ALT or AST > 5 × ULN – Recurrence of ALT or AST > 3-5 × ULN and combined with TBL > 1.5-2 × ULN	Permanently discontinue ORPATHYS.
– ALT or AST > 5 × ULN and TBL is not higher than baseline level or ULN – ALT or AST > 3 × ULN, TBL rises to 1-2×ULN – ALT or AST > 3-5 × ULN occurs again, but TBL is not above baseline level or ULN	Interrupt treatment with ORPATHYS and repeat liver function tests twice a week – If returns to Grade 1 (near baseline level) or baseline level within 1 week, reduce the dose by 1 level, and repeat liver function test twice a week for 6 weeks. – Otherwise, permanently stop using this product.
Hypersensitivity / Allergic reaction	
All Grades	See Section “Warnings and precautions” for management of hypersensitivity / allergic reactions.

Adverse drug reaction	**Dose modification**
QTc Prolongation	
Grade 3 (QTcF prolongation to ≥ 501 msec) or > 60 msec change from baseline on at least two separate ECGs	– Interrupt ORPATHYS. Perform regular ECGs until resolution to QTcF ≤ 480 msec (Grade 1). Restart ORPATHYS at reduced dose level (See as per Table 1). – If QTcF does not resolve to ≤ 480 msec within 21 days, ORPATHYS should be discontinued permanently.
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	ORPATHYS should be permanently discontinued; consult with a cardiologist for further management as clinically indicated (See Section “Warnings and precautions”).
Other	
Grade 3 toxicity	– Interrupt ORPATHYS. If recovered to Grade 1 within 7 days resume at the same dose or a reduced dose, as considered clinically appropriate, as per Table 1. – If not recovered to Grade 1 within 7 days, ORPATHYS should be discontinued permanently.
Grade 4 toxicity	– Interrupt ORPATHYS. If recovered to Grade 1 within 7 days, resume at a reduced dose, as per Table 1. – If not recovered to Grade 1 within 7 days, ORPATHYS should be discontinued permanently.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; ULN, upper limit of normal; ≥, greater than or equal to; baseline, at the time of treatment initiation.
Note: the severity of adverse reactions will be graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Co-administration with CYP3A4 inducers and CYP1A2 inhibitors

Strong CYP3A4 Inducers: Avoid the concomitant use of strong CYP3A4 inducers (e.g. rifampicin and phenytoin) (see Section “Interactions”).

Strong and moderate CYP1A2 inhibitors: Avoid the concomitant use of strong and moderate CYP1A2 inhibitors (e.g. fluvoxamine and ciprofloxacin) while patients are on treatment with ORPATHYS. If not

possible, decrease ORPATHYS dose to 100 mg twice a day when co-administered with strong CYP1A2 inhibitors and 200 mg twice a day with moderate CYP1A2 inhibitors (see Section “Interactions”).

Method of administration

ORPATHYS should be taken immediately after a meal.
Tablets should be swallowed whole with water and not chewed, crushed, dissolved, or divided.
ORPATHYS should not be ingested if it is broken, cracked, or otherwise not intact.

Special populations

Renal impairment

No dose modification is recommended in patients with mild, moderate, and severe renal insufficiency. Only limited data are available for patients with severe renal impairment (see Section “Pharmacokinetics”). No data available for patients with end-stage renal disease.

Hepatic impairment

No dose reduction is required for patients with mild and moderate hepatic insufficiency. Due to limited data in patients with moderate hepatic insufficiency, caution should be exercised. ORPATHYS has not been studied in patients with severe hepatic impairment and is not recommended in those patients.

Paediatric patients

The safety and efficacy of ORPATHYS in paediatric patients < 18 years old have not been established.

Elderly patients

No dose modification in starting dose is required for elderly patients ≥ 65 years old.

Contraindications

Known hypersensitivity to the active substance or to any of the excipients listed in Section “Excipients” (see Section “Hypersensitivity/Allergic Reactions in ”Warnings and precautions”).

Warnings and precautions

Drug-induced liver injury

Transaminase elevations have occurred in patients treated with ORPATHYS in monotherapy and in combination with osimertinib in clinical trials (see Section “Undesirable effects”), particularly during the first 6 weeks of treatment. Prior to the introduction of weekly monitoring, one fatal case of drug-induced liver injury was reported for a patient treated with ORPATHYS 600 mg once daily as monotherapy. Liver function tests (including ALT, AST and total bilirubin) should be performed prior to

the start of treatment with ORPATHYS, and weekly during the first 3 months of treatment, and then on a monthly basis or as clinically indicated. Based on liver function test results, withhold, reduce the dose, or permanently discontinue ORPATHYS (see Section “Dosage/Administration”).

Hypersensitivity / Allergic Reactions

Serious hypersensitivity reactions have occurred in patients treated with ORPATHYS as monotherapy and in combination with osimertinib in clinical trials (see Section “Undesirable effects”), typically in the first 6 weeks of treatment. Hypersensitivity reactions usually involve a constellation of symptoms indicating multi-organ involvement such as fever and/or rash together with others including chills, flu-like symptoms, pruritus, vomiting, deranged liver function tests, cytopenias, myalgia and/or arthralgia and hypotension and can be confused with infection.
Patients experiencing serious hypersensitivity reactions including worsening in the number or severity of symptoms due to suspected savolitinib-related hypersensitivity should be considered for immediate intervention as per local practice and treatment discontinuation.
Symptoms of hypersensitivity, including hypotension, may be more severe when restarting savolitinib treatment after interruption, particularly during the first 6 weeks of treatment. If the diagnosis of hypersensitivity is uncertain or the potential benefit is considered to outweigh the risk, savolitinib may be resumed at the same dose in a facility equipped to manage serious hypersensitivity reactions.
Patients should be advised to contact their healthcare provider if they experience suspected hypersensitivity symptoms and should not rechallenge without medical supervision.

A fatal case of Stevens-Johnson syndrome (SJS) has been reported for 600 mg once daily savolitinib in combination with osimertinib in a dose ranging lung cancer clinical trial. Patients experiencing SJS must discontinue savolitinib immediately and receive appropriate treatment. Refer also to the full prescribing information of osimertinib.

QTc prolongation

QTc prolongation was reported in a limited number of patients in clinical trials and fatal events have been observed in isolated cases where a causal relationship with savolitinib cannot be ruled out (see Section “Undesirable effects” and “Properties/Effects”). Clinical trials did not enrol patients with baseline QTc of > 470 msec for females and > 450 msecs for males, or patients with congenital long QTc syndrome. In patients at risk of developing QTc prolongation, including patients with known electrolyte disturbances, congestive heart failure, or taking concomitant medicinal products known to have QTc prolongation effects, monitoring is recommended as clinically indicated (See Section “Dosage/Administration”). Refer also to the prescribing information of osimertinib.

Venous Thromboembolic Events (VTE)

Venous thromboembolic (VTEs) events, including deep vein thrombosis and pulmonary embolism have occurred during clinical trials with ORPATHYS in combination with osimertinib (see Section

“Undesirable effects”). Prophylactic anticoagulation is recommended in high-risk patients, per prescriber´s judgment, and based on local guidelines to prevent first and recurrent VTEs.
Use of Vitamin K antagonists is not recommended due to potential DDIs.

ILD/Pneumonitis

ILD/Pneumonitis events have occurred with ORPATHYS in combination with osimertinib during clinical trials (see Section “Undesirable effects”).
Monitor patients for pulmonary signs and symptoms indicative of ILD. If new or worsening pulmonary signs or symptoms suggestive of ILD are observed, ORPATHYS and osimertinib should be interrupted, and a full diagnostic workup should be performed. If ILD / pneumonitis is confirmed, treatment should be permanently discontinued.

Cardiac Events

Cardiac events (defined as cardiac failure; diastolic dysfunction; ejection fraction decreased and right ventricular failure) have occurred during clinical studies with ORPATHYS in combination with osimertinib (see Section “Undesirable effects”).
For patients with cardiac risk factors receiving ORPATHYS in combination with osimertinib, conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors.
Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue ORPATHYS and osimertinib (see Section “Dosage/Administration”).

Pregnancy testing

Women of childbearing age should undergo a pregnancy test before starting treatment (see section "Pregnancy, lactation").

Interactions

Effect of other medicinal products on ORPATHYS

Based upon in vitro liver microsomes, hepatocytes and S9 incubations savolitinib is predominantly metabolized by CYP450 enzymes (CYP1A2, CYP2C19, CYP2D6, and CYP3A4) and non-CYP450 enzymes (aldehyde oxidase) see also section “Pharmacokinetics”.
In vitro, savolitinib was shown to be a substrate of both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but not Organic Anion Transporter Polypeptides (OATP) 1B1 and 1B3. A clinically relevant drug drug interaction (DDI) is unlikely with inhibitors of P-gp and BCRP.

Table 3. Drug interactions with ORPATHYS that affect savolitinib

Strong CYP3A4 inducers	
Clinical Impact	– Strong CYP3A4 inducers may reduce the exposure of ORPATHYS, which may reduce clinical benefit.
Prevention or management	– Avoid concomitant use with strong CYP3A4 inducers.
Data	– A study was conducted in healthy subjects to assess the PK of savolitinib when administered alone and in combination with rifampicin. The geometric mean ratio (GMRs) (90% CIs) for savolitinib in combination with rifampicin compared to savolitinib alone were 0.45 (0.41, 0.50) and 0.39 (0.34, 0.43), respectively, for the Cmax and AUC of savolitinib. – PBPK modelling suggests moderate CYP3A inducers may not change savolitinib exposure when co-administered
Strong CYP1A2 inhibitors	
Clinical Impact	– ORPATHYS is a substrate of CYP1A2. Strong CYP1A2 inhibitors increase savolitinib exposure, which may increase the risk of ORPATHYS adverse reactions.
Prevention or management	– Avoid concomitant use with strong CYP1A2 inhibitors. – If concomitant use cannot be avoided, reduce the dose of ORPATHYS to 100 mg twice a day and monitor patients for adverse reactions.
Data	– A study was conducted in healthy subjects to assess the PK of savolitinib when administered alone and in combination with fluvoxamine. The GMRs (90% CIs) of Cmax and AUCinf for savolitinib in combination with fluvoxamine compared to savolitinib alone were 1.95 (1.67, 2.28) and 3.25 (2.87, 3.68), respectively.
Moderate CYP1A2 inhibitors	
Clinical Impact	– ORPATHYS is a substrate of CYP1A2. Moderate CYP1A2 inhibitors increase savolitinib exposure, which may increase the risk of ORPATHYS adverse reactions.
Prevention or management	– Avoid concomitant use with moderate CYP1A2 inhibitors. – If concomitant use cannot be avoided, reduce the dose of ORPATHYS to 200 mg twice a day and monitor patients for adverse reactions.
Data	– The PBPK model-predicted GMRs (90% CIs) of Cmax and AUCinf for savolitinib in combination with ciprofloxacin

	compared to savolitinib alone were 1.31 (1.29,1.34) and 1.57 (1.54,1.61), respectively.
Strong CYP3A4 inhibitor	
Data	– A study was conducted in healthy subjects to assess the PK of savolitinib when administered alone and in combination with itraconazole. The GMRs (90% CIs) of Cmax and AUC for savolitinib in combination with itraconazole compared to savolitinib alone were 1.05 (0.88, 1.26), 1.08 (0.96, 1.22), respectively. This study result indicates strong CYP3A4 inhibitor itraconazole had no effect on savolitinib exposure.
Moderate CYP1A2 inducer	
Data	– The population pharmacokinetic analysis did not identify smoking status as having a significant impact on savolitinib PK. The dose-normalized AUCss was reduced by 6% and 7% in former and current smokers, respectively, compared to never smokers.
Gastric pH altering agents	
Data	– A study was conducted in healthy subjects to assess the PK of savolitinib when administered alone and in combination with famotidine 40 mg (2 hours earlier). The GMRs (90% CIs) for savolitinib in combination with famotidine compared to savolitinib alone were 0.79 (0.68, 0.92) and 0.87 (0.81, 0.94), respectively, suggesting no clinically meaningful impact on savolitinib PK.

Effects of ORPATHYS on other drugs

In vitro the potential for savolitinib to inhibit drug metabolising CYPs has been studied to a concentration of 300 µM. Under these conditions, savolitinib is an in vitro inhibitor of CYP2C8, CYP2C9, CYP2D6 and CYP3A4. It is not an inhibitor (IC_{50} values >300 µM) of CYP1A2, CYP2A6, CYP2B6, CYP2C19 or CYP2E1. The major metabolite of savolitinib (M8) is an in vitro inhibitor of CYP2C8 and CYP2D6, but is not an inhibitor of all the CYPs tested. In vitro M44 (a major circulating metabolite of savolitinib) is no inhibitor of the tested CYPs.
Clinical data showed savolitinib does not inhibit CYP3A4 and a substrate of CYP3A4 can be co-administered (table 4). No clinical data is available about the savolitinib-mediated potential inhibition of other enzymes tested; co-administration with substrates CYP 2C8, 2C9, and 2D6 should be avoided.

In vitro, the potential for savolitinib to inhibit UGT1A1, UGT1A4, UGT1A9, UGT2B7 and UGT2B15 has been studied to a concentration of 300 µM. Under these conditions savolitinib is a weak inhibitor of UGT1A1 and UGT2B15. A clinically relevant DDI is unlikely with the substrates of UGT1A1 and UGT2B15. M8 is not an inhibitor of UGT1A1 or UGT2B7, other UGTs were not investigated. The potential for UGT inhibition by M44 was not investigated.
Savolitinib is an in vitro inducer of CYP1A2, CYP2B6, and CYP3A4 mRNA in human hepatocytes. The in vitro CYP induction potential of M8 and M44 has not been tested. No clinical data about savolitinib-mediated CYP induction is available.
Savolitinib is an in vitro inhibitor of P-gp, BCRP, OATPB1, OATPB3, MATE1 and MATE2-K but not an inhibitor of OAT1, OAT3, BSEP and OCT2 at clinically relevant concentrations.
M8 is an in vitro inhibitor of MATE1 and OCT2 but not P-gp, BCRP, OATP1B1, OATP1B3, MATE2-K, OAT1 and OAT3 at clinically relevant concentrations. M44 is not an in vitro inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, MATE1, MATE2K, OAT1, OAT3 and OCT2 at clinically relevant concentrations. Based on in vitro data clinically relevant DDI with substrates whose disposition is dependent on P-gp, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K cannot be excluded (table 4).
No interaction studies with oral contraceptives have been conducted (please see section "Pregnancy lactation).

Table 4 Drug interactions with ORPATHYS that may affect other drugs

Substrates of MATE1/2K and OCT2	
Clinical Impact	ORPATHYS is a weak inhibitor of MATE1/2K and/or OCT2**.** The exposure of substrates of MATE1/2K and OCT2 may increase when co-administered with ORPATHYS.
Prevention or management	Use caution when ORPATHYS is co-administered with substrates of MATE1/2K and OCT2.
Data	The effects of savolitinib on the PK of metformin (substrate of OCT2 and MATE1/2K) were evaluated in healthy subjects as part of a drug cocktail. The GMR (90% CI) of metformin Cmax and AUCinf in combination with savolitinib compared to metformin alone were 1.58 (1.49, 1.68) and 1.43 (1.35, 1.51), respectively.
Substrates of CYP3A4	

Data	A study was conducted in healthy subjects to assess the effects of a single dose savolitinib on the PK of oral midazolam (a sensitive CYP3A4 probe substrate). The GMRs (90% CIs) for Cmax and AUC when dosed in combination with savolitinib or alone were 0.84 (0.70, 1.01) and 0.97 (0.92, 1.01), respectively. This study result indicates that savolitinib had no inhibitory effect on the pharmacokinetics of midazolam (CYP3A4 substrate) when co-administered.
Substrates of P-gp	
Data	The effects of savolitinib on the PK of digoxin (substrate of P-gp) were evaluated in healthy subjects as part of a drug cocktail. The GMR (90% CI) of digoxin Cmax and AUCinf with the combination of savolitinib compared to digoxin alone were 1.23 (1.07, 1.40) and 0.96 (0.89, 1.04), respectively, suggesting savolitinib had no effect on the pharmacokinetics of the substrate of P-pg (digoxin) when co-administered.
Substrates of OATP1B1/3 and BCRP	
Data	The effects of savolitinib on the PK of rosuvastatin (substrate of OATP1B1/3 and BCRP) was evaluated in healthy subjects as a part of drug cocktail. The GMR (90% CI) of rosuvastatin Cmax and AUCinf with savolitinib compared to rosuvastatin alone were 1.30 (1.18, 1.43) and 1.25 (1.16, 1.35), respectively, suggesting savolitinib had no effect on the pharmacokinetics of the substrate of OATP1B1/3 and BCRP (rosuvastatin) when co-administered.
Substrates of OAT1/3	
Data	The effects of savolitinib on the PK of furosemide (substrate of OAT1/3) was evaluated in healthy subjects as part of a drug cocktail. The GMR (90% CI) of furosemide Cmax and AUCinf in combination with savolitinib compared to furosemide alone

	were 1.01 (0.95, 1.07) and 1.04 (0.98, 1.09), respectively, suggesting savolitinib had no effects on the pharmacokinetics of the substrate of OAT1/3 (furosemide) when co-administered.

QT interval

Since savolitinib may prolong the QT interval, the concomitant administration of medicinal products known to prolong the QT interval or of medicinal products that may cause torsade de pointes should be carefully considered.

Pregnancy, lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving ORPATHYS. A pregnancy test should be performed on women of childbearing potential prior to initiating treatment, and verified as negative prior to initiating treatment, and re-testing considered throughout treatment.

Contraception in males and females

Patients should be advised to use highly effective non-hormonal contraception methods during treatment and for the following periods after completion of treatment with ORPATHYS for at least 1 week.

Pregnancy

There are no data from the use of savolitinib in pregnant women. Studies in animals have shown reproductive toxicity (see Section “Preclinical data”). ORPATHYS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether savolitinib or its metabolites are secreted in human milk. Due to the potential risk to the breast-fed child, mothers should be advised to avoid breastfeeding during treatment with ORPATHYS.

Fertility

There are no data on the effect of ORPATHYS on human fertility. Results from animal studies have shown that savolitinib has effects on male and female reproductive organs and could impair fertility (see Section “Preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Overall summary of the safety profile

Unless specified otherwise, the safety population described in the special warnings and precautions for use reflects exposure to ORPATHYS in 1,171 patients who received ORPATHYS as monotherapy (N=574) or in combination with osimertinib (N=597) in non-small cell lung cancer (NSCLC) and other tumour types at different dosing regimens.

In Table 5 below, the safety profile reflects 597 patients with NSCLC treated with ORPATHYS range of daily dosages, including 300 mg twice a day in combination with osimertinib 80 mg once a day in the SAVANNAH study. For the combination patients (N=597), 48% were exposed for 6 months or longer, and 24% were exposed for more than one year.

The safety profile presented may be attributable to ORPATHYS, osimertinib, or both drugs, and represents the safety profile of treatment with the combination.

For ORPATHYS in combination with osimertinib patients (N=597), the most common adverse drug reactions (reported at frequency ≥ 20%) were oedema peripheral (47%), nausea (43%), fatigue (34%), rash (29%), vomiting (25%), diarrhoea (24%), decreased appetite (23%) and paronychia (23%)

Serious adverse drug reactions were reported in 16% of patients. The most common serious adverse reactions reported in ≥ 1% of patients were venous thromboembolism (6%), pyrexia (3%), interstitial lung disease (2%), and vomiting (1%).

Dose reductions of ORPATHYS due to adverse drug reactions were reported in 17% of patients. The most common adverse reaction (reported at frequency ≥ 2%) leading to dose reduction of ORPATHYS was oedema peripheral (6%), nausea (3%) and fatigue (2%).

Treatment discontinuation of ORPATHYS due to adverse drug reactions were reported in 12% of patients. The most common adverse reaction (reported at frequency ≥ 2%) leading to treatment discontinuation was interstitial lung disease (2%) and pyrexia (2%).

List of adverse drug reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10‘000 to < 1/1000); very rare (< 1/10‘000) and not known (cannot be estimated from available data).

Table 5. Adverse drug reactions (savolitinib (multiple dosing regimens) in combination with osimertinib 80 mg once a day (N=597))

MedDRA SOC	MedDRA Term*	Any Grade (%)	≥ Grade 3 (%)
Infections and Infestations	Paronychia[a]	Very common (23)	Common
	Thrombocytopenia[a]	Very common (13)	Common

MedDRA SOC	MedDRA Term*	Any Grade (%)	≥ Grade 3 (%)
Blood and lymphatic system disorders	Neutrophil count decreased[a]	Very common (13)	Common
	Anaemia	Very common (11)	Common
	Lymphocyte count decreased	Common	Uncommon
Immune system disorders	Hypersensitivity	Common	Common
Metabolism and nutrition disorders	Hypoalbuminaemia	Very common (10)	Common
	Decreased appetite	Very common (23)	Common
	Hypocalcaemia	Common	Uncommon
	Hypokalaemia	Common	Common
Vascular disorders	Venous thromboembolism[a]	Very common (16)	Common
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[a]	Common	Common
	Epistaxis	Common	0
Gastrointestinal disorders	Nausea	Very common (43)	Common
	Diarrhoea	Very common (24)	Common
	Vomiting	Very common (25)	Common
	Stomatitis[a]	Very common (14)	Uncommon
Hepatobiliary disorders	Alanine aminotransferase increased	Very common (11)	Common
	Aspartate aminotransferase increased	Very common (11)	Common
	Blood alkaline phosphatase increased	Common	Common
	Gamma glutamyl transferase increased	Common	Common
	Liver function test increased[a]	Common	Uncommon
	Drug-induced liver injury	Uncommon	Uncommon
	Blood bilirubin increased	Uncommon	Uncommon
Skin and subcutaneous disorders	Rash[a]	Very common (29)	Common
	Pruritus	Very common (13)	Uncommon
	Dry skin[a]	Common	Uncommon
	Alopecia	Common	0
General disorders and administration site conditions	Oedema peripheral[a]	Very common (47)	Common
	Fatigue[a]	Very common (34)	Common
	Pyrexia[a]	Very common (18)	Uncommon
Investigations	Amylase increased	Common	Uncommon

MedDRA SOC	MedDRA Term*	Any Grade (%)	≥ Grade 3 (%)
	Blood creatinine increased	Common	Uncommon
Cardiac Disorders	Electrocardiogram QT prolonged	Common	Uncommon
	Cardiac Failure	Uncommon	0
	Diastolic dysfunction	Uncommon	0
	Ejection Fraction decreased	Common	Uncommon
	Right ventricular failure	Uncommon	Uncommon

a. Amylase increased includes PTs of amylase increased, and hyperamylasaemia.
Blood creatinine increased includes PTs of blood creatinine increased, and hypercreatininaemia.
Dry skin includes PTs of dry skin, and skin fissures.
Fatigue includes PTs of fatigue, malaise, and asthenia.
Interstitial lung disease includes PTs of Interstitial lung disease, pneumonitis, and organising pneumonia.
Liver function test increased includes PTs of Liver function test increased,and hypertransaminasaemia.
Neutrophil count decreased includes PTs of neutrophil count decreased, and neutropenia.
Oedema peripheral includes PTs of oedema, oedema peripheral, localised oedema, peripheral swelling, swelling face, scrotal oedema, face oedema, generalised oedema, and oedema genital.
Paronychia includes PTs of paronychia, nail disorder, nail dystrophy, and nail infection.
Pyrexia includes PTs of pyrexia, and hyperpyrexia.
Stomatitis includes PTs of stomatitis, mouth ulceration, and mucosal inflammation.
Rash includes PTs of rash, rash erythematous, rash macular, rash maculo-papular, dermatitis, dermatitis acneiform, skin toxicity, folliculitis, erythema, dermatitis and bullous.
Thrombocytopenia includes PTs of Platelet count decreased, and thrombocytopenia
Venous thromboembolism includes PTs of deep vein thrombosis, embolism, axillary vein thrombosis, jugular vein thrombosis, superficial vein thrombosis, pulmonary embolism.

Description of specific adverse reactions (SAVANNAH study: savolitinib 300 mg twice a day in combination with osimertinib 80 mg once a day)

Drug-induced liver injury

In the SAVANNAH study, drug induced liver injury led to treatment discontinuation in 1% of patients. Transaminase elevations generally occurred within the first 6 weeks of treatment. There were no fatal liver injury events reported. Patients should be monitored for hepatotoxicity and managed as recommended in Sections “Dosage/Administration” and “Warnings and precautions”.

Hypersensitivity / allergic reactions

In the SAVANNAH study, there was no treatment discontinuation due to hypersensitivity. There were no fatal hypersensitivity events reported in the SAVANNAH study (see Section “Warnings and precautions).

QTc Prolongation

In the SAVANNAH study, QTc prolongation led to dose reduction of ORPATHYS in 1% of patients (see Section Warnings and precautions).

Venous Thromboembolic Events (VTE)

The incidence of VTE in the SAVANNAH study was 25% (N=101), 6% in savolitinib monotherapy studies (N=574) and 15.9% in clinical studies of ORPATHYS in combination with osimertinib (N=597). In the SAVANNAH study, VTE events of Grade ≥3 severity occurred in 7% patients and a fatal VTE event occurred in 1% patient. 1% of patients had VTE leading to permanent discontinuation of ORPATHYS (see Section “Warnings and precautions”)

ILD / Pneumonitis

In the SAVANNAH study, patients with past or active ILD/pneumonitis were excluded. ILD/pneumonitis led to dose interruption of ORPATHYS in 2% patients and to permanent discontinuation of ORPATHYS in 2% patients. There were no fatal ILD/pneumonitis events (see Section “Warnings and precautions).

Cardiac Events (including cardiac failure; diastolic dysfunction; ejection fraction decreased and right ventricular failure)

In the SAVANNAH ORPATHYS 300 mg BID + osimertinib arm, patients with congestive heart failure (New York Heart Association [NYHA] ≥Grade 2) were excluded. Cardiac events do not led to dose interruption of ORPATHYS in any patients and led to permanent discontinuation of ORPATHYS in 1 %. There were 1% patients with fatal cardiac events (see Section “Warnings and precautions).

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

There is no specific treatment in the event of ORPATHYS overdose. Physicians should observe patient, follow general supportive measures and should treat symptomatically.

Properties/Effects

ATC code

L01EP03

Mechanism of action

Savolitinib is a potent, highly selective, central nervous system (CNS)-penetrant small molecule inhibiting MET kinase at the enzyme and cellular level. MET inhibition results in suppression of major signal transduction pathways including the RAS/MAPK and PI3K/AKT pathways involved in cell proliferation, survival and migration, leading to inhibition of MET overexpressed or amplified cell lines

in vitro. Inhibition of MET also sensitizes MET overexpressed or amplified/EGFRm+ cells to EGFR inhibition.
In non-clinical studies, savolitinib has shown single agent antitumour activity against tumours with constitutive MET activation. In addition, a MET-amplified and osimertinib-resistant patient derived xenograft model showed that whereas savolitinib monotherapy only demonstrated significant tumour growth inhibition, the combination of savolitinib and osimertinib resulted in tumour regressions.

Pharmacodynamics

Cardiac Electrophysiology

The effect of savolitinib on QTc interval prolongation was evaluated in a TQT-study in healthy volunteers with 600 mg savolitinib dose. Based on observed data, at 600 mg savolitinib, the upper limit of the two-sided 90% confidence interval for the maximum mean ΔQTcF was 12.18 msec.

Clinical efficacy

The efficacy of ORPATHYS in combination with osimertinib was evaluated in the SAVANNAH study, a Phase 2 multi-cohort, multi-centre study that enrolled adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) whose tumours had MET overexpression and/or amplification, and who had disease progression on or after osimertinib therapy. Patients were required to have MET-overexpressed and/or MET-amplified NSCLC in tumour samples after progression on osimertinib therapy, as determined by a central laboratory test. Among patients enrolled into the study, the efficacy population consisted of 80 patients with MET-overexpressed (≥ 90% of tumour cells with IHC 3+ staining) and/or MET-amplified (≥ 10 MET gene copies by FISH) NSCLC and who were treated with 300 mg savolitinib twice daily in combination with 80 mg osimertinib once daily. Patients were treated until unacceptable toxicity, or the investigator determined that the patient was no longer experiencing clinical benefit post progression of disease as determined by investigator assessment via RECIST 1.1 criteria. Assessment of tumour status was performed every 6 weeks for the first 7 months, and every 8 weeks thereafter, or until disease progression (whichever came first). Patients in the efficacy population must have had documented radiologic disease progression following treatment with osimertinib. All patients in the efficacy population received one prior line of osimertinib therapy. Patients previously treated with chemotherapy and/or immunotherapy in the metastatic setting were excluded from the efficacy population.
Baseline characteristics of the efficacy population were as follows: median age 66 years (range 29 to 83), 51% aged ≥ 65, 14% aged ≥ 75 years old, 70% female, 71% white, 26% Asian; 53% never smokers, 95% had adenocarcinoma histology, 98% had metastatic disease, 40% had a World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 60% had a performance status of 1, and 39% had CNS metastases detected at study entry.
The primary endpoint was objective response rate (ORR; complete response [CR] or partial response [PR]) according to RECIST 1.1 by investigator assessment. Secondary endpoints included overall

response rate (ORR) by blinded independent central review (BICR), duration of response (DoR) by investigator assessment and BICR, as well as patient-reported outcomes (PRO).

Efficacy results from SAVANNAH for the efficacy population by investigator assessment and blinded independent central review (BICR) are summarised in Table 6.

Table 6: Efficacy results from SAVANNAH by investigator assessment and BICR assessment

Efficacy parameter	**300 mg twice a day savolitinib + 80 mg osimertinib (N=80)**	
	Investigator assessment	**BICR assessment**
ORR		
Number of responses (n), Response Rate, % (95% CI)	45 56.3 (44.7, 67.3)	44 55.0 (43.5, 66.2)
CR, n (%)	1 (1.3)	1 (1.3)
PR, n (%)	44 (55.0)	43 (53.8)
DoR		
Median DoR, months (95% CI)	7.1 (5.6, 9.6)	9.9 (6.0, 13.7)
Patients remaining in response at 6 months, % (95% CI)*	62.1 (44.9, 75.3)	74.5 (57.6, 85.5)
Patients remaining in response at 9 months, % (95% CI)*	39.5 (23.9, 54.7)	53.6 (36.0, 68.3)

BICR: blinded independent central review; CI: confidence interval; CR: complete response, DoR: duration of response; ORR: objective response rate, PR: partial response
Response requires confirmation after 4 weeks
* Calculated using the Kaplan-Meier technique

Efficacy results were observed consistently in other pre-defined subgroups, including race (Asian, non-Asian), sex (male, female), age (< 65, ≥ 65), and presence of brain metastasis at study entry (yes, no).

A BICR assessment of central nervous system (CNS) efficacy by RECIST 1.1 was performed in 14 patients identified to have measurable CNS metastases on a baseline brain scan. A CNS ORR of 43% (6/14 patients; 95% CI: 17.7, 71.1) was observed.

Pharmacokinetics

Absorption

Following a single dose across the 100 to 1000 mg dose range, savolitinib was rapidly absorbed at all doses with the geometric mean (minimum to maximum) T_{max} ranging from 0.95 hour to 4 hours (0.5 to 8) across all regimens.

Mean savolitinib C_{max} and AUC were increased by 3% and 17%, respectively, following administration of 600 mg dose within 30 mins of a high fat meal (fat accounted ≥ 50% with total calories of 800 kcal – 1000 kcal) as compared to fasted condition.
The absolute bioavailability of savolitinib was 69%.

Distribution

The in vitro plasma protein binding of savolitinib was 71.3% in humans and was not concentration dependent. The population pharmacokinetics model-predicted typical value of volume of distribution is 173 L. 29% of the free plasma savolitinib and 0.80% of administered dose reaches into the brain in healthy volunteers

Metabolism

Based upon studies of in vitro liver microsomes and S9 fractions, savolitinib is metabolized by several metabolic enzymes, including both CYP450 enzymes (mainly CYP1A2) and some non-CYP enzymes (aldehyde oxidase, UDP-glucuronosyltransferases). In human plasma, savolitinib represented 22.4% of drug related material and metabolite M8 (AZ14117045, demethylation and glucuronidation) and M44 (mono-oxidation on the pyrazine ring and glucuronidation) represented a mean of 36% and 13% of the drug related AUC, respectively. Eight other metabolites all together accounted for remaining 29% of the drug related material with each being < 10%. Based on hADME results, savolitinib is likely to be eliminated after metabolism mainly through CYP1A2 (fm~32.3%) with minor contributions from other metabolic pathways: CYP2C19 (fm~13.5%), CYP2D6 (fm~7.6%), CYP3A4 (fm~9.1%), AO (fm~18.4%).

Elimination

Savolitinib plasma concentrations decreased with time and a population pharmacokinetic analysis estimated mean half-life of savolitinib was around 4 hours, and oral clearance (CL/F) was 31.7 (L/h). More than half of the administered savolitinib was eliminated in urine (55.7%) and slightly lesser amounts in feces (38.4%). Unchanged savolitinib was a minor component and accounted for a mean of 4% of the excreted dose.

Linearity/non-linearity

Across the dose ranges of 100 mg to 1000 mg once a day savolitinib exposure increased in a dose proportional manner. After multiple doses with BID regimen (300 mg to 500 mg), savolitinib exposure increased slightly more than dose-proportional manner.

Kinetics in specific patient groups

Effects of Age, Sex, Ethnicity, Body Weight, Baseline albumin, and Smoking status:
As part of a population pharmacokinetic analysis no clinically significant differences in the pharmacokinetics of savolitinib were observed based on age (the median (minimum-maximum) age

was 63 (23-92) years), sex (females (n=514), male (n=484)), ethnicity (Whites (n=404), Asians (n=556), Blacks or African Americans (n=14) and Others (n=24)), body weight (median (minimum-maximum) body weight was 62.3 (36-177) kg), baseline albumin (median (minimum-maximum) value of albumin (g/L) at baseline was 39.6 (19.0-54.0), smoking status (current smokers = 42, former smokers = 267, never smokers = 457, status unknown = 232).

Effects of Renal Function: Based on population pharmacokinetic analysis of 437 patients with mild renal impairment (CLcr 60 to < 90 mL/min), 223 patients with moderate renal impairment (CLcr 30 to < 60 mL/min), 7 patients with severe renal impairment (CLcr 15 to < 30 mL/min) and 331 patients with normal renal function (≥ 90 mL/min), the savolitinib apparent clearance (and exposure) were similar; the maximum decrease in CL/F was 22% in the severe renal impairment group compared to the normal renal function. The pharmacokinetics of savolitinib in patients with end-stage renal disease (CLcr < 15 mL/min) are unknown.

Effects of Hepatic Function: The population pharmacokinetic analysis indicated that there was no significant change in savolitinib exposure associated with mild ((total bilirubin ≥ ULN to 1.5 times ULN and AST > ULN , n=113) or moderate (total bilirubin between 1.5 to 3 times ULN and any AST, n=4) hepatic impairment compared to patients with normal hepatic function (n = 881) when analyzed using the NCI-ODWG criteria (see section “Dosage/Administration”). The pharmacokinetics of savolitinib in patients with severe hepatic impairment (total bilirubin 3 to 10 times ULN and any AST) are unknown.

Preclinical data

Repeat-dose toxicity

Myocardial/epicardial inflammation (rats) and myocardial degeneration (rats and dogs) was observed at total plasma exposures ≥ 33-fold those observed at the intended clinical dose. Chronic progressive cardiomyopathy was seen following a longer duration of dosing in rats at ≥ 3-fold those observed at the intended clinical dose.
Changes in the kidney (reversible tubular dilatation, urothelial hyperplasia, papillary duct epithelial hypertrophy and tubular atrophy) and urinary tract (epithelial hyperplasia [with or without inflammatory cell infiltration] in the urinary bladder and ureters, associated with calculi) were observed after chronic exposure in rats at total plasma exposure ≥ 10-fold those observed at the intended clinical dose.

Mutagenicity and carcinogenicity

Savolitinib was considered not to be genotoxic in vitro or in vivo.
Carcinogenicity studies have not been conducted.

Reproductive toxicity

Embryofoetal/Developmental toxicity

In rat and rabbit oral embryofoetal development studies there were effects on maternal weight, reduced foetal weight, and foetal survival, and an increase in malformations and/or variants at total plasma exposures (AUC) from 5-fold (rabbit) and 0.7-fold (rat) to those observed in humans at the clinical dose.

Fertility

Seminiferous tubular degeneration/cellular debris in the epididymis was observed in dogs at total plasma exposures ≥ 3-fold those observed at the intended clinical dose. Changes in the reproductive tract in the rat (atrophy of the prostate uterus, cervix and vaginal epithelium and prominent follicular atresia of the ovaries) were observed at total plasma exposures ≥ 33-fold those observed at the intended clinical dose.
In a combined oral male and female fertility and early embryonic development toxicity study in rats there was a reduction in fertility and decrease in the number of live foetuses at total maternal plasma exposures approximately 18-fold those observed at the intended clinical dose. When assessed alone at 17-fold there was no effect on male fertility.

Other information

Incompatibilities

Not applicable.
Effects on diagnostic methods

When considering the use of ORPATHYS in combination with osimertinib, MET overexpression or amplification in tumour specimens should be determined using a validated test method (see Section ”Properties/Effects”).

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in original package not above 30°C.

Keep out of the reach of children.

Instructions for handling

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

Authorisation number

70151

Packs

ORPATHYS 100 mg film-coated tablets: Bottle with 180 film-coated tablets [A].

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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