13 November 2025
EMA/CHMP/310589/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inluriyo

International non-proprietary name: imlunestrant

Procedure No. EMEA/H/C/006184/0000

Note

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

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List of abbreviations

ABC	advanced breast cancer
AE	adverse event
AI	aromatase inhibitor
AKT	protein kinase B
BC	breast cancer
BID	twice daily
BIRC	blinded independent review committee
CDK4/6	cyclin-dependent kinase 4/6 inhibitor
CI	confidence interval
CFS	chemotherapy-free survival
CQA	critical quality attribute
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DoR	duration of response
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EDR	early discrepancy rate
EEC	endometrioid endometrial cancer
ER	oestrogen receptor
ESMO	European Society of Medical Oncology
*ESR1*m	oestrogen receptor 1-mutation
ET	endocrine therapy
FDA	Food and Drug Administration
FTIR	Fourier Transform Infrared spectroscopy
GC	gas chromatography
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2 negative
HPLC	high-performance liquid chromatography
HR	hazard ratio
ICH	International Council for Harmonisation
IM	intramuscular

Imlun+abema	imlunestrant plus abemaciclib
IPC	in-process controls
ITT	intention to treat
KF	Karl Fisher
LLDPE	linear low-density polyethylene
LRD	late discrepancy rate
MI	myocardial infarction
MO	major objection
MS	mass spectrometry
MTD	maximal tolerated dose
MTOR	mammalian target of rapamycin
NMR	Nuclear Magnetic Resonance
ORR	objective response rate
OS	overall survival
PARs	proven acceptable range
PCTFE	polychlorotrifluoroethylene
PD	pharmacodynamic
PDA	photodiode array
PFS	progression free survival
Ph. Eur.	European Pharmacopoeia
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
PR	partial response
PVC	polyvinylchloride
QC	quality control
QD	once daily
QTPP	quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SERD	selective oestrogen receptor degrader

SERM	selective oestrogen receptor modulator
SOC	standard of care
TDAR	T-cell dependent antibody response
TEAE	treatment emergent adverse event
TEC	therapeutic effective concentration
UV	ultraviolet
XR(P)D	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 20 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Inluriyo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2022.

The applicant applied for the following indication:

Inluriyo is indicated:

- *as a monotherapy for the treatment of adult patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor 1 (ESR1)-mutated, advanced or metastatic breast cancer, previously treated with an endocrine based regimen, and*
- *in combination with abemaciclib for the treatment of adult patients with ER-positive, HER2-negative, advanced or metastatic breast cancer, previously treated with endocrine based regimen.*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request for consideration

1.5.1. New active Substance status

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

1.6. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Peter Mol Co-Rapporteur: Boje Kvorning Pires Ehmsen

The application was received by the EMA on	20 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2025
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	31 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 April 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2025
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection for study J2J-OX-JZLC at 2 clinical investigator sites in the USA and in Mexico between 25 and 28 March 2025 and between 31 March and 4 April 2025 respectively and at the sponsor site in the USA between 24 April and 1 May 2025. The outcome of the inspection carried out was issued on	3 July 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 August 2025
The CHMP Rapporteurs circulated the updated CHMP and PRAC	12 September 2025

Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 October 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 October 2025
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 November 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	11 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Inluriyo on	13 November 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	13 November 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a marketing authorisation for the medicinal product Inluriyo (imlunestrant) with the following therapeutic indication:

Inluriyo is indicated:

- *as a monotherapy for the treatment of adult patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor 1 (ESR1)-mutated, advanced or metastatic breast cancer, previously treated with an endocrine based regimen, and*
- *in combination with abemaciclib for the treatment of adult patients with ER-positive, HER2-negative, advanced or metastatic breast cancer, previously treated with endocrine based regimen.*

2.1.2. Epidemiology and risk factors

Breast cancer (BC) is the leading cause of cancer in women and the leading cause of cancer deaths in women (Bray et al, *CA*: *A Cancer Journal for Clinicians*, 2018). In men, breast cancer is rare (Siegel et al 2022). It is estimated that 2.3 million new cases of breast cancer occurred worldwide in women in 2022 (Bray et al. 2024). Over two-thirds of breast cancers express the oestrogen receptor (ER), which is a key driver of breast cancer initiation and progression (Bray et al. 2024). ER+ advanced breast cancer (ABC) is incurable and, therefore, considered a serious and life-threatening disease, with a median OS of 3 to 5 years (Hortobagyi et al. 2022; Meegdes et al. 2023; Cardoso et al. 2024). About 157,100 women were estimated to have died from breast cancer in the EU in 2020 (Ferlay et al, International Journal of Cancer, 2021). In terms of absolute numbers, metastatic BC was still the leading cause of death from all cancers in women, accounting for ~3.6% of all deaths in women and 1.8% of all deaths in Europe in 2015 (Dafni et al, Breast Care, 2019).

2.1.3. Biologic features

BC is a heterogeneous disease comprising different subtypes, which can be identified through molecular biomarkers that also act as predictive factors. It is categorised into different histopathologic subtypes based on the expression of the oestrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor 2 (HER2) receptor overexpression or gene amplification. Oestrogen receptor (ER), and progesterone receptor (PR) are together referred to as hormone receptor (HR). Of the new cancers diagnosed worldwide each year, about 70%-80% are hormone receptor (HR)-positive (Joe et al, *UpToDate*, 2021).

ER is a transcription factor that regulates the expression of oestrogen-responsive genes by binding to a specific DNA sequence found in their regulatory regions. Two major isoforms of the oestrogen receptor have been identified, ERα and ERβ: however, the role of ERβ in cancer remains unclear. The two isoforms are encoded by two genes located on different chromosomes (*ESR1* on chromosome 6 and ESR2 on chromosome 14) and regulate different specific genes.

Recent ASCO/College of American Pathologists guidelines still support the classification of ER+ breast cancer being > 1% by immunohistochemistry staining. Similar principles apply to PR testing, which is used primarily for prognostic purposes in the setting of an ER-positive cancer. HR+/HER2− breast cancer is characterized by hormone receptor positivity (> 1% IHC expression of the oestrogen receptor [ER] and/or progesterone receptor) and lack of HER2 expression (IHC score of 0, 1+, or 2+ confirmed as negative by in situ hybridization [ISH]) (Allison et al., 2020, Wolff et al., 2018). Other therapeutically relevant biomarkers to be assessed include phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) in ER/PR-positive, HER2-negative MBC.

Endocrine therapy (ET) comprises different strategies as suppression of oestrogen production or directly targeting the oestrogen receptor (ER). Steroidal/nonsteroidal aromatase inhibitors (AI) (e.g. exemestane/letrozole and anastrozole and exemestane) exert their action by blocking androgen to oestrogen conversion, thus lowering the levels of circulating oestradiol (E2) and, therefore, reducing the activation of ER. Direct targeting of ERα is achieved by selective oestrogen receptor modulator (SERM) (e.g. tamoxifen) and selective oestrogen receptor degrader (SERD) (e.g. fulvestrant, elacestrant). SERMs compete with oestrogen for ER binding and show mixed agonist/antagonist capabilities in a tissue-specific fashion. Meanwhile, SERDs create an unstable protein complex that induces ER protein degradation via the proteasome.

Several mechanisms regarding ER have been considered to drive resistance to anticancer drugs. Within these, alterations in *ESR1* are some of the most well-established and the main subject of interest to this date. *ESR1* mutations are characteristically more frequent in advanced disease, after endocrine therapy and mostly AI, rather than in primary BC. Mutations in *ESR1* are found in the ligand-binding domain (LBD), favouring constitutive ER activation independent from oestrogen and resistance to AIs. However, *ESR1* mutated tumours can still present sensitivity to tamoxifen or fulvestrant. Mutations in Y537S and D538G are the most frequently described mutations. All *ESR1* LBD mutations cause complete AI resistance; however, preclinical studies indicate Y537S has the highest transactivation activity and the greatest relative resistance to tamoxifen, fulvestrant, and some of the novel SERDs and SERMs. In addition, Y537S-specific *ESR1* mutations are reported as drivers of resistance to fulvestrant plus palbociclib combination therapy (O'Leary et al, Cancer Discovery, 2018; Dustin et al, Cancer, 2019; Hernando et al, International Journal of Molecular Sciences, 2021; Jeselsohn et al, Nature Reviews Clinical Oncology, 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmed by pathological assessment. Disease stage is assessed according to the Tumour, Node, Metastasis (TNM) system.

A number of previous studies on patients with MBC have demonstrated that compared with wild-type *ESR1*, *ESR1* mutation led to worse progression-free survival (PFS) and overall survival (OS) (Chandarlapaty et al, JAMA Oncology, 2016).

2.1.5. Management

The aim of treatment is to increase PFS and OS. Key clinical factors to consider when determining the choice for systemic treatment for women are (1) pre- versus postmenopausal status at the time of presentation, (2) de novo metastatic versus recurrence, (3) disease-free interval and type of adjuvant therapy, (4) tumour burden including bone-only versus visceral disease, (5) performance status and medical comorbidities, and (6) for patients who have progressed on frontline treatment to consider the

previous treatments they received and the response, duration of response, and tolerability to those previous therapies (Gennari et al. 2021).

The current first-line standard of care (SOC) for locally advanced or metastatic ER+/HER2- breast cancer is endocrine therapy, with either aromatase inhibitors or fulvestrant, plus a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (palbociclib, ribociclib, abemaciclib). The optimal sequence of endocrine-based therapy is uncertain after progression on CDK4/6 inhibitors and limited data is available post-CDK4/6 inhibitor treatment. Subsequent treatment involves changing the ET backbone generally to intra-muscular SERD (fulvestrant) given alone or combined with targeted agents (alpelisib/capivasertib) based on presence of targetable tumour mutations or with everolimus in a biomarker-unselected population. For patients with tumours harbouring a germline BRCA1 or BRCA2 mutation, and who have progressed on endocrine therapy or for whom endocrine therapy is not suitable, a PARP inhibitor (olaparib or talazoparib) can be used. An oral SERD, elacestrant, can be given alone to men and postmenopausal women harbouring *ESR1*-mutated tumours (Bidard et al. 2022). *ESR1* mutations resulting in ligand-independent activation have been reported in up to 50% of ABC tumours in patients previously treated with ET (Zundelevich et al. 2020; Bhave et al. 2024), and are associated with worse outcomes (Reinert et al. 2017). Alternatively, tamoxifen can be applied. Some patients with aggressive disease or refractory to ET-based interventions may receive chemotherapy (Cardoso et al. 2024; NCCN 2024).

Efficacy with current ET-based treatment options, either as monotherapy or in combination with a targeted therapy, in the second-line setting remains limited. Median PFS in patients who have received prior ET + CDK4/6i and receiving subsequent second-line ET is only 2 to 7 months (Bidard et al. 2022; Lindeman et al. 2022; Kalinsky et al. 2023; Turner et al. 2023; Kalinsky et al. 2024). Therefore, an unmet medical need remains in the ABC population after progression on first-line treatment with the aim to improve long-term outcomes of PFS and OS and to delay the need for chemotherapy treatment.

2.2. About the product

Imlunestrant is an antagonist and degrader of wild-type and mutant oestrogen receptor α (ERα), leading to inhibition of oestrogen receptor-dependent gene transcription and cellular proliferation in ER+ breast cancer cells.

The final indication is:

Inluriyo is indicated as monotherapy for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen (for biomarker-based patient selection, see section 4.2).

In pre- or perimenopausal women, or men, Inluriyo as monotherapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Treatment with Inluriyo should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with Inluriyo based on the presence of an activating *ESR1* mutation in tumour or in plasma specimens, using a CE-marked *in vitro* diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating *ESR1* mutation should be assessed by an alternative validated test.

Posology

The recommended dose of imlunestrant is 400 mg orally (two 200 mg film-coated tablets), once daily.

It is recommended that treatment is continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Dose adjustments

If dose reduction is necessary, the dose should be decreased by 200 mg. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1 and 2. The treatment should be discontinued for patients unable to tolerate 200 mg once daily.

Table 1 Recommended dose modification for increased ALT and AST

Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during Inluriyo therapy, and as clinically indicated.

Toxicity[a]	Dose modification
Persistent or Recurrent Grade 2 AST or ALT, if baseline was normal	Suspend until toxicity resolves to baseline or Grade 1 if baseline was normal Dose reduction is not required
Grade 3 AST or ALT if baseline was normal **Or** Grade 2 or above AST or ALT if baseline was abnormal **Or** AST or ALT > 8 × ULN (whichever is the lower threshold)	Suspend until toxicity resolves to baseline or Grade 1 if baseline was normal Resume at 200 mg dose level or discontinue if receiving 200 mg daily
Grade 4 AST or ALT if baseline was normal	Discontinue dosing
AST or ALT ≥ 3 × ULN concurrent with total bilirubin (TBL) ≥ 2 × ULN if baseline was normal in the absence of cholestasis **Or** AST or ALT ≥ 2 × baseline concurrent with TBL ≥ 2 × ULN if baseline was abnormal, in the absence of cholestasis	Discontinue dosing

[a]NCI CTCAE v5.0
ULN: upper limit of normal

Table 2 Recommended dose modification for adverse reactions (except increased ALT and AST)

Toxicity [a]	Dose modifications
Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend until toxicity resolves to baseline or ≤ Grade 1 Dose reduction is not required
Grade 3 (except non-hepatic asymptomatic laboratory changes)	Suspend until toxicity resolves to baseline or ≤ Grade 1 Resume at next lower dose level or discontinue if receiving 200 mg daily
Grade 4 (except non-hepatic asymptomatic laboratory changes)	Suspend until toxicity resolves to baseline or ≤ Grade 1 Resume at next lower dose level or discontinue if receiving 200 mg daily Closely monitor on resuming treatment

[a] NCI CTCAE 5.0

Missed dose

If a dose is missed, it can be taken up to 6 hours after the time it is usually taken. After more than 6 hours, the dose should be skipped for that day. An additional dose should not be taken. On the next day, the dose should be taken at the usual time.

2.3. Type of Application and aspects on development

This application under an article 8(3) legal basis of Directive 2001/83/EC (as a complete and independent application) is based on data from the pivotal phase 3 EMBER-3 study, together with supportive data from the phase 1 EMBER study.

Specific CHMP guidelines relevant for the current application: Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.6, 18 November 2023).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablet containing 200 mg of imlunestrant (as imlunestrant tosylate), as active substance.

Other ingredients for the tablet core are: croscarmellose sodium (E 468), hydroxypropylcellulose (E 463), magnesium stearate (E 470b), cellulose, microcrystalline (E 460).

Other ingredients for the film-coating are: macrogols (E 1521), poly (vinyl alcohol) (E 1203), talc (E 553b), titanium dioxide (E 171).

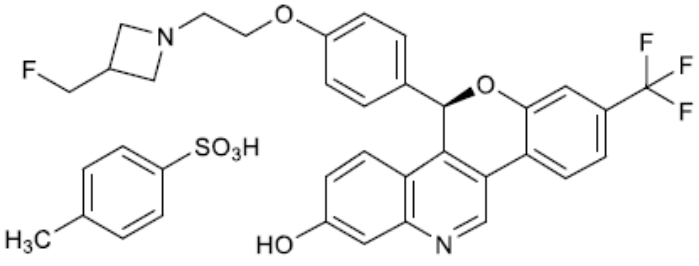
The product is available in polychlorotrifluoroethylene (PCTFE) / polyvinylchloride (PVC) blister sealed with aluminium foil.

2.4.2. Active Substance

2.4.2.1. General Information

The chemical name of imlunestrant tosylate is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol;4-methylbenzenesulfonic acid corresponding to the molecular formula $C_{29}H_{24}F_4N_2O_3$ (base); $C_{29}H_{24}F_4N_2O_3.C_7H_8O_3S$ (salt). It has a molecular weight of 524.52 g/mol (base) and 696.71 g/mol (salt) and the following structure:

Figure 1 active substance structure



The chemical structure of imlunestrant tosylate was elucidated by a combination of MS, FTIR, UV, 1H-NMR, 13C-NMR, 19F-NMR and elemental analysis. The solid state properties of the active substance were measured by DSC and XRPD.

The active substance is a white to practically white to yellow powder and is insoluble in water and is slightly hygroscopic.

Imlunestrant exhibits stereoisomerism due to the presence of one chiral centres; it is manufactured as a single enantiomer. Enantiomeric purity is controlled routinely by chiral HPLC.

A comprehensive polymorph screen produced one crystalline form, Form 1. Polymorphic identity is controlled in the active substance by XRD. The active substance is consistently manufactured as polymorphic Form 1 and the solid state remains stable during storage

2.4.2.2. Manufacture, process controls and characterisation

The manufacturing process has been described in sufficient detail and it is summarised in Scheme 1 below.

The active substance is synthesised in four chemical transformation steps. During the procedure a major objection (MO) was raised regarding the need to redefine the starting material to ensure a better control of impurities, including regioisomers. MO1 was addressed by providing further justification on the acceptability of this starting material in line with ICH Q11 and ICH Q11 Q&A, including 6 steps in the manufacture of the starting material and by demonstrating the adequacy of the control strategy for the fate and purge of the related impurities; the proposed starting material was hence accepted. A second MO (MO2) requested that another starting material was also redefined as it was not considered acceptable in view of the fact that its introduction is followed by only one isolated intermediate. The applicant addressed MO2 by providing further justification on the acceptability of this starting material in line with ICH Q11 and ICH Q11 Q&A. Hence, also this starting material was accepted.

The choice of two starting materials is considered acceptable in accordance with guidance. It can, hence, be concluded that the active substance is synthesised using well defined starting materials with acceptable specifications.

Potential and actual impurities were well discussed with regards to their origin and characterised.

An adequate discussion on the carry-over and control of impurities from the starting materials has been provided.

No class 1 solvents or heavy metal catalysts are used. The class 3 solvent acetone is used in the last step of the synthesis and it is controlled in the active substance specification.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The proposed specification limits are supported by batch data and an extensive discussion on the purge and faith of possible impurities.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Process changes have been made to the synthetic route during development to improve yield, quality and control of the process. Changes introduced have been presented in sufficient detail and have been justified.

For the development and optimisation of the manufacturing process a QbD approach was applied. A risk assessment was performed to identify process parameters potentially critical to the quality of the drug product and intermediates. Multiple univariate and multivariate experiments were performed to evaluate the impact of changes in process parameters on purity and impurities of the process intermediates and final active substance. PARs and target settings have been defined for the critical process parameters and are included in the manufacturing process description. No design space is claimed. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

It was justified that the quality of the intermediates and active substance was independent of the manufacturing scale. One manufacturer was initially responsible for the manufacture of the whole synthesis of the active substance. The manufacture of was transferred to a different manufacturer . Equivalence between the active substance manufactured at these different sites was demonstrated by batch data on multiple batches from each site, showing comparable results.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance will be packaged in a linear low-density polyethylene (LLDPE) primary liner which contains an antistatic additive. The LLDPE liner will be placed in a laminated foil liner. The liners may then be placed in an appropriate container. Sufficient information on the container closure system has been provided. The release control of the material is in general acceptable and the primary LLDPE material complies with the relevant Ph.Eur. monograph and EU Regulation for food contact materials.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specification includes tests for identity (IR - Ph. Eur.), crystal form (XRPD - Ph. Eur.), assay (HPLC), impurities (HPLC), enantiomeric impurity (HPLC), residual solvents (GC), description (visual), water content (KF - Ph. Eur.), residue on ignition (sulfated ash, Ph. Eur.), and particle size (laser diffraction).

The proposed specifications are considered acceptable and are based on batch data and relevant guidelines.

An adequate discussion on the carry-over and control of potential impurities from the synthesis has been provided in support of the specification.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The proposed limits for impurities, water content and residue of ignition have been tightened in line with batch data. The active substance specification is acceptable.

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

Batch analysis data on 70 pilot batches of the active substance, manufactured using synthetic route 3, which is representative of the commercial process, are provided. One batch was manufactured at

commercial scale at the commercial manufacturing site according to the commercial process. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

For the active substance a retest period of 36 months is claimed when stored between 1 °C and 30 °C in the commercial container closure system.

Stability data from six pilot scaled batches of active substance, stored in the intended commercial package, for up to 24 months at long term (30 °C /65% RH) and for up to 6 months at accelerated conditions (40 °C /75% RH) have been provided. The stability batches are representative for the active substance manufactured at the commercial manufacturing site. The batches used in the stability studies were manufactured by synthetic route 3, which is representative for the commercial process.

The following parameters were investigated: description, assay (as salt and free base), impurities, (enantiomer), crystal form (XRPD) and water (KF). The analytical methods used were the same as for release. No trends or changes were observed in any of the tested parameters. All tested parameters were within the specifications.

Furthermore, the stability of the polymorphic form at refrigerator temperature was demonstrated.

Photostability testing following the ICH guideline Q1B was performed on samples of the active substance; the active substance is not sensitive to light exposure.

Results on stress conditions were also provided. Solid samples of imlunestrant tosylate were stressed under heat, humidity, light conditions. Solutions of imlunestrant tosylate were stressed under heat, light, oxidation and pH range (1 to 13). The analytical methods used were stability indicating.

The on-going studies will be continued up to at least 36 months according to the stability protocol. A commitment to place the first three production batches on long term stability studies through the proposed retest period has been provided and is in accordance with ICH Q1A(R2).

Although no temperature storage restrictions are strictly needed in view of the stability data showing that the active substance is stable at long-term and accelerated conditions, no objection is made to the proposed storage condition.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

The finished product is a white, capsule shaped film-coated tablet of 14.0 x 7.5 mm, debossed with "LILLY" on one side and "1717" and an elongated 4-point starburst on the other side. Each film-coated tablet contains imlunestrant tosylate equivalent to 200 mg imlunestrant.

Imlunestrant tablets are provided in individual blister cavities formed from thermoformed plastic film, which are sealed with aluminium foil lidding. The plastic thermoformed film is a 2-layer laminate composed of polychlorotrifluoroethylene (PCTFE) and polyvinylchloride (PVC).

Sufficient detail on finished product composition has been provided in 3.2.P.1.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

. Compatibility of the formulation ingredients was confirmed by the stability studies. Adequate justification has been provided for not controlling the functionally related characteristics of the excipients.

Pharmaceutical development of the finished product contains QbD elements.

The quality target product profile (QTPP) was defined. The critical quality attributes identified include description, identification, potency, purity, content uniformity, and release.

The formulation and manufacturing development have been evaluated through the use of risk assessment, design of experiments and other modeling techniques to identify the critical product quality attributes and critical process parameters.

Although, capsule formulations were initially developed in dose strengths of 50 mg and 100 mg, to support Phase 1 studies, due to the increase in dose projection, a 200-mg strength tablet formulation was developed, which was used in both phases 1 and 3 clinical studies. The formulation used during clinical studies is the same as that intended for marketing.

The formulation components and levels were selected for suitability to deliver the 200 mg dose strength.

A formulation risk analysis was performed to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies.

Acceptable compressibility and release results demonstrated the robustness of the formulation.

For the development of the manufacturing process a preliminary process risk assessment was performed. The operations identified as process step with medium risk on CQAs were further investigated to mitigate the potential risk from medium to low.

Several experiments were conducted at small and commercial scale equipment to explore ranges of process parameters. Acceptable compressibility and release results demonstrated the robustness of the formulation and the manufacturing process.

During the development of the QC dissolution method, different media were considered. During the procedure a MO (MO3) was raised requesting further justification for the choice of dissolution method conditions. A related MO (MO4) was raised requesting to tightening the dissolution limit. To address MO3, the applicant provided a head-to-head comparison of dissolution results (n=12) for a representative production batch with two different method conditions. To address MO4, the applicant agreed to tighten the dissolution limit. It was concluded that the proposed QC dissolution method conditions were considered acceptable. The discriminatory power of the proposed dissolution method was demonstrated. The QC dissolution method, with the amended acceptance criteria, is considered adequate.

The primary packaging is Polychlorotrifluoroethylene (PCTFE) / Polyvinylchloride (PVC) blister sealed with aluminium foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process is considered a standard manufacturing process.

The level of detail in the manufacturing process description has been updated during the procedure, it is now considered adequate.

Design spaces have been proposed for the manufacturing process of the medicinal product. The use of design space is considered of low risk.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The in-process controls are adequate for this type of manufacturing process.

The proposed hold time for the bulk product is supported by stability data.

The manufacturing process has been validated on three full scaled batches manufactured at the commercial site. Process parameters were set in line with process description provided. All results complied with the acceptance criteria. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product release specifications include appropriate tests for this kind of dosage form: identity (HPLC), assay and degradation products (HPLC), description (visual), uniformity of dosage units (Ph. Eur.), dissolution (UV – Ph. Eur.), dye identity – titanium (UV).

The proposed finished product specifications are clearly presented. The proposed release and shelf life limits were based on batch and stability data, and relevant guidelines. The shelf life limit for assay has been tightened during the procedure in line with batch data.

Although toxicologically qualified, the limits for specified impurities have been tightened to NMT 0.2%, in line with ICH Q3B threshold.

Not performing microbial limit testing at release of the product is justified for this solid oral dosage form since the risk of microbiological contamination is low.

The QC dissolution limit has been tightened during the procedure, as discussed in the pharmaceutical development section.

The proposed specification tests and limits are acceptable. The finished product is released on the market based on the above release specifications.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The finished product is indicated for advanced cancer and falls within the scope of ICH S9 and ICH M7 guideline does not apply. Nitrosamines can be controlled at or below ICH Q3B qualification threshold which is 0.2% based on a maximum daily dose of 400 mg.

Based on the information provided, it is accepted that the risk of nitrosamine impurities in the active substance or the related finished product is adequately controlled. Therefore, no additional specific control measures are deemed necessary.

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

Bulk batch data from three full scale batches manufactured at the commercial site were provided. All results comply with the finished product specification. Adequate justification has been provided that in this case the bulk product batch data is representative of the (packed) finished product and thus it is justified that the finished product specification can be set based on the currently provided data in combination with the stability data of finished product in its commercial packaging. However, since the primary packaging step is an integral part of the manufacturing process, and it is necessary to ensure the quality of the finished product, the batch analyses information provided in module 3 of the finished product (3.2.P.5.4) is expected to be conducted on the product in its primary packaging material. In order to address this expectation, the applicant is recommended to provide post approval batch release data generated on the packed finished product of the first three batches to be placed on the market. (**REC1**)

2.4.3.4. Stability of the product

Stability data from three pilot scale batches of the finished product stored under long term conditions and under accelerated condition according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. For those parameters included in the finished product specification, all results comply with the finished product specification.

However, the applicant is recommended to present stability results from the remaining 36-month testing point of primary stability study when available (**REC 2**).

It has been demonstrated that the proposed HPLC method is stability indicating by a forced degradation study.

Results of hold time studies support the claimed hold time for the bulk tablets when stored under conditions which do not exceed 30 °C.

In addition, samples of the finished product were placed under open-dish thermal/humidity studies and exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Product. The stability results remained within the proposed specifications. Based on the accelerated stability, open dish and photostability studies, the proposed storage condition 'This medicinal product does not require any special storage conditions' is justified.

Based on available stability data, the proposed shelf-life of 3 years without any storage conditions, as stated in the SmPC (sections 6.3 and 6.4), are acceptable.

Adventitious agents

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

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed in the manufacture of the finished product. The design spaces have been adequately verified.

During the procedure four major objections were raised. MO1 and MO2 pertained to the redefinition of the starting materials, the applicant resolved both MOs by justifying the adequacy of both starting materials and their control strategy, hence they did not need to be redefined. MO3 and MO4 pertained to the dissolution method conditions and QC dissolution specification limit. To resolve MO3, the applicant justified the method by additional data. MO4 was addressed by tightening the dissolution limits, as requested by the CHMP.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the provision of batch release data (packed product) post approval (**REC1**) and the provision of 36 months stability data, when available (**REC2**). These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to provide post approval, batch release data generated on the packed finished product of the first three batches to be placed on the market.
2. The applicant is recommended to present stability results from the remaining 36-month testing point of primary stability study when available.

2.5. Non-clinical aspects

2.5.1. Introduction

Inluriyo (Imlunestrant; LY3484356; LY3484356 tosylate;) is an orally bioavailable, next generation, noncovalent-binding selective oestrogen receptor degrader (SERD). It is a potent degrader and pure antagonist of wild-type and mutant oestrogen receptor α (ER; ERα) encoded by the gene Oestrogen Receptor 1 (*ESR1*).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The Applicant conducted several *in vitro* and *in vivo* studies to assess the primary PD of imlunestrant. Cellular and murine xenograft studies were conducted in oestrogen receptor (ER)-positive breast cancer models, with or without oestrogen receptor gene 1 (*ESR1*) mutations, along with an evaluation of imlunestrant's functional additivity or synergy with the CDK4/6 inhibitor abemaciclib. These primary pharmacology studies are therefore relevant for the indicated patient populations.

Primary pharmacology – in vitro

In study QSB111, the binding affinity (Ki) of imlunestrant to full length human ERα wild-type (WT), ERα mutant, and ERβ receptors was determined using competitive radioligand binding analysis. High binding affinity was shown to ERα (Ki = 0.637 nM), ERα mutant (Y537S) receptor (Ki = 2.8nM) and ERβ (Ki = 0.111 nM).

Study QSB112 investigated the mechanism of action of imlunestrant in degrading or downregulating ERα levels as well as downstream effects on the transcriptional target progesterone receptor (PRα). Imaging assays in immunostained human MCF7 breast cancer cells demonstrated that imlunestrant caused potent degradation of ERα (IC50 = 3.1 nM) and inhibition of PRα (IC50 = 41.3 nM). The degradation of ERα by the pharmaceutical salt form imlunestrant tosylate was comparable to the free base form. In a MCF7 CRISPR cell line with a *ESR1* Y537N mutation, ERα was not analyzed, though it was shown that PRα was inhibited by imlunestrant (IC50= 13 nM).

In study ONCO149, the degradation potency of ERα by imlunestrant was further examined in a panel of *ESR1* WT and mutant breast cancer cell lines by immunoblotting. Results showed that imlunestrant dose-dependently degraded ERα proteins in MCF7, T47D, HCC1428, ZR-75-1, T47D CRISPR (mutant *ESR1* Y537N), and ST941/C PDX (mutant *ESR1* Y537S) with a potency similar to fulvestrant. The inhibitory effect was clearly visible from 4 nM. In addition, imlunestrant decreased PR levels in both T47D *ESR1* WT and *ESR1* Y537N cell lines, indicating functional suppression of ERα activity.

In study ONCO150, inhibition of ERα-mediated gene transcription by imlunestrant was investigated using 17β-estradiol-stimulated ERα wild-type breast cancer cells (MCF-7) and qRT-PCR. Imlunestrant inhibited the expression of ERα target genes (PGR, PDZK1, AREG, RASGRP1, WISP2, and GREB1) in a concentration-dependent manner from 40 nM. The potency of imlunestrant was comparable to that of fulvestrant.

In study QSB113, the functional effect of imlunestrant on cell proliferation was tested in various *ESR1* WT (MCF7, T47D), *ESR1* Y537N mutant (MCF7 CRISPR, T47D CRISPR) and *ESR1* Y537S mutant (ST941/C, PDX) human breast cancer cells. Imlunestrant demonstrated potent anti-proliferative activity (IC50s ranging from 3 to 17 nM) in all cell lines. Anti-proliferative activity of imlunestrant tosylate was comparable to the free base form.

Study QSB129 further evaluated the anti-proliferative activity of imlunestrant in a breast cancer cell panel. 11 of 12 ER+ cell lines displayed sensitivity to imlunestrant (IC50<100 nM), while none of the ER- cell lines were sensitive to imlunestrant (IC50>2 µM).

Study QSB129 tested the anti-proliferative activity of imlunestrant combined with CDK4/6 inhibitor abemaciclib in five naïve WT *ESR1* breast cancer cell lines. The combination was additive in MCF7 and synergistic in T47D, ZR-75-1, ZR-75-30 and EFM-19. The rationale of this *in vitro* combination study was based on the need for combination therapy to overcome acquired resistance to endocrine therapies.

In study ONCO204, the pharmacological activity of imlunestrant metabolites was studied using imaging assays in immunostained cells. Metabolism studies (see non-clinical PK section) showed that the M1) and M2 () metabolites have relevant exposure in animal species and human. These two metabolites did not cause potent ER degradation (IC50 at least 20x higher as compared to imlunestrant tosylate) in MCF7 *ESR1* WT cells as well as in MCF7 CRISPR *ESR1* Y537N and D538G cells. Absence of ER agonism was also shown (no PR induction). ER functional antagonism was studied in MCF7 CRISPR *ESR1* Y537N and D538G cells and showed that M1 and M2 did not cause potent PR inhibition (IC50 at least 40x higher as compared to imlunestrant tosylate). Furthermore, both metabolites showed minimal/no functional anti-proliferative activity as compared to the parent compound in MCF7 *ESR1* WT cells (IC50 at least 100x higher), MCF7 CRISPR *ESR1* Y537N cells (IC50 at least 60x higher) and D538G cells (IC50 at least 20x higher). Of note, this study showed that imlunestrant tosylate was not effective in the D538G cells (cell proliferation IC50 900 nM) as compared to the Y537N cells (cell proliferation IC50 10 nM) or WT cells (cell proliferation IC50 5 nM).

Primary pharmacology – in vivo

In study ONCO151, in vivo target gene inhibition of ERα regulated genes by imlunestrant was tested using *ESR1* wild-type (MCF7 xenograft) and mutant (ST941/C *ESR1*-Y537S PDX) breast cancer models. NOD SCID mice implanted with subcutaneous tumour cells were administered imlunestrant orally at 3, 10, or 30 mg/kg, once daily (QD) for 3 days. Tumours, brain tissue and plasma were collected for PK and qPCR analyses at timepoints up to 168 h after the last dose. In both the *ESR1* wild-type and the *ESR1* mutant model, imlunestrant caused sustained inhibition of tumour PGR expression (>75% inhibition) up to 96 h. Imlunestrant exposure was at least 12x higher in tumour compared to plasma. PK/PD modelling was used to determine TEC50 and TEC80 (threshold effective concentrations) in plasma and tumour for human dose prediction calculations (data not shown). This study also showed exposure in the brain (higher than plasma, but lower than tumour).

Study ONCO152 examined the effect of imlunestrant on tumour growth in *ESR1* wild-type CDX models (MCF7, T47D, ZR-75-1 and HCC1428) and an *ESR1* mutant (Y573S) PDX model. The MC7 model was orthotopic, the other models were subcutaneous. Imlunestrant was administered orally once daily for up to 42 days. CDX mice were supplemented with oestradiol to support the growth of ER+ tumours. Imlunestrant caused ≥70% tumour inhibition or regression from the lowest dose tested (3 or 10 mg/kg) in all models, as compared to the control group. Higher doses up to 30 mg/kg had no stronger effect except in the T47D model. In the *ESR1* wild-type models, a group of animals receiving fulvestrant (5 mg once weekly SC) was included as a comparison. Efficacy of imlunestrant was comparable to fulvestrant (except in the ZR-75-1 model where fulvestrant was inactive). The salt form imlunestrant tosylate was tested in the MCF7 model and had comparable efficacy to imlunestrant. In the *ESR1* mutant (Y573S) PDX model, 3 mg/kg to 30 mg/kg imlunestrant showed dose-related tumour growth inhibition (33% to 94%).

In study ONCO167, the effect of imlunestrant on tumor growth and survival was evaluated in a model of ER+ intracranial tumours. Mice were orthotopically implanted with MCF7 luciferase-labelled MCF7 (MCF7-fLuc) cells (*ESR1* wild-type) and dosed with imlunestrant orally once daily for 28 days. From 10 to 60 mg/kg, imlunestrant dose-dependently suppressed tumour cell growth (as measured by luminescent output via imaging). After treatment cessation, tumours continued growing and survival was monitored for 15 days. Survival was strongly improved by treatment with imlunestrant (at least 75% versus 0% in the control group) at all doses.

Study ONCO220 examined the anti-tumour activity of imlunestrant tosylate in combination with CDK4/6 inhibitor abemaciclib in the T47D ER+ breast cancer xenograft model. Daily oral treatment for 28 days with 5 mg/kg imlunestrant tosylate or 50 mg/kg abemaciclib alone resulted in 81.5% and 66% tumour growth inhibition, respectively, as compared to the control group. Combined treatment of

imlunestrant tosylate and abemaciclib had an additive effect and nearly completely inhibited tumour growth (tumour regression in 4 animals, >90% tumour growth inhibition in 1 animal) at the end of the dosing period.

Further combination studies (ONCO228) were done in *ESR1* WT CDX as well as *ESR1* mutant PDX models. Mice were treated orally once a day with imlunestrant tosylate for 27 to 56 days, depending on the model. In the ZR-75-1 and T47D CDX models, single imlunestrant treatment caused >80% tumour growth inhibition, and combination with the mTOR inhibitor everolimus or the PI3Ka inhibitor alpelisib, respectively, had an additive effect leading to tumour regression. In most PDX models with *ESR1* mutations (E380Q, D538G or Y537S), including ones with resistance or reduced sensitivity to fulvestrant, imlunestrant alone caused strong tumour growth inhibition (>75%) at 5 and 10 mg/kg and tumour regression at 15 and 45 mg/kg. While imlunestrant did not inhibit the proliferation of MCF7 cells with the *ESR1* D538G mutation *in vitro*, the *in vivo* efficacy was shown in PDX models harbouring this mutation. Imlunestrant combined with the CDK4/6 inhibitor abemaciclib often led to a stronger effect, as shown by a significant additivity at the end of the dosing period or a visibly more sustained inhibition until the end of the study (2-6 weeks post-treatment). In an *ESR1* Y573S PDX model with palbociclib resistance, imlunestrant tosylate treatment was slightly less potent, leading to ~50% tumor growth inhibition at 15 mg/kg, though a clear additive effect was shown when combined with abemaciclib. Imlunestrant was generally more potent than fulvestrant, also when either SERD was combined with abemaciclib.

2.5.2.2. Secondary pharmacodynamic studies

The selectivity of imlunestrant as antagonist of ER was investigated over other nuclear hormone receptors, 33 kinases and 8 human GPCRs.

The selectivity of imlunestrant for ERα over other nuclear steroid hormone receptors was examined *in vitro* via a competition binding assay using cell lysates from human embryonic kidney cells (HEK293) overexpressing human AR, GR, MR, or PGR (Report QSB111). Imlunestrant had strong binding activity to ERα (Ki of 0.64 nM) and only weak binding activity to the other nuclear steroid hormone receptors tested (at least 1734-fold selectivity over ERα).

The activity of imlunestrant was tested in a human kinase panel using a biochemical assay (Report QSB128). Imlunestrant was inactive against all 33 kinases tested (IC50 > 20 μM).

The activity of imlunestrant towards 8 recombinant human GPCRs was assessed using cell-based assays (Report QSB128). The endpoint measured in each assay was calcium mobilization, intracellular cAMP concentration, or β-arrestin recruitment, depending on the GPCR and mode of activity (inhibition versus activation). Imlunestrant was shown to be inactive on all receptors tested at 1 μM. However, at the maximum concentration (13.8 or 10 μM depending on the assay), imlunestrant showed more than 50% activity on the following receptors: 5HT2B (85% stimulation and 89% inhibition), adrenergic α1A (104% inhibition), adrenergic β1 (86% inhibition), adrenergic β2 (51% inhibition), dopamine D2L (86% stimulation), and muscarinic M2 (53% inhibition). The safety margin is estimated to be ~3000x, as compared to the human steady state unbound Cmax of ~0.164 ng/mL (~0.313 nM considering the molecular weight of imlunestrant as free base) at the recommended dosage of 400 mg QD.

An *in vivo* study was performed in rats to confirm that imlunestrant does not act as an agonist of ERα in the uterus. In contrast to the positive controls tamoxifen and estradiol, 4 oral daily doses of imlunestrant up to 75 mg/kg did not cause increased uterine weight and is therefore considered not uterotrophic.

2.5.2.3. Safety pharmacology programme

In vitro cardiac safety assays were performed. The most common mechanism responsible for drug-induced prolongation of QT interval in humans is inhibition of potassium current through the hERG channel. In a GLP hERG patch clamp assay (190112.FMD), imlunestrant inhibited potassium current through the cardiac hERG channel by up to 27.8% at 1 µM. Higher concentrations of imlunestrant could not be tested due to practical limitations. Since the IC50 was not determined, it is unknown if the safety margin is sufficiently high. Given an IC50 of at least 1 µM, the safety margin is estimated to be at least ~3000x, as compared to the human steady state unbound Cmax of 0.164 ng/mL (~0.313 nM considering the molecular weight of imlunestrant as free base) at a dosage of 400 mg QD.

In a Nav1.5 patch clamp assay, performed as part of the non-GLP secondary PD study QSB128, imlunestrant did not inhibit the NaV1.5 cardiac sodium channel at concentrations up to 10 µM.

2.5.2.4. Pharmacodynamic drug interactions

No dedicated pharmacodynamics interaction studies were performed. The combination of imlunestrant with abemaciclib in the *in vitro* and *in vivo* primary pharmacodynamic studies show additive potential with regard to anti-tumour effect.

2.5.3. Pharmacokinetics

Analytical Methods

Analytical methods were validated for imlunestrant in rat plasma and cynomolgus monkey plasma. The studies do not include a GLP statement. It was stated that the GLP principles of working were applied. According to ICHM10, if an analysis method is used for analysis of samples from a GLP study, the validation should also be done under GLP. The validated methods described are used to analyse samples from GLP studies. The Applicant provided an overview of studies performed under GLP and stated that the validation was also performed under GLP conditions.

Metabolites M1 and M2 were also analysed with LC-MS/MS methods. As the metabolites were only evaluated qualitatively in the metabolite evaluation studies, no validation report was submitted.

Single-dose pharmacokinetics

Single-dose pharmacokinetics of imlunestrant were studied in mice, rats and cynomolgus monkeys. In rats and cynomolgus monkey studies with both male and female animals were performed, whereas in mice only male animals were studied. A single IV bolus of either 0.5 mg/kg or 1 mg/kg was administered to mice, rats and monkeys. Overall, this resulted in a slow clearance in mice (3.19 mL/min/kg) and moderate clearance in rats and monkeys, with Cl values of 15.2 and 15.5 mL/min/kg and 17.4 and 23.7 mL/min/kg in the different studies respectively. In humans, after IV administration of 400 mg the Cl was 5.5 mL/min/kg (assuming a 70 kg body weight, study JZLE). After per os (PO) administration the apparent clearance was 39.5 mL/min/kg. This is also reflected in the measured half-life, which is 29.6 hours in humans in the IV study, 20.5 hours in mice, 9.1 and 9.88 hours in rats and 8.33 and 12.7 hours in cynomolgus monkeys after IV administration. Volume of distribution is substantial in all species (3.89-12.9 L/kg) and in humans (10.56 L/kg, study JZLE).

After PO administration of doses between 3 mg/kg – 100 mg/kg imlunestrant was absorbed with a Tmax ranging from 3-8 hours (4 hours in humans). Cmax was high in mice, moderate in rats and lowest in cynomolgus monkeys. In rats the increase is Cmax was about dose proportional between 30 mg/kg and 100 mg/kg doses, but less than dose proportional between 3 mg/kg and 30 mg/kg. A similar pattern is observed for the AUC. This is probably due to the bioavailability of the compound. In

mice, bioavailability was 44.2% (10 mg/kg PO), in monkeys 8.41% (30 mg/kg PO) and in humans 10.5% (at the recommended dose of 400 mg PO). For rats, the bioavailability was 62.3% at a 3 mg/kg PO dose, but only 32.2% at the 30 mg/kg PO dose. It seems therefore, that the bioavailability of imlunestrant is dependent on the dose administered. In cynomolgus monkeys the bioavailability for the 3 mg/kg PO dose was not calculated, however, a calculation with the dose-normalized AUCs for 0.5 mg/kg IV and 3 mg/kg PO from study PABZ18, the bioavailability would be approximately 7.99% at 3 mg/kg PO. Although the increase in C_{max} and AUC between the 3 mg/kg and 30 mg/kg PO dose is less than dose proportional, which could indicate a higher bioavailability at the low dose compared to the high dose. In monkeys, this does not appear to be the case based on these study results.

Repeat-dose toxicokinetic

Four repeat-dose toxicokinetic analyses were performed in healthy male and female SD rats as part of repeat-dose toxicity studies. Study durations were 2 weeks, 4 weeks, 3 months and 6 months. Doses ranged from 10-1000 mg/kg/day and were administered orally, once daily. The 2-week study was a non-GLP study, the other studies were all GLP. Toxicokinetic parameters were mostly consistent across the studies. Sex differences were not identified in any of the studies.

T_{max} in rats ranged from 4-24 hours. However, a T_{max} of 4-8 hours appears to be the general T_{max} for the lower doses (≤150 mg/kg/day) and values of 12-24 hours were observed in high doses (≥300 mg/kg/day). Increases in dose resulted in increased C_{max} and AUC. For the lower doses these increases appear to be dose proportional in rats, however, in the higher doses (≥150 mg/kg/day) the increase becomes less than dose proportional. Accumulation was observed in rats, but it was very limited to approx. 2-fold. In the GLP studies the highest accumulation was 2.59, observed in the 4-week rat study in the male 300 mg/kg/day group. Slightly higher accumulation ratios were observed in the non-GLP 2 week study with 3.79 (sex combined) in the 1000 mg/kg/day group.

Two additional toxicological studies (genotoxicity and phototoxicity) were performed in healthy rats, in which toxicokinetic parameters were assessed. In the non-GLP toxicokinetics study to support the genotoxicity studies, the toxicokinetic profile was in line with the profile seen in the repeat-dose studies in rats, besides the fact that there was no increase in C_{max} and AUC with increasing dose.

In the GLP phototoxicity study, female Long-Evans rats were used (n = 3/group) for toxicokinetic analysis. Doses were 5, 60 or 1000 mg/kg/day, orally, once daily for 4 consecutive days. Toxicokinetics were only assessed on day 4. T_{max} was short in this study (2-4 hours) in all dose groups. C_{max} and AUC increased dose proportionally between the 5 and 60 mg/kg/day groups, but less than dose proportional between the 60 and 1000 mg/kg/day groups, similar to the toxicokinetics observed in SD rats in the other studies, which can be explained by differences in bioavailablity between low and high doses.

One pilot, GLP, EEFD study was performed in pregnant SD rats. Rats were orally dosed once daily from GD6 through GD17 with doses of 0.3, 3 or 30 mg/kg/day. Toxicokinetics were assessed at GD6 and GD17. T_{max} was 8 hours at all timepoints at all doses. C_{max} and AUC increased dose proportionally, similar to what was observed at low doses in healthy rats. Values of AUC at similar doses administered to non-pregnant rats were also similar, as were the accumulation ratios over time, which ranged from 1.41 – 2.23 in pregnant animals.

Toxicokinetic data for cynomolgus monkeys were available from three repeat-dose studies. The first non-GLP study of 7 days tested 100 mg/kg/day and 1000 mg/kg/day doses, but with only 1 animal/sex/dose. Two GLP studies were conducted of 28 days and 105 days in length. Doses ranged from 15 mg/kg/day to 600 mg/kg/day administered orally, once daily. Toxicokinetic parameters were relatively consistent across the three studies. In none of the studies sex differences between male and female animals were observed. Overall, the T_{max} was moderate, ranging in general from 3-11 hours. In

the highest dose of 1000 mg/kg T_{max} values of 24 hours were observed, however only 1 animal/sex/group was used. It appears the T_{max} does increase slightly at the higher dose of 600 mg/kg/day compared to the lower doses of up to 150 mg/kg/day.

In all monkey studies the C_{max} and AUC increased with increasing dose, however, in a less than dose proportional manner. Over time, no substantial accumulation (>2-fold difference in AUC) was observed in the 28 day study, except for males at 30 mg/kg/day (ratio 2.27). In the 105-day study there was a large variability in accumulation ratios between individual animals, especially in the 600 mg/kg/day group (range of 0.76-10.3-fold accumulation), mainly due to poor solubility and low bioavailability seen in this high-dose group.

Distribution

In vitro studies showed high plasma protein binding of imlunestrant in all animal species tested. In mice the binding was lowest, with 99.83%, followed by rats (99.90%), monkeys (99.92%) and dogs (99.93%). Binding to human plasma was measured at 99.89%. Therefore, the free fraction in humans is higher than in rats (1.1-fold), monkeys (1.38-fold) and dogs (1.57-fold).

Two *in vivo* studies were performed. A QWBA study with [^{14}C]-imlunestrant in Long Evans rats revealed extensive tissue distribution of imlunestrant. Besides high concentrations in GI tract, liver and to some extent kidneys, substantial amounts were also observed in lung tissue, harderian gland, and eyes. Concentrations in uveal tract were high through to the end of the study at 672 hours and concentrations seem to be declining only very slowly. There was no difference in concentration of imlunestrant between pigmented and unpigmented skin. Both male and female animals were used and no sex differences were observed. Imlunestrant distributed to male and female reproductive tissues in low to moderate amounts, but were not detected any more after 120 hours. Distribution to the brain was also observed, with a tissue:plasma ratio of 6.84 (whole brain).

The whole blood to plasma ratios were 1.10 for male rats and 1.36 for female rats. $K_{WB/P}$ of imlunestrant was 0.94 at 0.02 µM, 0.95 at 0.2 µM, and 1.11 at 10 µM in human samples.

One mice study with imlunestrant at an IV dose of 1 mg/kg was performed to assess the distribution of imlunestrant to brain, liver and spleen. Brain:plasma ratio was 0.117 at 0.5h and 0.209 at the 2h timepoint. Therefore, imlunestrant does distribute to the brain but in a lesser extent than in the rat, where tissue:plasma ratio was >1. In humans, it was demonstrated imlunestrant is a substrate for P-glycoprotein, which indicates in humans there is an active efflux from the brain. The liver:plasma ratios were 2.97 and 3.33 at 0.5h and 2.0h. Spleen:plasma ratios were 1.28 and 1.75 at the two time points respectively. Besides a clearly lower distribution to the brain, it appears the distribution in mice is overall more limited compared to the rat. In rats the liver:plasma ratios were >100 for both males and females, while in mice the ratios were 2.97 and 3.33 at the two analysed timepoints.

For monkeys, there is no tissue distribution data available. Placental transfer was not studied in rats nor monkeys.

Metabolism

The *in vitro* metabolism of imlunestrant was evaluated using liver microsomes and hepatocytes from mice, rats, dogs, monkeys and humans. After incubation of imlunestrant in hepatocytes, 2µM for 4 hours, 1 day, and 7 days, the sulfate (M2) and glucuronide (M1) metabolites were the prominent metabolites in mouse, rat, dog, monkey, and human hepatocyte cultures. In liver microsomes the metabolic turnover was low. All human metabolites determined *in vitro* were also present in the toxicological animal species, being rats and monkeys.

The *in vivo* metabolism of imlunestrant was studied after oral administration of [^{14}C]-imlunestrant to male and female SD rats. Plasma and brain tissue were collected from intact rats given an oral dose at

100 mg/kg (n=39M/39F SD rats). The main metabolite identified was M1. This metabolite accounted for 5.4-18.1% of radioactivity in plasma of male rats and 3.2%-18.9% in plasma from female rats, indicating no sex differences in metabolism. Parent imlunestrant was present at 81.9%-94.6% in male rat plasma and 81.1-96.8% in female rat plasma. No other metabolites accounted for more than 1% of the total radioactivity in plasma. In brain, only imlunestrant was detected.

In human plasma (clinical study Study JZLE), metabolite M1 was identified as a major metabolite at 19.9% of radioactivity in the circulation. M2 was not a major metabolite at 4.47% of radioactivity in circulation. Metabolite M1 is not pharmacologically active *in vitro.*

No dedicated *in vivo* metabolism study was conducted in monkeys.

A matrix-normalized relative exposure study was performed with plasma samples collected in the rat and monkey 4-week repeat-dose toxicity studies (300 mg/kg dose in rats and 600 mg/kg dose in monkeys, which were the highest doses tested in non-clinical toxicological studies). Samples came from small sample sizes of n=2 for male monkeys and n = 3 for female monkeys and n = 3 for both male and female rats. The concentrations of metabolites M1 and M2 from these samples were then compared to those in samples from a clinical phase 1 study (J2J-MC-JZLA) in humans after a daily 200 mg oral dose. The ratio of the relative exposure between pre-clinical species and humans for M1 and M2 were then calculated. Mixtures of human, rat and monkey plasma were used, for which no LC-MS/MS method has been validated.

For M1 the exposure ratio to humans was 5.40 for male rats and 4.82 for female rats and 3.01 and 4.20 for male and female monkeys respectively. Metabolite M2 was low in rats (exposure multiple of 0.95 and 0.03 in male and female rats respectively) but was adequate in monkeys with exposure multiples of 3.58 for male monkeys and 2.62 for female monkeys, compared to a human dose of 200 mg. The therapeutic dose in humans of imlunestrant according to the SmPC, however, is 400 mg once daily. Therefore, the Applicant extrapolated the 200 mg dose to a 400 mg dose based on the linearity of the PK of imlunestrant in this range. It was assumed the metabolite formation was also linear, as the routes of metabolism (sulfation, glucuronidation and CYP3A4 metabolism) are not considered prone to saturation. The exposure multiples of the metabolites M1 and M2 were therefore halved, being 2.70 and 2.41 for M1 in male and female rats respectively. M1 exposure multiples in monkeys were 1.51 and 2.10 for males and females respectively. M2 exposure multiples were 0.475 and 0.0015 in male and female rats and 1.79 and 1.31 in male and female monkeys respectively.

Excretion

Excretion of imlunestrant was studied in intact and bile duct cannulated rats. A single oral dose of 30 mg/kg (150 µCi/kg) was administered to intact male and female rats (N=4/sex). A single oral dose of 100 mg/kg (150 µCi/kg) was administered to male, BDC rats (N=4). Recovery was >100% in all groups. In rats, faeces was the primary route of excretion. <1% of the administered dose was recovered in urine in all groups and dose levels. In intact rats imlunestrant accounting for 86% and 95% of the dose in male and female rats, respectively. Radioprofiling of faeces extract from males revealed the presence of four metabolites, whereas only one metabolite (M5) was quantified from female faeces. The largest metabolite in faeces was M2, accounting for 9.4% of the radioactive dose in male rats. Metabolites M4, M5, and M6 were all <1.5% of the dose.

In bile duct cannulated rats 52.7% of the radioactive dose was found in bile and the other half (50.3%) in faeces. Only 0.23% was recovered from urine. This would indicate that at least approx. 50% of the dose was absorbed after oral administration of imlunestrant to rats in this study. In bile, parent drug and four metabolites were identified. M1 was the most abundant metabolite at 43% of radioactive dose. Other metabolites (M2-M4) accounted for 5%, 1% and 1% or radioactivity respectively. Parent drug imlunestrant accounted for only 0.5% in bile. Since M1 is abundant in bile, but absent in faeces, it

may be hydrolysed in the GI tract before excretion through the faeces. Metabolite M3 was also absent in faeces.

No dedicated *in vivo* excretion study was conducted in monkeys.

In humans, imlunestrant excretion was similar to the profile seen in rats. 97.3% of a radioactive, therapeutic dose was excreted via faeces and only 0.278% via urine. 7 metabolites were found in the faeces. Parent imlunestrant accounted for 61.8%. M2 accounted for 20.9% and metabolites M5, M10, M7, M8, M9 and M11 accounted for ≤5.1% of the radioactive dose each. The main excretion profile is therefore comparable with the profile seen in rats. In humans more minor metabolites are excreted, but parent imlunetstrant is the main component of faecal excretion, followed by M2 as the main metabolite.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No stand-alone single dose toxicity study was conducted. In repeat-dose toxicity studies, no mortality or clinical observations indicative of acute toxicity were observed in the first days of dosing.

2.5.4.2. Repeat dose toxicity

Table 3 Repeat-dose toxicity studies in rats

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/kg /day)	**Exposure[A]**		**Major findings & NOAEL**
			C_{max} ng/ml	AUC_{0-24h} ng*h/ml	
Repeat-dose toxicity studies					
Rat (Sprague Dawley) 2 w PO Non-GLP (130-699)	Main: 5M/5F	0	-	-	**Mortalities:** 1x 1000 mg/kg/day male found dead on D8 (treatment-related; stomach ulceration); 2x 1000 mg/kg/day females were found dead on D9 (cause unknown, considered treatment-related). All surviving 1000 mg/kg animals were terminated early on D9 due to poor conditions. **Main phase:** ***≥30 mg/kg:*** ↓ RBC/HGB/HCT; ↓ RET (M); ↓ TPROT/ALB/GLOB (F); ↑ ovary weight; follicular cysts in ovaries; atrophy in uterus, cervix and vagina; vacuolated macrophages in lung alveoli (M); ↑ adrenal gland weight (F).
		30	456	7785	
		300	5560	122500	
		1000[B]	21250	303500	

					≥300 mg/kg: ↓ body weight; ↓ food intake; thin appearance; piloerection; ↑ ALT/AST; ↑ NEUT/MONO/LYMPH; ↓ TPROT/ALB/GLOB (M); ↓ PLAT; individual hepatocyte necrosis and vacuolated Kupffer cells in the liver; ↓ hematopoietic cellularity in bone marrow (F); lymphoid depletion in thymus and spleen; ↓ uterus weight; ↓ spleen weight (M); vacuolated macrophages in lung alveoli (F); vacuolated macrophages in small intestine and spleen; diffuse cortical hypertrophy in adrenal gland; erosion/ulcer in the glandular stomach. ***=1000 mg/kg:*** ↓ activity; abnormal faeces; dehydration; ↑ aPTT (F); ↓ hematopoietic cellularity in bone marrow (M); centrilobular necrosis in the liver (M); medulla vacuolation in adrenal gland (M); focal cortical angiectasis/cystic degeneration in adrenal gland (F); erosion/ulcer and squamous hyperplasia in non-glandular stomach. **Reproductive NOAEL not determined** **Non-reproductive NOAEL = 300 mg/kg**
Rat (Sprague Dawley) 4 w + 2 w PO GLP (8002568)	Main: 10M/10F Recovery: 5F/5M TK: 3-10F/3-10M	0 30 100 300	- 926 2893 5205	- 13600 38350 101300	**<u>Mortalities:</u>** 2x 300 mg/kg/day males were euthanized on D17 and D28 in poor condition (cause unknown, considered treatment-related). 1x 300 mg/kg/day male was found dead on D29 (cause unknown, considered treatment-related). **<u>Main phase:</u>** ***≥30 mg/kg****:* ↑ body weight/body weight gain (F); ↓ body weight gain (M); ↑ food intake (F); ↑ ALP/ALT (F); ↓ TPROT/ALB (F); ↓ RDW (M); ↑ RDW (F); ↓ PLAT (M); ↑ RET (F); ↑ PTT (F); ↑ ovary weight; enlarged ovaries; cysts in ovaries; ↓ uterus weight; small uterus/cervix; atrophy in uterus, cervix and vagina; ↓ lymphoid cellularity and necrosis in mesenteric lymph node; ↓ adrenal gland weight; small adrenal gland (F); cortical atrophy in adrenal gland; ↓ pituitary gland weight (F); hyperplasia in the non-glandular stomach.

					≥100 mg/kg: ↑ WBC/LYMPH/BASO; ↑ MONO/EOS (F); ↑ RET (M); ↑ thymus weight (F); ↑ liver weight (M); ↓ cellularity and necrosis in spleen; vacuolated macrophages and erythrocytosis in mesenteric lymph node; vacuolated macrophages in lungs and small intestine ***=300 mg/kg:*** ↓ body weight (M); ↓ food intake (M); dehydration; thin appearance; salivation; ↑ AST (F); ↑ ALT (M); ↓ TPROT/ALB (M); ↑ CREAT; ↑ UN (M); ↑ NEUT; ↑ MONO (M); ↓ EOS (M); ↑ LUC (F); ↑ RBC/HCT/HGB (M); ↓ PLAT (F); ↑ PT (M); ↓ thymus weight (M); ↑ liver weight (F); ↓ lymphoid cellularity and necrosis in thymus; ↓ hematopoietic cellularity in bone marrow (M); ↓ lymphoid cellularity and necrosis in mandibular lymph node and GALT; sinusoid macrophage vacuolation in the liver; tubular degeneration and tubular vacuolation and dilatation in the kidney (M); small prostate gland/seminal vesicles; ↑ adrenal weight (M), adrenal gland enlargement; cortical hypertrophy in adrenal gland. **<u>Recovery phase</u>** <u>(only for control and 300 mg/kg/day animals):</u> ***≥300 mg/kg:*** ↑ body weight gain (M); ↑ food intake; ↑ ALP (F); ↓ TPROT/ALB (F); ↑ RDW; ↑ PT (F); ↑ ovary weight; enlarged ovaries; cysts in ovaries; ↓ uterus weight; small uterus/cervix; atrophy in uterus, cervix and vagina; vacuolated macrophages in lungs **Reproductive NOAEL not determined** **Non-reproductive NOAEL = 100 mg/kg**
Rat (Sprague Dawley) 13 w + 6 w PO GLP (8003221)	Main: 10M/10F Recovery: 5F/5M TDAR: 5F/5M TK:	0 10 30 150	- 416 1325 4465	- 7355 22750 80700	**<u>Main phase:</u>** ***≥10 mg/kg:*** ↑ body weight/body weight gain (F); ↓ body weight/body weight gain (M); ↑ food intake (F); ↓ food intake (M); prolonged diestrus (14 consecutive days); ↑ ALP; ↓ TPROT/ALB (F); ↑ RBC/RDW (F); ↑ PT; ↑ kidney weight (M); ↑ spleen weight (F); ↑ lymphoid cellularity in spleen (F); ↑ ovary weight; follicular/luteal cysts in ovaries; ↑ corpora lutea number; ↓

	3-9F/3-9M				uterus/cervix weight; small uterus/cervix; atrophy in uterus, cervix and vagina; epithelial hypertrophy/hyperplasia in alveolus/duct in the mammary gland; ↓ adrenal gland weight; ↓ cortical vacuolation in adrenal gland (M); cortical atrophy in adrenal gland; ↓ pituitary gland weight; cellular hypertrophy in pars distalis of pituitary gland (F). ***≥30 mg/kg****:* ↑ WBC/LYMPH/MONO (F); ↓ RET (M); ↑ RET (F); epithelial vacuolation in epididymis; ↑ hematopoietic cellularity in bone marrow (F); ↓ lymphoid cellularity in thymus (M); lymphoid single cell necrosis in thymus (F); tubular degeneration/regeneration in the kidney (F); vacuolated macrophages in small intestine ***=150 mg/kg:*** liquid/soft feces; salivation; ↓ TPROT (M); ↑ WBC/LYMPH/MONO (M); ↑ NEUT/BASO; ↓ PLAT; cytoplasmic vacuolation of lymphocytes; enlarged ovaries; mass/nodule in ovaries; granulosa cell hyperplasia in the ovary; ↓ lymphoid cellularity and single cell necrosis in spleen (M); ↓ lymphoid cellularity and single cell necrosis in mandibular and mesenteric lymph node; retrograde nephropathy and inflammation in the kidney (F); urothelial hyperplasia in urinary bladder/ureter (F); tubular degeneration/regeneration in the kidney (M); vacuolated macrophages in mandibular and mesenteric lymph node; **Recovery phase** (only control and 150 mg/kg/day animals): ***=150 mg/kg:*** ↓ body weight gain (F); prolonged diestrus (6-10 consecutive days); ↓ CHOL (M); ↓ TPROT/ALB (F); ↑ RBC/RDW/RET (F); ↑ ovary weight; follicular/luteal cysts in ovaries; granulosa cell hyperplasia in the ovary; epithelial vacuolation in epididymis; ↑ hematopoietic cellularity in bone marrow (F); tubular degeneration/regeneration in the kidney (M); pelvic inflammation in the kidney

					(F); vacuolated macrophages in small intestine; ↓ pituitary gland weight. **Reproductive NOAEL not determined** **Non-reproductive NOAEL = 150 mg/kg**
Rat (Sprague Dawley) 26 w + 12 w PO GLP (8003353)	Main: 15M/15F Recovery: 5F/5M TDAR: 5F/5M TK satellites: 3-9F/3-9M	0	-	-	**Mortality:** 1x 60 mg/kg/day male found dead on D258 (treatment-related; spontaneous histiocytic sarcoma in multiple organs); 1x 150 mg/kg/day male euthanized on D176 in poor condition (not treatment-related; mass in thymus); 2x 150 mg/kg/day females euthanized on D82 and D106 in poor condition (treatment-related; urinary obstruction) **Main phase:** ***≥10 mg/kg:*** ↑ body weight/body weight gain (F); ↓ body weight/body weight gain (M); ↑ food intake (F); ↓ food intake (M); ↑ ALP (F); ↑ RBC/HGB/HCT (F); ↓ MCV (F); ↓ RDW (M); ↑ ovary weight; enlarged ovaries; follicular/luteal cysts in ovaries; granulosa cell hyperplasia in ovaries; ↓ uterus/cervix weight; small uterus/cervix; atrophy in uterus and vagina; lens degeneration in the eye; epithelial hypertrophy/hyperplasia in alveolus/duct in the mammary gland; tubular degeneration/regeneration in kidney (M); pelvis inflammation in kidney (F); transitional cell hyperplasia in urinary bladder (F); ↓ lymphoid cellularity in spleen (M); ↑ hematopoietic cellularity in bone marrow; vacuolated macrophages in mesenteric lymph node (M); cellular debris in lumen and decreased sperm cellularity in epididymis; spermatid retention in testis; ↓ adrenal gland weight (F); ↓ pituitary gland weight (F); cellular hypertrophy pars distalis in pituitary gland (F). ***≥30 mg/kg:*** ↓ TPROT/ALB (F); ↓ RET (M); ↓ PLAT; ↑ PT (F); ↑ kidney weight (M); single incidence of transitional cell carcinoma in urinary bladder (1xM); tubular degeneration/regeneration in kidney (F); hyaline cast in kidney;
10	606	9565			
30	1430	23950			
60	2425	42450			
150	4315	72450			

					atrophy in cervix; ↓ lymphoid cellularity in spleen (F); ***≥60 mg/kg:*** ↑ WBC/LYMPH/MONO (F); cytoplasmic vacuolation of lymphocytes; vacuolated macrophages in small intestine (F); glomerulopathy in kidney (M); transitional cell hyperplasia in urinary bladder (M); ***=150 mg/kg:*** ↑ ALT; ↑ ALP (M); ↑ WBC/LYMPH/MONO (M); accumulation multicentric lamellar bodies cytoplasm; enlarged mesenteric lymph node; glomerulopathy in kidney (F); vacuolated macrophages in small intestine (M); central/focal posterior cortical lens opacity. **<u>Recovery phase</u>** <u>(only control and 60 and 150 mg/kg/day animals):</u> ***≥60 mg/kg:*** ↓ body weight (M); lens degeneration in the eye; tubular degeneration/regeneration in kidney (M); follicular/luteal cysts in ovaries; granulosa cell hyperplasia in ovaries; spermatid retention in testis; transitional cell hyperplasia in urinary bladder (F); vacuolated macrophages in mesenteric lymph node; ↓ pituitary gland weight (F); cortical vacuolation in adrenal gland (F). ***=150 mg/kg:*** central/focal posterior cortical lens opacity. **Reproductive NOAEL not determined** **Non-reproductive NOAEL = 10 mg/kg**

[A] Mean C_{max} and $AUC_{0\text{-}24h}$ of male and female animals on last study day.
[B] Mean C_{max} and $AUC_{0\text{-}24h}$ of male and female animals on day 8, due to mortality.

Table 4 Repeat-dose toxicity studies in monkeys

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure[A]**		**Major findings & NOAEL**
			C_{max} ng/ml	$AUC_{0\text{-}24h}$ ng*h/ml	
Repeat-dose toxicity studies					

Monkey (Cynomolgus) 1 w PO Non-GLP (130-698)	Main: 1M/1F	100 1000	553 2525	8755 42350	**<u>Main phase:</u>** ***≥100 mg/kg:*** soft/watery faeces (F); Kupffer cell vacuolation ***=1000 mg/kg:*** ↓ body weight; soft/watery faeces (M), dehydration (M); ↑ ALT; hepatocyte necrosis in the liver; macrophage infiltration in small intestine; **NOAEL 100 mg/kg/day**
Monkey (Cynomolgus) 4 w PO GLP (8002569)	Main: 3M/3F	0 30 150 600	- 181 407 877	- 2755 6480 12700	**<u>Main phase:</u>** ***≥30 mg/kg:*** ↑ ovary weight; follicle cysts in ovaries; vacuolated macrophages in mesenteric lymph node (M). ***≥150 mg/kg:*** soft/liquid faeces (F); ↑ ALT (F); vacuolated macrophages in small intestine; vacuolated macrophages in mesenteric lymph node (F). ***=600 mg/kg:*** soft/liquid faeces (M); ↑ ALT (M) ↑ AST (F); vacuolated macrophages in lung and spleen. **Reproductive NOAEL not determined** **Non-reproductive NOAEL = 600 mg/kg**
Monkey (Cynomolgus) 15 w PO GLP (8003147)	Main: 4M/4F	0 15 100 600	- 118 390 1395	- 1800 6850 25800	**<u>Main phase:</u>** ***≥15 mg/kg:*** ↓ spleen weight; ↓ thymus weight (M); ↑ ovary weight; cysts in ovaries; atrophy in cervix, uterus and vagina; ↓ hematopoietic cells in bone marrow (F); ↓ lymphoid cellularity in spleen (F). ***≥100 mg/kg:*** vacuolated macrophages in mesenteric lymph node and lung; ***=600 mg/kg:*** vomitus; salivation; soft/liquid faeces; reduced appetite; thin appearance (F); ↑ ALT; ↓ thymus weight (F); liver discoloration; pigmentation of Kupffer cells in liver; vacuolated macrophages in small intestine; ↓ hematopoietic cells in bone marrow (M); ↓ lymphoid cellularity in spleen (M); ↓ lymphoid cellularity in thymus. **Reproductive NOAEL not determined** **Non-reproductive NOAEL = 600 mg/kg**

[A] Mean C_{max} and $AUC_{0\text{-}24h}$ of male and female animals on last study day.

2.5.4.3. Genotoxicity

The genotoxic potential of imlunestrant was evaluated in a standard battery of assays in accordance with ICH S2(R1) and OECD guidelines. These included an *in vitro* Ames test, an *in vitro* micronucleus assay in human TK6 cells, an *in vivo* micronucleus assay in rat bone marrow, and an *in vivo* Comet assay in rat liver and duodenum.

Imlunestrant was tested in five bacterial strains (S. typhimurium TA98, TA100, TA1535, TA1537, and E. coli WP2 uvrA) with and without metabolic activation (Study 00353453). Cytotoxicity was observed at low doses (≥50 µg/plate without metabolic activation and ≥160 µg/plate with metabolic activation). No dose-related increase in revertant colonies was observed, and the test was valid based on appropriate controls. Imlunestrant is considered to be negative for inducing mutagenicity in this assay up to the cytotoxic dose.

In an *in vitro* micronucleus assay, TK6 cells were treated with imlunestrant for 4 hours (±S9) and 27 hours (-S9) (study AG12ER.361CRESTITCH.BTL). No statistically significant increase in micronucleus formation was observed in non-activated conditions at 4 hour (≤14 µg/mL) and at 27 hour (≤11.3 µg/mL). However, a significant and dose-dependent increase in micronuclei was observed in the presence of S9, suggesting a potential genotoxic effect. Mechanistic evaluation using CREST staining indicated a mixed clastogenic and aneugenic response.

In an *in vivo* rat bone marrow micronucleus assay, rats were dosed orally at 500, 1000, and 2000 mg/kg/day for two consecutive days (AG12ER.1250211CH.BTL). No appreciable reduction in the polychromatic erythrocyte (PCE) to erythrocyte (EC) ratio was observed, indicating no cytotoxicity. Additionally, no statistically significant increase in micronucleated PCEs was detected. The positive control (cyclophosphamide) confirmed assay validity. Imlunestrant was concluded to be negative for micronucleus induction *in vivo*.

In the *in vivo* Comet Assay, imlunestrant was administered to female rats at doses of 500, 1000, and 2000 mg/kg/day for two consecutive days, with comet assay evaluation in liver and duodenum (Study 130-1137). Exposure in the models used for *in vivo* genotoxicity assessment was demonstrated by a non-GLP toxicokinetic study replicating the *in vivo* assay conditions (Study 8451175), and selection of rat liver and duodenum for the Comet assay because these tissues are highly exposed to imlunestrant-related material in rats. No statistically significant increases in % tail intensity were observed at any dose level, and no increase in Comet "clouds" was noted. The assay controls performed as expected, confirming test validity. Imlunestrant was considered negative for DNA strand breaks in liver and duodenum.

2.5.4.4. Carcinogenicity

According to the ICH S9 Guideline, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer. Nevertheless, a 6-month carcinogenicity study in transgenic rasH2 mouse was conducted to support possible extensions to other indications.

Hemizygous transgenic rasH2 mice received daily administration of imlunestrant at 5, 375, 750 and 1500 mg/kg/day via oral gavage. Due to deteriorating general clinical condition, animals at 1500 mg/kg were terminated between days 6 and 16 and no histopathological evaluation was performed. Thus, the exact nature of the morbidity remained undetermined. There were no effects on mortality or survival rate at 750 mg/kg/day. An increase in the incidence and/or severity of neoplastic and proliferative changes were observed in the ovary of females given ≥ 5 mg/kg/day. These changes included benign and malignant granulosa cell tumours, mixed sex cord stromal tumours, hypertrophy/hyperplasia of the stromal cells and hyperplasia of granulosa cells. Non-neoplastic

proliferative changes were noted in the testis at all doses (Leydig cell hypertrophy/hyperplasia) and in the stomach in both sexes at ≥ 375 mg/kg/day (squamous mucosa hyperplasia).

2.5.4.5. Reproductive and developmental toxicity

Table 5 Reproductive and developmental toxicity studies

Study details Species Treatment period Route GLP status (Study ID)	**No:Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure[A]**		**Major (alt salient) findings & NOAEL**
			C_{max} ng/ml	$AUC_{0\text{-}24h}$ ng*h/ml	
Embryo-fetal toxicity studies (NOAELs highlighted)					
Rat (Sprague Dawley) GD 6-17 PO GLP (9001840)	Main: 10F TK: 4-12F	0	-	-	<u>F_0 dams:</u> *≥0.3 mg/kg:* ↓ food intake; enlarged uterus. *≥3 mg/kg:* ↓ body weight; fluid accumulation in uterus; thick uterus; discoloration of uterus. *=30 mg/kg:* cysts in ovaries; ↑ preimplantation loss. <u>F1 litters:</u> *≥0.3 mg/kg:* ↓ live fetuses; ↑ total, early and late resorptions. *≥3 mg/kg:* ↑ postimplantation loss; external malformations (subcutis, face, head/neck, limb, mouth, paw, tail), visceral malformations (brain, mouth), skeletal malformations (skull), external variations (subcutis), visceral variation (brain) **F_0 NOAEL not determined** **F_1 NOAEL not determined**
		0.3	9	180	
		3	116	2180	
		30	902	15600	

[A] Mean C_{max} and $AUC_{0\text{-}24h}$ of female animals on Gestational Day 17.

2.5.4.6. Toxicokinetic data

See section 2.5.3. Pharmacokinetics.

2.5.4.7. Local Tolerance

Imlunestrant is intended to be administered orally. The assessment of local tolerance to the GI tract is covered in the repeat-dose toxicity studies.

2.5.4.8. Other toxicity studies

<u>Immunotoxicity:</u>

Immunotoxicity was not evaluated in dedicated studies. Immune effects were evaluated in repeat-dose studies and included WBC count, histopathology, immunophenotyping (blood, spleen, thymus in rats; blood in monkeys) and T-cell dependent antibody response (TDAR) analysis.

Across rat studies, female WBC counts were dose-dependently increased reaching significance at 30 mg/kg in the 3-months study. In males, WBC counts were unaffected at low, but increased at higher doses across studies. No imlunestrant-related changes in WBC counts were observed in monkeys.

In rats, imlunestrant induced shifts in lymphocyte populations in blood, spleen and thymus. In monkeys, imlunestrant did not induce any meaningful changes in TLC or relative percentage of lymphocyte populations. Immunophenotyping was in general challenged by drug-induced autofluorescence especially at high doses in both species.

In rats, dose-dependent reversible cytoplasmic vacuolization of circulating lymphocytes was observed from 60 mg/kg across repeat-dose studies. Further, vacuolization of macrophages was observed in multiple tissues including the small intestinal wall but was limited to minimal occurrence in mesenteric lymph nodes and lungs at low doses. In monkeys, vacuolization of macrophages was also observed in multiple and similar tissues as in rats; spleen, lungs and mandibular lymph nodes (600 mg/kg), in small intestinal lamina propria (≥150 mg/kg) and in mesenteric lymph nodes at low dose levels (≥15 mg/kg).

In rats, reversible decreases in cellularity and in some cases necrosis of lymphocytes/single cell necrosis was observed in lymphoid tissues across studies; thymus, spleen, (mandibular/mesenteric) lymph nodes, and GALT. At low doses in the 6-month study, decreases/necrosis were limited to lymph nodes, thymus and spleen. Decreased cellularity was correlated to decreased spleen weight which was significant in males ≥10 mg/kg. In monkeys, splenic decreases in cellularity were observed at all dose levels and were correlated to decreased organ weight in both sexes. Thymus cellularity was decreased at high doses (600 mg/kg), and organ weight and size at the low dose (15 mg/kg), at least in females.

T-cell dependent antibody response (TDAR) was evaluated in satellite animals in 3- and 6- month rat studies and in the 3-month study in monkeys. Rats were challenged once with KLH in the 3-month study versus twice in the 6-month study. Imlunestrant affected T-cell dependent antibody responses across studies but because animals mounted anti-KLH IgM and IgG responses it was concluded that effects on seroconversion did not functionally suppress the immune response and were considered non-adverse. In monkeys, imlunestrant had no effect on immunocompetence confirmed by TDAR.

Impurities:

The specification limit of specified impurities is above the qualification threshold for the drug substance (0.15%) or the drug product (0.2%). The impurities can be qualified considering the dose tested in non-clinical studies relative to clinical levels.

Two impurities were negative in an Ames test, but positive in an *in vitro* micronucleus assay in human TK6 cells.

Phototoxicity:

A GLP-compliant neural red uptake phototoxicity (NRU-PT) assay in BALB/c 3T3 mouse fibroblasts was conducted with imlunestrant tosylate, following OECD Guideline 432 (study 20183318). Imlunestrant tosylate demonstrated phototoxic potential as the photoirritancy factor (PIF=20-25) and mean photo effect (MPE=0.76-0.82) exceeded the thresholds (PIF>5 and MPE>0.15).

Hence, a GLP-compliant *in vivo* study was performed to evaluate the effects of oral administration (QDx4) of imlunestrant tosylate on eyes and skin in pigmented rats (study 20405711). Imlunestrant tosylate was considered phototoxic to skin at 1000 mg/kg/day (ICH S10 maximal dose), though the

observed redness was minimal (grade 1). No ocular effects were observed. The NOEL for phototoxicity was 60 mg/kg/day, which was associated with Cmax of 1540 ng/mL. The safety margin is estimated to be ~9x as compared to the human steady state Cmax of 164 ng/mL at a dosage of 400 mg QD.

Dermal and ocular irritation:

Two GLP-compliant irritation studies were done. In the first study (Study 20183102), imlunestrant applied dermally at 2000 mg/kg to rats caused only limited irritation during the 14 days observation period. Most animals showed no or barely perceptible erythema. Minimal eschar and skin flaking was incidentally observed. In the second study which followed OECD Guideline 437 (study 19AD29.350055), imlunestrant applied topically at 20% w/v to isolated bovine corneas did not cause any irritation.

2.5.5. Ecotoxicity/environmental risk assessment

Table 6 Summary of main study results

Substance (INN/Invented Name): imlunestrant			
CAS-number (if available): 2408840-26-4 (free base)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	3.29 at pH 5 5.13 at pH 7 5.55 at pH 9	Potential PBT: Y
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	5.55	
	BCF	429, 291 L/kg_{ww}	not B
Persistence	DT50 Values are derived from the OECD 308 or OECD 307 study below and have been recalculated to 12°C	$DT_{50,\ soil}$ 429-658 d $DT_{50,\ sediment}$ >1000 d	vP
Toxicity	NOEC	0.43 µg/L	T
PBT-statement :	imlunestrant is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw,\ default}$	2.0	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)	imlunestrant is an endocrine active substance		Y
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	S_w = 39.9 mg·L^{-1} S_w = 1.58 mg·L^{-1} S_w = 0.587 mg·L^{-1}	pH 5 pH 7 pH 9
Adsorption-Desorption soil 1=silty clay loam soil 2=sandy loam soil 3=loamy sand soil 4=clay loam Sludge 1 = BAS Sludge 2 = DAS Sludge 3 = EAS	OECD 106	$K_{FOC,\ soil\ 1}$ = 2.98x10^5 L/kg_{oc} $K_{FOC,\ soil\ 2}$ = 1.38x10^6 L/kg_{oc} $K_{FOC,\ soil\ 3}$ = 2.38x10^6 L/kg_{oc} $K_{FOC,\ soil\ 3}$ = 1.82x10^6 L/kg_{oc} $K_{FOC,\ sludge\ 1}$ = 2.66x10^4 L/kg_{oc} $K_{FOC,\ sludge\ 2}$ = 3.15x10^4 L/kg_{oc} $K_{FOC,\ sludge\ 3}$ = 3.08x10^4 L/kg_{oc}	List all values
Biodegradation in activated sludge	OECD 314B	k_2 = 0.004731 d^{-1} DT_{50} = 147 d	At 20.7°C
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 2.4/3.8 d $DT_{50,\ sediment}$ = 501/>1000 d	DT_{50}s at 20°C 1 / 2

Sediment 1 = silty clay loam Sediment 2 = loamy sand		$DT_{50,\ total\ system}$ = >1000/>1000 d CO_2 = 0.26/0.61% NER = 31.0/14.7% $NER_{type1\ (reversible\ bound)}$ = 10.9/5.6% Transformation products >10% = N			at test end, sed 1/2 at test end, sed 1/2 at test end, sed 1/2
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	EC10	3.6	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC EC10	1.06 31.7	µg/L µg/L	reproduction reproduction
Fish, Extended one generation reproduction test/*P. promelas*	None, but following OECD 240	NOEC	0.43	µg/L	body weight F1 males
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000 *	mg/L	respiration
Phase IIb Studies					
Bioaccumulation/ *L. macrochirus*	OECD 305	BCF_{KgL} BCF_{KgL}	429 291	L/kg_{ww} L/kg_{ww}	%lipids: 5% %lipids: 5%
Aerobic and anaerobic transformation in soil Soil 1 = sandy loam Soil 2 = sandy clay loam Soil 3 = clay loam Soil 4 = loam	OECD 307	$DT50_{soil1}$ =202 d $DT50_{soil2}$ = 200 d $DT50_{soil3}$ = 310 d $DT50_{soil4}$ = 272 d CO_2 (max) = 0.68% NER (max) = 47% Transformation products >10% = N			 at test end, soil1 at test end, soil2
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	⩾761	mg/kg_{dw}	N transformation
Terrestrial Plants, Growth Test/ *A. cepa* *G. max* *H. annuus* *L. perenne* *R. sativus* *S. lycopersicum*	OECD 208	 NOEC NOEC NOEC NOEC NOEC NOEC	 ≥1000 ≥1000 111 333 333 111	 mg/kg_{dw} mg/kg_{dw} mg/kg_{dw} mg/kg_{dw} mg/kg_{dw} mg/kg_{dw}	no effects on height, weight, survival and germination for *A. cepa* and *G. max* emergence height, weight height, weight height, weight, germination
Collembola, Reproduction Test/*F. candida*	OECD 232/ISO 11267	NOEC	309	mg/kg_{dw}	reproduction
Sediment dwelling organism/*C. riparius*	OECD 218	NOEC EC10	68 131	mg/kg_{dw} mg/kg_{dw}	emergence, reproduction ♂ emergence
Sediment dwelling organism/*L. variegatus*	OECD 225	EC10 NOEC	110 139	mg/kg_{dw} mg/kg_{dw}	nr of living worms
Sediment dwelling organism/*H. azteca*	OPPTS 850.1770	NOEC	283	mg/kg_{dw}	survival, growth, reproduction

* In the ERA, the water solubility of imlunestrant at pH 7 was used as 'NOEC', since the test outcome highly exceeds the water solubility.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The Applicant conducted several *in vitro* and *in vivo* studies to assess the primary PD of imlunestrant. Cellular and murine xenograft studies were conducted in oestrogen receptor (ER)-positive breast cancer models, with or without oestrogen receptor gene 1 (*ESR1*) mutations, along with an evaluation of imlunestrant's functional additivity or synergy with the CDK4/6 inhibitor abemaciclib. These primary pharmacology studies are, therefore, relevant for the indicated patient populations.

In vitro, high binding affinity was shown to not only WT ERα and mutant ERα (Y537S), but also to ERβ. Upon request, the Applicant provided *in vitro* data showing that the binding of imlunestrant to Erβ has an antagonising as well as stabilising effect. Comparable effects on ERβ have been shown with approved SERDs including antagonist potency of fulvestrant and ERβ stabilisation by elacestrant. The functional consequences of these effects are unknown.

Imlunestrant was shown to be a potent inducer of ERα degradation, leading to reduced expression of transcriptional targets and, ultimately, inhibition of *in vitro* cell proliferation at clinically relevant concentrations in both *ESR1* WT and *ESR1* mutant cells. In cells with the *ESR1* D538G mutation, which is the most common clinical mutation, imlunestrant degraded ER to a lesser degree and did not inhibit proliferation.

It was shown that imlunestrant can act synergistically when combined with a CDK4/6 inhibitor in naïve WT *ESR1* cell lines, though it was not determined whether this combination has efficacy in *ESR1* mutated breast cancer cells which have become insensitive to treatment with other SERDs and/or CDK4/6 inhibitors. Nevertheless, since anti-tumour activity of imlunestrant alone and in combination with abemaciclib was studied *in vivo*, no further *in vitro* investigation is necessary.

Studies with the M1 and M2 metabolites of imlunestrant, which have relevant exposure in animal species and human (see section 2.5.3.) , indicated that clinically relevant pharmacological activity of these metabolites is not expected.

In vivo, imlunestrant caused tumour growth inhibition or even regression in *ESR1* WT and *ESR1* mutant (Y537S, E380Q, D538G) models of human breast cancer. Combination with abemaciclib enhanced efficacy, even in resistant models (i.e. resistant or reduced sensitivity to fulvestrant or palbociclib). PK/PD modelling was used to determine TEC80 (threshold effective concentration) in plasma and tumour for human dose prediction calculations, though the TEC80 and the number of patients reaching the TEC80 are not clinically relevant, given that there appears to be no correlation between the concentration of imlunestrant and progression-free survival (see section 2.6. Clinical aspects).

The selectivity of imlunestrant as antagonist of ER was shown over other nuclear hormone receptors, 33 kinases and 8 human GPCRs. Overall, the evaluation of the secondary PD of imlunestrant is considered rather limited given that off-target screens generally consist of a broad panel of 100+ targets, including ion channels, enzymes, and receptors. This leaves uncertainties about potential off-targets that have not been investigated.

Upon request, the Applicant provided, during the evaluation, information on the potential effects of imlunestrant on bone and brain given the known role of ER in these tissues. Bone architecture was not affected in the toxicology studies and no clinical association was found between imlunestrant and bone disorders in treated patients. Microscopic findings in the pars distalis of the pituitary of imlunestrant-treated rats were considered a result of ER inhibition and a secondary effect of hormonal disruption in the hypothalamus-pituitary-gonadal axis. Clinically, however, there were no TEAEs indicative of

hypothalamus and pituitary disorders caused by imlunestrant. Taken together, the potential for on-target, off-tissue effects of imlunestrant in patients can be considered low.

In vitro safety pharmacology assessments did not identify any concerns. In line with the ICH S9 Guideline, *in vivo* safety pharmacology assessments were incorporated into the GLP repeat-dose toxicity studies. There were no toxicity findings related to cardiovascular, central nervous or respiratory systems.

Pharmacokinetics

The Applicant submitted a comprehensive package of non-clinical pharmacokinetic studies. Pharmacokinetic and toxicokinetic data is available for mice, rats and monkeys. In none of the species sex differences are observed. Between species there appear to be some differences in imlunestrant kinetics. First, the bioavailability is moderate in mice (44% at 10 mg/kg PO), dose dependent in rats (32% at 30 mg/kg PO and 62% at 3 mg/kg PO) and low in monkeys (8.4% at 30 mg/kg PO, 8% at 3 mg/kg PO). In humans, at therapeutic dose, the bioavailability is approx. 10%. Elimination rates also differ, being relatively fast in monkeys, moderate in rats and slow in humans and mice, although there appears to be also some variability between the elimination half-life found in different studies within the same species.

Other differences are observed in distribution, where distribution in rats is more extensive than in mice. There are no data from distribution in monkeys. Furthermore, the free fraction of imlunestrant is slightly higher in human plasma (0.11%) than in rat plasma (0.10%) and monkey plasma (0.08%). The ratio between free fraction in human plasma versus monkey plasma is 1.38-fold. This should be considered when analysing the results and exposure multiples from the toxicological studies. Metabolism profiles were studied in detail in rats only, where M1 was found as the main metabolite in males and females. M1 is also a main metabolite in humans. Metabolite M2 was only found in substantial amounts in monkeys and was almost absent in rat plasma. Excretion was only studied in rats and humans and was found to be very similar. The majority of the dose is excreted in faeces, with only a very small percentage (<0.5%) excreted in urine.

Overall, it can be concluded that rats and monkeys are suitable non-clinical species for the safety assessment of imlunestrant. The pharmaco-and toxicokinetics are similar enough to human pharmacokinetics to be representative.

Toxicology

Repeat-dose studies were conducted in rat and monkey. The primary target organs in both rat and monkey were female and male reproductive tissues (i.e. ovaries, uterus, cervix, vagina, epididymis and testis) and the mammary gland. In general, all these findings were observed from the lowest tested dose, demonstrated dose-dependent incidence and severity, are in line with the pharmacology of imlunestrant and other SERDs, and were (partially) reversible.

In rats, sporadic changes in organ weight of the pituitary and adrenal glands were observed. Decreased adrenal gland weights were correlated to vacuolization and hypertrophy in males and atrophy in females. Non-reversible decreases in pituitary gland weights were correlated to hypertrophy in pars distalis in females. Decreases in pituitary gland weights were observed at all dose levels in both sexes but appeared most evident in females. Histopathological findings were observed ≥10 mg/kg. The mechanism of the observed changes remains unknown, but is likely related to the pharmacology of imlunestrant. Similar effects have been reported for other SERDs. No organ weight or histopathological changes in endocrine glands were observed in monkeys. Overall, the provided data support a low clinical risk of serious imlunestrant-related adverse effects on the pituitary or adrenal glands.

The imlunestrant-related effects on pituitary and adrenal glands are adequately reflected in section 5.3 of the SmPC with exposure margins where it states that non-adverse atrophy or hypertrophy of the adrenal cortex, which occurred at exposures at least 4-times greater than human exposure (AUC_{0-24}) at 400 mg.

Across species, clinical symptoms were primarily related to the gastrointestinal (GI) tract. Similar adverse drug reactions related to the GI tract were observed in patients which is reflected in the SmPC. Tissue distribution studies showed high concentrations of imlunestrant in GI tract tissues in rats. Findings of mononuclear infiltration (monkeys only), gastric erosion and ulceration, haemorrhage, dark foci, hyperplasia, macrophage vacuolation in the intestine and mesenteric lymph nodes) were observed. Gastric effects were in general non-dose-dependent, of minimal severity and may be attributed to local irritation caused by high oral drug loads via gavage, but the exact mechanism remains unknown. In rats, findings were observed across groups including controls, and occurred at ≥ 4-fold higher exposure than expected in humans suggesting low clinical risk. In monkeys, gastric dark foci and minimal haemorrhage were reported without any meaningful pattern in dose-dependency or affected sex, but at exposure levels below clinical (~0.75-fold). Findings were absent in controls, suggesting an imlunestrant-related effect. However, the literature indicates that similar gastric findings are common spontaneous lesions in the species used. The minimal severity, non-progressive nature, and lack of clear dose-dependency do not support an imlunestrant-related origin, and the non-clinical findings are likely unrelated to the clinically observed GI bleeding.

Urinary obstruction led to mortality in the high dose female animals of the 6-month rat study. These animals had bacterial pyeolonephritis in the kidney (inflammation) and cystitis (inflammation) with transitional hyperplasia, dilatation and haemorrhage in the urinary bladder, extending to the vagina and cervix. Transitional cell hyperplasia was also observed in the urinary bladder of other female rats at all dose levels, and in male rats treated with 60 and 150 mg/kg/day. This finding was dose-dependent in incidence and severity, and partially reversible upon recovery. Since imlunestrant is primarily excreted via the faeces and not via urine (<1 %), this is likely not related to local retention of irritating materials. In the 6-month transgenic ras H2 mouse carcinogenicity study, inflammation was noted in the urinary bladder, often accompanied with urothelial hyperplasia. Although the findings were not observed in concurrent historical control data from the test facility, the lack of dose-dependency does not indicate a clear relation to imlunestrant treatment. In addition, these hyperplasia findings did not progress to neoplasms in the transgenic mice carcinogenicity study. Altogether, the human relevance of transitional cell hyperplasia in the urinary bladder of the rat remains uncertain. Although transitional cell hyperplasia in the urinary bladder is not observed with other SERDs, the potential risk for secondary malignancies is unlikely to negatively impact the B/R profile of imlunestrant, considering the prognosis of the current patient population. The findings are adequately described in SmPC section 5.3.

Limited to rats, other treatment-related histopathological findings in the urinary tract were limited to the kidney and included tubular degeneration/regeneration, pelvis inflammation, hyaline casts and retrograde nephropathy glomerulopathy. Findings were mostly dose-dependent in incidence and severity, likely attributed to imlunestrant-induced modulation of oestrogenic activity, were reversible and did in general not correlate with any urinary function parameters. No aberrant increases in creatinine were reported in the clinical trials. Considering this, the risk of renal toxicity in patients receiving the recommended dose of 400 mg/day is low. The renal histopathological findings occurring at the lowest dose level (tubular degeneration and inflammation of the renal pelvis) are reflected in section 5.3 of the SmPC with exposure margins.

In monkeys, slight increases in liver enzymes were observed without microscopic correlates at clinically relevant exposure margins. Rats also demonstrated similar findings, albeit mostly at exposure levels

far exceeding clinical levels. Increases in liver enzymes are reported in humans, and are considered treatment-related.

In the 6-month rat study, lens degeneration and increased incidence of cortical lens opacity were observed in rats following chronic administration at multiple dose levels. Cortical lens opacity was not fully reversible after recovery. However, since there were no ocular findings in monkeys, nor where there any adverse effects in humans, the clinical relevance is likely low.

The Applicant provided a thorough evaluation of haematologic, lymphoid, and coagulation effects, including consideration of sex differences. Although considered drug-related, findings were in general minimal to mild in severity and non-dose-dependent. Based on a weight-of-evidence approach, no relevant safety concerns were identified. The observed sex differences were plausibly attributed to oestrogen-related mechanisms, including differences in circulating oestrogen levels and tissue-specific expression of oestrogen receptors between males and females.

Lymphoid cellularity was variably affected in the spleen and thymus across species. Consistent decreases were observed in the thymus of both species and in the spleen of monkeys across studies, whereas effects in the rat spleen appeared variable, influenced by sex and treatment duration.

Based on the provided evidence, a direct depressive effect of imlunestrant on lymphoid cellularity, at least in the spleen, of monkeys cannot be ruled out. Nevertheless, the findings did not correlate with decreased circulating lymphocyte levels or signs of immunosuppression evaluated by TDAR. Considering also the minimal severity, it is agreed that the findings in monkeys are unlikely to represent a clinically relevant safety risk to the intended patient population.

In female rats, increased splenic lymphoid cellularity of low incidence and severity was observed at all dose levels. The underlying mechanism remains unclear. Although potentially imlunestrant-related, increases were limited to rats, were of low severity, and occurred at exposure levels associated with a 10-fold safety margin relative to expected clinical exposure. Based on these considerations, the findings are considered species-specific and of limited clinical concern at the recommended clinical dose of imlunestrant.

Decreased lymphoid cellularity and single-cell necrosis in the spleen and thymus generally correlated with reduced organ weights. The underlying mechanism remains unclear. However, the findings are considered likely related to an exaggerated on-target off-tissue pharmacological effect of imlunestrant, involving antagonism and degradation of oestrogen receptors in oestrogen-responsive tissues, including lymphoid organs such as the spleen and thymus.

Tissue immunophenotyping of spleen and thymus was performed in rats but not in monkeys. In rats, increased lymphocyte counts in spleen and thymus were observed, mainly in females, with splenic changes showing some dose-related trend but occurring only at exposures ≥17-fold above human levels. These shifts were largely reversible and did not impair immune function (TDAR preserved). In monkeys, no concerning WBC changes were noted; neutrophil increases were mild, non-significant, and possibly stress-related, with no histopathological inflammation. Overall, findings were inconsistent across species, seen at exposure margins well above those expected clinically, and are considered of low clinical relevance. Although transiently increased in rats, WBC changes were considered of no clinical concern across species. In monkeys, neutrophil increases were non-significant, possibly stress-related, and with no histopathological findings of inflammation.

Overall, imlunestrant appears to exert a degree of immunostimulatory activity in female rats, but as findings were inconsistent across species, seen at exposure margins well above those expected clinically, they are considered of low clinical relevance.

Platelet counts were decreased in rats across studies while inconsistent increases were observed in prothrombin time. Increases in females were observed at all doses across studies and in males only after 3 months. Prothrombin time changes were limited to rats; however, similar platelet decreases were noted across dose levels in male monkeys and inconsistently in females in the 3-month study. Although it cannot be excluded that the observed effects may be related to imlunestrant, changes were of small magnitude, non-dose-dependent, and reversible across species. Therefore, it is considered highly unlikely that the observed changes in platelet count and prothrombin time pose a clinically relevant risk to patients at the recommended dose of imlunestrant.

Imlunestrant causes reversible vacuolation due to phospholipidosis from drug accumulation in lysosomes. Findings were non-adverse, organ-limited, and of low clinical risk, though observed in rats and monkeys at exposures near clinical levels. This is adequately reflected in SmPC section 5.3.

Imlunestrant demonstrated no mutagenic potential in the Ames test and no genotoxic effects in *in vivo* assays (micronucleus and Comet assay). However, a positive response was observed in the *in vitro* micronucleus assay in the presence of metabolic activation, with evidence of both clastogenic and aneugenic effects. The absence of *in vivo* genotoxicity suggests that the *in vitro* findings may not be biologically relevant at clinically relevant exposures. Overall, imlunestrant is not considered genotoxic under the conditions tested. This is reflected in SmPC section 5.3.

According to ICH S9 Guideline, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer. Nevertheless, a 6-month carcinogenicity study in transgenic rasH2 mouse was conducted to support possible extensions to other indications. Imlunestrant, given at oral doses of 5, 375, or 750 mg/kg, caused an increased incidence of benign and malignant sex cord stromal tumours (granulosa and mixed cell) in the ovaries at all dose levels. These doses correspond to 2-, 32-, and 41-times the human AUC at the recommended dose. Induction of such tumours is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-oestrogen. This is adequately reflected in SmPC section 5.3.

No dedicated fertility study was conducted, and the monkeys used in the repeat-dose toxicity studies were sexually immature, precluding adequate assessment of potential effects on the male reproductive organs. Based on several pharmacology-related findings in the reproductive tract in the repeat-dose toxicity studies and the mode of action of imlunestrant, adverse effects on the female and male reproductive system are anticipated, and this is adequately reflected in SmPC section 4.6. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Inluriyo. Several pharmacology-related findings in the reproductive tract were observed in the repeat-dose toxicity studies.

Administration of imlunestrant to pregnant rats during the period of organogenesis led to maternal toxicity, early delivery, embryo lethality, and teratogenic foetal effects at maternal exposures less than or equal to human therapeutic exposure. These findings were all related to the pharmacological action of imlunestrant and are in line with findings for other SERDs, and are adequately reflected in the SmPC sections 5.3 and 4.6, where it is highlighted that although there are no data from the use of imlunestrant in pregnant women, imlunestrant can cause foetal harm when administered to pregnant women and should not be used during pregnancy and in women of childbearing potential not using contraception. If pregnancy occurs while taking Inluriyo, the patient must be informed of the potential hazard to the foetus and potential risk of miscarriage.

No early embryonic development study, pre- and postnatal development study or juvenile toxicity study was conducted. This is in line with the recommendations for an indication falling under the ICH S9 Guideline and therefore agreed. However, considering that the intended patient population includes pre- and perimenopausal women, and that the transfer of imlunestrant into the milk has not been investigated and cannot be excluded, a contraindication during breastfeeding is considered

appropriate. This approach aligns with warnings for other approved SERDs indicated for both pre- and perimenopausal women, such as Faslodex (fulvestrant). This is adequately reflected in the SmPC sections 4.3, 4.6 and 5.3.

All relevant impurities were adequately qualified in line with ICH Q3A and Q3B guidelines, given that the indication of imlunestrant falls under the ICH S9 Guideline.

Imlunestrant demonstrated phototoxic potential in an *in vitro* neural red uptake phototoxicity (NRU-PT) assay in BALB/c 3T3 mouse fibroblasts. In a subsequent *in vivo* study, imlunestrant was considered phototoxic to skin at 1000 mg/kg/day (ICH S10 maximal dose), though the observed redness was minimal (grade 1). No ocular effects were observed. The NOEL for phototoxicity was 60 mg/kg/day, and the safety margin is estimated to be ~9x as compared to the human steady state C_{max}. Taken together with the lack of accumulation and short-lived exposure in skin, imlunestrant has a minimal clinical phototoxic risk.

Imlunestrant does not cause dermal or ocular irritation.

No dedicated studies to evaluate antigenicity, immunotoxicity, dependence or metabolites were performed. This is agreed.

ERA

Imlunestrant is not PBT nor vPvB.

Considering the above data, imlunestrant is not expected to pose a risk to the STP, surface water, groundwater and sediment compartment based on the prescribed use of imlunestrant. Imlunestrant is not expected to pose a risk to the environment via secondary poisoning.

2.5.7. Conclusion on the non-clinical aspects

The PD findings support imlunestrant's potential benefit for patients with *ESR1* mutations who have progressed on endocrine therapy.

From the pharmacokinetic point of view, the rat and cynomolgus monkey were the most relevant species for non-clinical efficacy and safety studies.

In general, the findings in toxicology studies are related to the pharmacological action. Relevant information has been reflected in section 5.3 of the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

A routine GCP inspection of the EMBER-3 (J2J-OX-JZLC) study was performed at 2 clinical investigator sites in the USA and in Mexico and at the sponsor site in the USA.

Table 7 Tabular overview of clinical studies

Study Identifier	Protocol Title	Number of Participants	Status
Biopharmaceutic and clinical pharmacology studies			
J2J-MC-JZLD	Evaluation of the Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Child-Bearing Potential	82	Completed
J2J-MC-JZLE	An Open-label, Two-part Study of the Disposition and Absolute Bioavailability of [14C]-LY3484356 in Healthy Females of Non-Childbearing Potential	16	Completed
J2J-MC-JZLG	Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment	27	Completed
J2J-MC-JZLI	The Effect of Imlunestrant on CYP2C8, CYP2C19, CYP2D6, P-gp, and BCRP Activity and the Effect of P-gp Inhibition on Imlunestrant Pharmacokinetics in Healthy Women of Non-childbearing Potential	113	Completed
J2J-MC-JZLK	The Effect of Repeat Dosing of Imlunestrant on CYP3A Activity in Healthy Women of Non-childbearing Potential	20	Completed
Phase 1a/1b clinical studies			
J2J-MC-JZLA (EMBER)	EMBER: A Phase 1a/1b Study of LY3484356 Administered as Monotherapy and in Combination with Anticancer Therapies for Patients with ER+ Locally Advanced or Metastatic Breast Cancer and Other Select Non-Breast Cancers	385	Completed
J2J-MC-JZLB (EMBER-2)	EMBER-2: A Phase 1, Open-Label, Preoperative Window Study Evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, HER2-Negative Breast Cancer	87	Completed
J2J-MC-JZLF	A Phase 1 Study of LY3484356 in Chinese Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer	17	Completed
Phase 3 clinical studies			
J2J-OX-JZLC (EMBER-3)	EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy	874	Primary outcome data cutoff : 24 June 2024

Abbreviations: BCRP = breast cancer-resistance protein; CSR = clinical study report; DBL = database lock; ER+ = oestrogen receptor positive; HER2- = human epidermal receptor 2 negative; P-gp = P-glycoprotein.

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
J2J-MC-JZLA (Ember) NCT04188548	Enrolment completed Study initiation: 27-Sep 2019 Phase 1a: Enrolled 81/120 planned Phase 1b: Enrolled 304/380 planned	Open-label, uncontrolled Phase 1a (dose escalation)/1b (dose expansion) study	Phase 1a cohort A1-A6: Imlunestrant 200, 400, 600, 800, or 1200 mg QD orally Phase 1b, 400 mg QD orally, cohort E1-10 as monotherapy or multiple combinations E1 (n=28): imlunestrant + abemaciclib	Mainly ER+, HER2- MBC and 8.6% ER+, EEC Cohort E1 and E3: ER+, HER2- MBC Exclusion criteria: Inflammatory BC, symptomatic central nervous system

			E3 (n=27): imlunestrant Treatment until disease progression, development of unacceptable toxicity, withdrawal of informed consent or other discontinuation criteria as outlined in the protocol	metastasis, carcinomatous meningitis, serious concomitant systemic disorders, or serious cardiac condition
J2J-OX-JZLC (Ember-3) NCT04975308	Enrolment completed Study initiation: 04-Oct 2021 Arm A: Enrolled: 331/320 planned Arm B: Enrolled: 330/320 planned Arm C: Enrolled: 213/220 planned	Open-label, randomized, controlled Phase 3 study	Imlunestrant 400 mg QD orally Fulvestrant 500 mg, IM Exemestane 25 mg QD, orally Abemaciclib 150 mg BID, orally Arm A: Imlunestrant Arm B: Fulvestrant or exemestane (SOC) Arm C: Imlunestrant + Abemaciclib Treatment until disease progression, development of unacceptable toxicity, withdrawal of informed consent or other discontinuation criteria as outlined in the protocol	ER+, HER2- locally advanced or metastatic BC Progression on prior ET with or without CDK4/6i Exclusion criteria: Inflammatory BC, visceral crisis, symptomatic central nervous system metastasis, carcinomatous meningitis, serious concomitant systemic disorders, or serious cardiac condition, eligible for PARP inhibitor

QD: Once every day; BID: Twice daily: IM: Intramuscular; SOC: Standard of care, BC: Breast cancer; PARP: Poly (ADP-ribose) polymerase; ET: Endocrine therapy; ER: Oestrogen receptor; HER2: human epidermal growth factor receptor 2; EEC: Endometroid endometrial cancer

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Imlunestrant is a small molecule indicated for the treatment of oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, oestrogen receptor 1 (*ESR1*)-mutated, advanced or metastatic breast cancer as monotherapy.

Imlunestrant is formulated as 200 mg film-coated tablets. The recommended dose is 400 mg orally, once daily, to be taken at least 2 hours before or 1 hour after food.

The pharmacokinetics of imlunestrant was investigated in 7 Phase 1 studies, 1 Phase 1a/1b study and 1 Phase 3 study. In addition, the Applicant has undertaken a population PK analysis, using data from a food effect/drug interaction study in healthy women, from the Phase 1a/1b study in patients with breast cancer and selected non-breast cancers, from a Phase 1 study in post-menopausal women with breast cancer and from the Phase 3 study in patients with breast cancer.

Population PK analysis

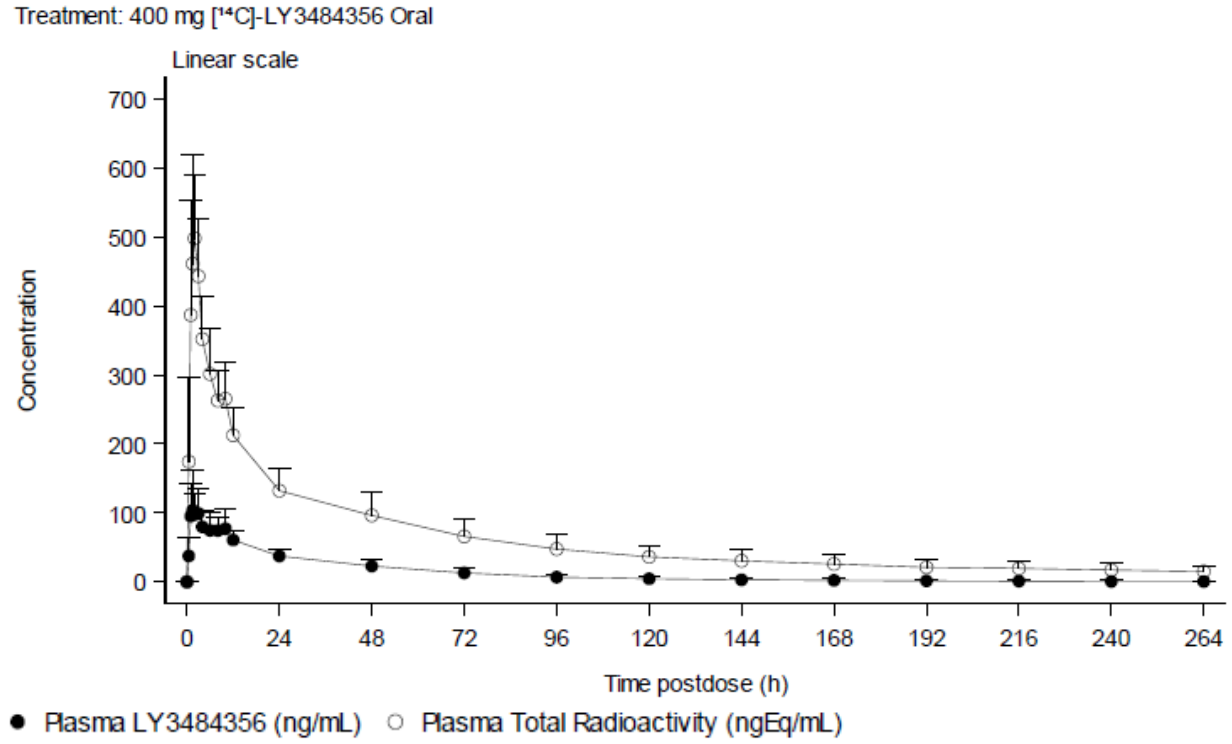
Population PK analysis was performed using a 2-compartment structural model parameterized in terms of CL/F, Vc/F, Vp/F, and Q/F with 3 transit compartments for absorption. Two covariates met the criteria for inclusion in the final model: body weight (effect on CL/F, Q/F, Vc/F, and Vp/F) and study population (effect on Vc/F). The studies JZLA, JZLB, JZLC and JZLD were included in the population PK

analysis. The pop PK population contained data from healthy female participants (n=64), patients with early stage, advanced or metastatic breast cancer (n=914) and patients with endometrioid endometrial cancer EEC (n=72). In total, 6895 evaluable imlunestrant concentrations obtained from 1050 participants were included in the popPK analysis. In total, 514 samples were excluded, of which 300 were BLQ pre-first dose and 18 were deemed outliers.

Absorption

Healthy female subjects received a single oral dose of 400 mg [^{14}C]-imlunestrant containing 100 µCi (administered as oral solution) following an overnight fast of at least 10 hours (study JZLE). Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432 and 456 h after dosing. Both imlunestrant and total radioactivity were absorbed with a median tmax of 2.00 hours. After Cmax, plasma concentrations of imlunestrant declined with a geometric mean $t_{1/2}$ of 33.4 hours. Total radioactivity declined with a geometric $t_{1/2}$ of 110 hours. In the remaining subjects, plasma concentrations of imlunestrant remained quantifiable in all participants until 168 hours post-dose; in 4 participants until 192 hours post-dose, and in 3 participants until 216 hours post-dose. One participant had quantifiable imlunestrant in plasma until 408 hours post-dose. Plasma concentrations of total radioactivity were quantifiable slightly longer than the parent drug; until 264 hours post-dose in all participants, until 384 hours post-dose in 2 participants, and until 480 hours post-dose in 1 participant. The geometric mean plasma imlunestrant:total radioactivity ratio was 0.191, 0.175, and 0.201 for $AUC_{(0\text{-tlast})}$, $AUC_{(0\text{-}\infty)}$, and Cmax, respectively, indicating that the majority of the total radioactivity was due to metabolites of imlunestrant.

Figure 2 Concentration-time relationship of imlunestrant and total radioactivity following a single oral dose of 400 mg [^{14}C]-imlunestrant to healthy female subjects (study J2J-MC-JZLE, part 1) (n=6)r



In study JZLA (EMBER), patients with breast cancer or endometrial cancer were treated with 200, 400, 600, 800 or 1200 mg/day for 28 days. Blood samples were collected on days 1 and 15 pre-dose and at 1, 2, 4, 6, 8 and 24 h post-dose. PK parameters are shown in the table below. Accumulation ratio was 2.59 on day 15 compared to day 1, at a dose of 400 mg/day. The mean (CV %) absolute bioavailability of imlunestrant after a single oral 400 mg dose is 10.5 % (32 %). The median time to reach peak plasma concentration (t_{max}) is approximately 4 hours.

Table 8 PK parameters following single (day 1) and multiple (day 15) oral imlunestrant doses of 200, 400, 600, 800 or 1200 mg daily to cancer patients (study J2J-MC-JZLA)

Day 1										
	200 mg		400 mg		600 mg		800 mg		1200 mg	
	N		N		N		N		N	
T_{max} (h)[a]	21	3.87 (1.83-7.63)	26	3.99 (1.92-5.87)	17	3.83 (1.83-7.57)	22	4.08 (1.83-6)	3	4.15 (3.82-7.7)
C_{max} (ng/mL)	21	35.7 (74)	26	81 (71)	17	90.8 (76)	22	147 (80)	3	285 (78)
$AUC_{(0-\infty)}$ (h*ng/mL)	19	933 (80)	26	2250 (74)	14	3220 (49)	22	3890 (101)	2	5890, 5190
$AUC_{(0-24)}$ (h*ng/mL)	20	443 (72)	26	975 (53)	15	1240 (59)	21	1790 (76)		3120 (16)
CL/F (L/h)	19	214 (80)	26	178 (74)	14	187 (49)	20	206 (101)	2	204, 231
Vz/F (L)	19	7550 (78)	26	7050 (65)	14	8230 (59)	20	7320 (87)	2	5770, 5780
$t_{1/2}$ (h)[b]	19	24.4 (9.34-42.9)	26	27.4 (11.5-509)	14	30.6 (14.3-64.5)	20	24.7 (11.1-256)	2	19.6, 17.3
Day 15										
	200 mg		400 mg		600 mg		800 mg		1200 mg	
	N		N		N		N		N	
T_{max} (h)[a]	19	4.00 (0.92-7.75)	21	4.08 (2.02-7.50)	18	4.19 (1.93-7.63)	15	3.90 (2.03-7.67)	3	6.00 (4.05-7.63)
$C_{max,ss}$ (ng/mL)	19	62.3 (57)	21	164 (47)	18	204 (44)	15	247 (66)	3	253 (20)
AUC_{τ} (h*ng/mL)	14	894 (64)	19	2480 (46)	9	3390 (33)	14	3670 (64)	2	4160, 3220
CL_{ss}/F (L/h)	14	224 (64)	19	161 (46)	9	177 (33)	14	218 (64)	2	289, 372
RA	14	2.57 (31)	19	2.59 (44)	6	2.45 (31)	14	1.92 (41)	2	1.57, 0.887
LI	13	1.26 (33)	19	1.02 (69)	6	0.98 (37)	13	0.854 (61)	1	0.547

Abbreviations: $AUC_{(0-24)}$ = area under the concentration versus time curve from time 0 to 24 hours; AUC_{τ} = area under the concentration versus time curve for the steady-state dosing interval; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from time 0 to infinity; CL/F = apparent clearance; CL_{ss}/F = apparent clearance at steady state; C_{max} = maximum observed concentration; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; CV = coefficient of variation; LI = linearity index, calculated as $AUC_{\tau}/AUC_{(0-\infty),Day\ 1}$; N = number of patients; RA = accumulation ratio, calculated as $AUC_{\tau}/AUC_{(0-24)}$, Day 1; $t_{1/2}$ = elimination half-life; T_{max} = time of maximum concentration; V_z/F = apparent volume of distribution.

[a] Median (range).

[b] Geometric mean (range).

Population PK modelling was used to simulate steady state exposure following doses of 200, 400, 600, 800 or 1200 mg/day. The results are shown in the table below.

Table 9 Simulated steady state exposures to imlunestrant according to the population PK model

Study	Starting Dose (mg QD)	N	$C_{max,ss}$ (ng/mL) [5th, 95th percentile]	$C_{min,ss}$ (ng/mL) [5th, 95th percentile]	$C_{av,ss}$ (ng/mL) [5th, 95th percentile]	$AUC_{0-24,ss}$ (ng*h/mL) [5th, 95th percentile]
JZLA	200	21	62.9 (50)	30.4 (63)	43.6 (54)	1040 (54)
	400	286	163 (50)	74.1 (58)	109 (50)	2610 (50)
	600	20	179 (39)	91.6 (39)	128 (35)	3060 (35)
	800	43	227 (48)	104 (63)	154 (51)	3700 (51)
	1200	3	296 (18)	124 (27)	196 (11)	4700 (11)
JZLB	200	28	58.6 (41)	30.6 (54)	42.7 (44)	1020 (44)
	400	30	137 (47)	64.9 (54)	94.1 (47)	2260 (47)
	800	28	235 (51)	112 (69)	164 (55)	3930 (55)
JZLC	400	527	141 (45) [70.6, 263]	71.2 (54) [31.0, 151]	100 (46) [48.5, 191]	2400 (46) [1160, 4580]
JZLD	200	20	67.3 (34)	44.7 (44)	55.8 (39)	1320 (38)
	400	44	107 (36)	69.2 (42)	88.2 (39)	2070 (37)
Pooled	200	69	62.3 (42)	34.1 (57)	46.4 (47)	1110 (46)
	400	887	146 (47)	71.8 (54)	102 (47)	2440 (47)
	600	20	179 (39)	91.6 (39)	128 (35)	3060 (35)
	800	71	230 (49)	107 (65)	158 (53)	3790 (52)
	1200	3	296 (18)	124 (27)	196 (11)	4700 (11)

Abbreviations: $AUC_{0-24,ss}$ = area under the concentration versus time curve from hour 0 to 24 hours postdose at steady state; $C_{av,ss}$ = average drug concentration under steady state conditions during multiple dosing; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; $C_{min,ss}$ = minimum concentration during a dosing interval at steady state; CV% = percent coefficient of variation; N = number of participants; QD = once daily.

The solubility of imlunestrant in aqueous media is low.

Absolute bioavailability

Healthy female participants of nonchildbearing potential (n=8) received a single oral dose of 400 mg imlunestrant as 2 × 200 mg tablets followed 4 hours later by a single IV dose of <100 µg of [^{14}C]-imlunestrant containing 1 µCi of radioactivity microtracer. The study was performed under fasting conditions. Actual doses of [^{14}C]-LY3484356 ranged from 44.55 to 45.95 µg. Blood samples were collected pre-dose and at 0.5, 1, 2, 4.08, 4.25, 4.33, 4.5, 4,75, 5, 6, 7, 8, 10, 12, 14, 16, 28, 52, 76, 100, 124, 148, 172, 196 h after dosing (study JZLE). Absolute bioavailability based on $AUC_{(0-\infty)}$ was 10.5%.

Bioequivalence

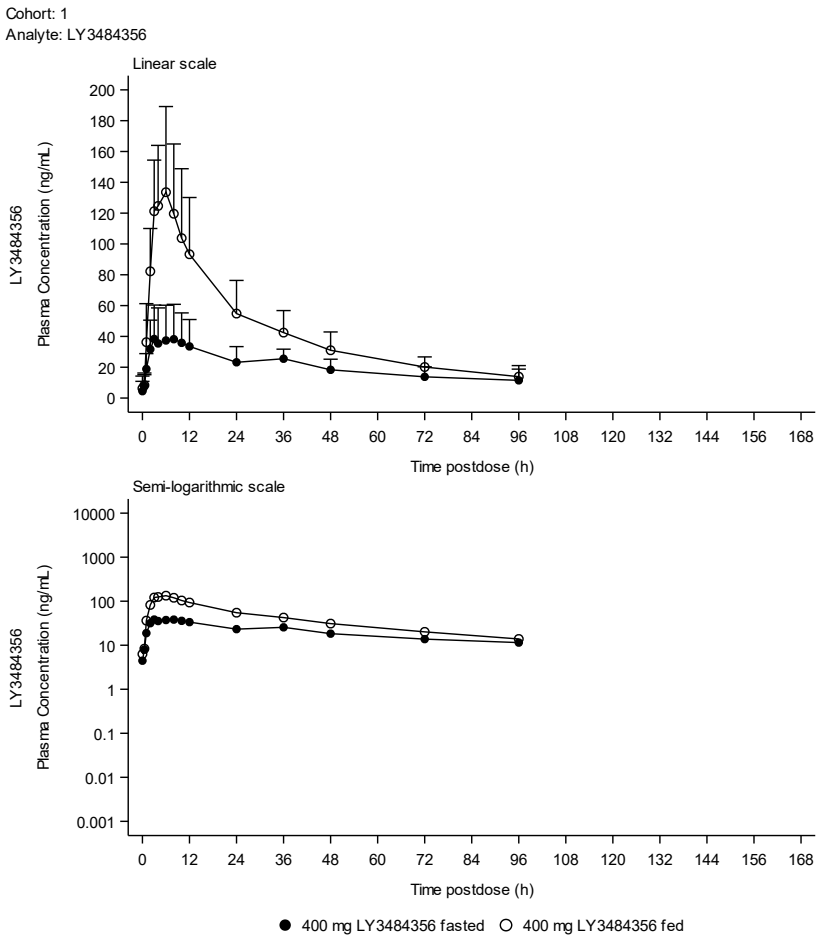
Initial Phase 1 clinical studies were conducted using neat drug substance filled into capsules (C1 capsule formulation, 50-mg strength) and drug substance blended capsules (C2 capsule formulation, 100-mg strength). To allow for a higher strength, 200 mg, while providing a smaller dosage form for better patient experience, a tablet formulation was developed (T1 tablet formulation, 200-mg strength). The T1 tablet formulation consists of imlunestrant tosylate, microcrystalline cellulose, hydroxypropyl cellulose, and croscarmellose sodium and magnesium stearate, and compressed into tablets with white film coating. T1 tablets were used subsequently in Phase 1 and exclusively in Phase 3 studies and represent the commercial formulation.

A popPK analysis was performed to evaluate the effect of capsule formulations (C1 and C2) and T1 tablet formulation on the PK of imlunestrant. In the popPK analysis, there were 64 subjects who received C1 and C2 capsule formulation and 982 subjects who received T1 tablet formulation. In the pop PK database the formulation was missing for 4 subjects. There was no statistically significant effect of formulation on the bioavailability and the absorption rate of imlunestrant.

Influence of food

To study the effect of a low fat meal on the PK of imlunestrant, healthy female participants (n=8) were randomized (1:1) in a 2-period crossover design to 1 of 2 treatment sequences (fasted/fed or fed/fasted) on Day 1 of Treatment Period 1 (study JZLD). The low-fat meal is reported to be relevant for the population of oncology patients. A single oral 400-mg dose of imlunestrant (2 × 200 mg tablets) was administered on Day 1 of Treatment Period 1 and Treatment Period 2, with a washout period of 4 days between doses of imlunestrant. PK parameters were calculated using non-compartmental procedures (Phoenix WinNonlin Version 8.1.1). Statistical analysis was performed on log-transformed Cmax, $AUC_{(0\text{-tlast})}$, and $AUC_{(0\text{-}\infty)}$ using a linear mixed-effects model with period, sequence, and treatment as fixed effects and participant as a random effect. The exposure was higher in the fed state than in the fasted state (AUC is approximately 2-fold and Cmax is nearly 4-fold) (see figure and table below). Supported by the low-fat meal studied in study JZLD, administration of imlunestrant 400 mg with a low-fat meal (approximately 400 - 500 calories with 100 – 125 calories from fat) increased C_{max} by 3.55-fold and $AUC_{(0\text{-}\infty)}$ by 2.04-fold compared to fasted administration. Imlunestrant exposures in the presence of a high-fat meal are unknown.

Figure 3 Mean plasma concentration profile of imlunestrant dosed in healthy female volunteers (n=8) in fasted and fed state (study JZLD)



Mean concentration values are plotted using nominal sampling times and only presented when at least 2/3 of the values are present and within time window

Status of Program: Production

Program Location: /cvn/projects/prj/ecb/programs/000000215173/dev/figures/f_pkc.sas

Date/Time Report Produced: 08NOV2022 6:58

Table 10 Effect of food on the PK parameters of imlunestrant (geometric mean + CV%; tmax median + minimum and maximum) in healthy female volunteers (n=8) (study JZLD)

Food state	$AUC_{(0\text{-tlast})}$	$AUC_{(0\text{-}\infty)}$	Cmax	Tmax
	ng.h/mL	ng.h/mL	ng/mL	h
Fasted	1830 (43%)	1810 (59%)	37.2 (51%)	8.0 (3.0-35.8)
Fed	3900 (36%)	4350 (39%)	143 (28%)	3.0 (2.0–8.0)
Ratio fed/fasted (90% CI)	1.99 (1.67-2.36)	2.04 (1.41-2.94)	3.55 (2.83-4.45)	-

Distribution

In plasma samples collected in the hepatic impairment study (study JZLG), following a dose of 400 mg, protein binding of imlunestrant ranged 99.93% to 99.96% for all participants and all timepoints. The blood to plasma ratio is reported to be approximately 0.99. In study JZLE, Vss/F in healthy subjects following a single oral dose of 400 mg was 5360 L. In the bioavailability part of study JZLE, Vss/F following a single oral dose of 400 mg was 11900 L. Based on the popPK analysis, the predicted Vc/F of imlunestrant in patients with locally advanced or metastatic breast cancer was 4310 L and Vp/F was 2280 L. In healthy subjects, predicted Vc/F was 8120 L and Vp/F 2280 L. In tumour samples from breast cancer patients, collected at the time of diagnosis and at the time of scheduled surgery or biopsy, imlunestrant concentrations increased with dose. In a population pharmacokinetic analysis, the mean (CV %) apparent central volume of distribution of imlunestrant is 4 310 L (69 %) in patients with advanced or metastatic breast cancer.

Elimination

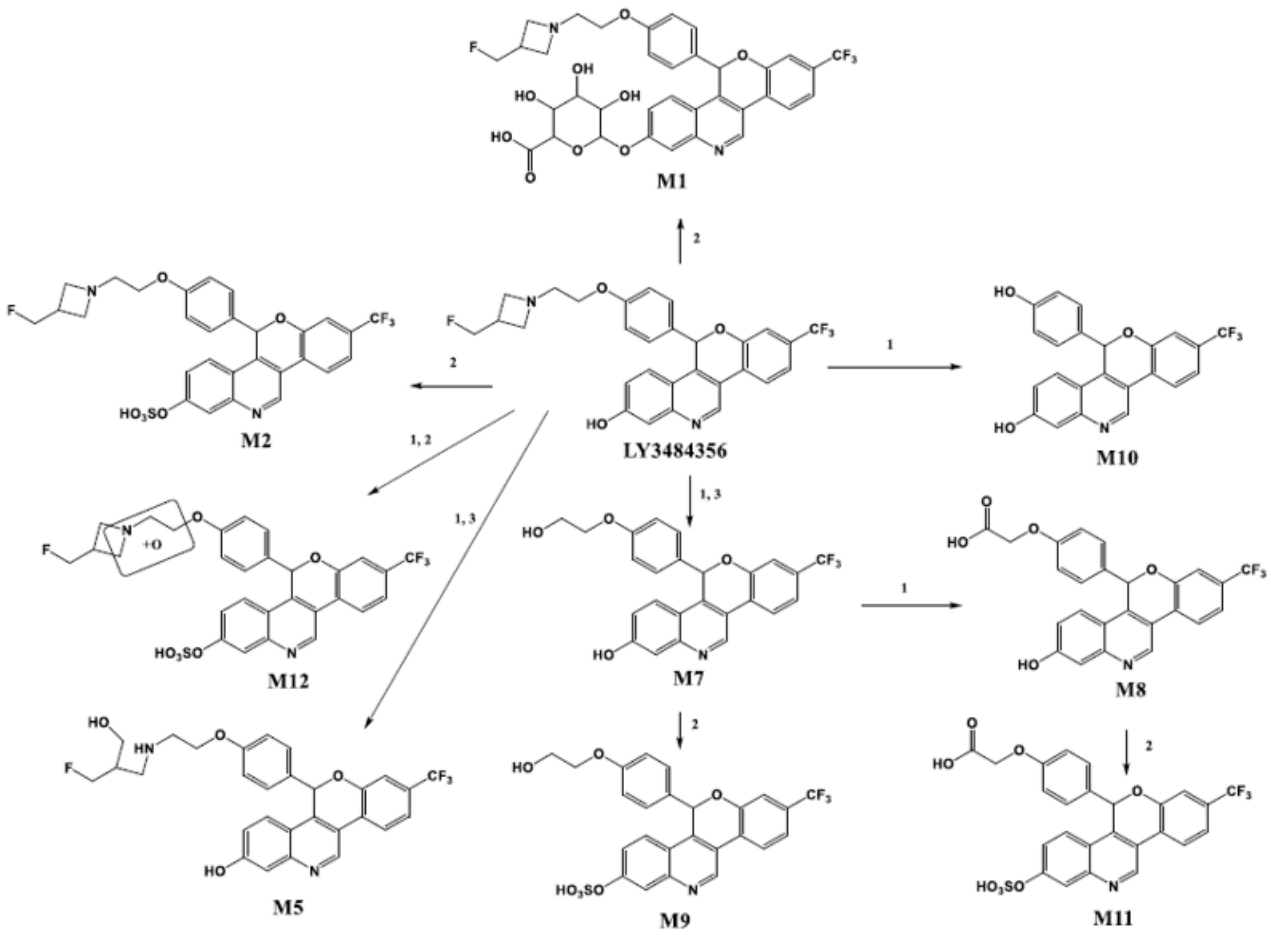
Following a single oral dose of 400 mg [^{14}C]-imlunestrant to healthy female subjects, 97.3% of the dose was excreted in faeces and 0.278% of the dose in urine. Since absolute bioavailability was 10.5%, about 3% of imlunestrant-related radioactivity in plasma is excreted via the urine and more than 90% via the bile. According to the population PK model, CL/F of imlunestrant was 166 L/h (51%) and $t_{1/2}$ was 30 hours. This is similar to values found in study JZLE (CL/F 128 L/h and $t_{1/2}$ 33.4 h).

In humans, imlunestrant is metabolized by sulfation, direct glucuronidation, and CYP3A4-mediated oxidation. The proposed metabolic scheme is shown in the below figure.

In vitro studies showed that CYP2D6 and CYP3A4 were responsible for <1% and 99.7%, respectively, of the hepatic CYP-mediated clearance of imlunestrant and that enzymes responsible for the glucuronidation of imlunestrant are UGT1A1 and UGT1A8, and to a lesser extent UGT1A3, UGT1A9, and UGT1A10. None of the elimination pathways involves polymorphic enzymes except of UGT1A1 (data not shown). Regarding UGT1A1, retrospective analyses on samples from studies JZLA and JZLD showed no relevant differences in exposure between normal, intermediate and poor metabolizers (data not shown).

In an in vivo study in healthy women (study JZLE), following a single radiolabelled 400 mg dose, unchanged imlunestrant constituted 19.8% of the circulating radioactivity in plasma, a phenolic glucuronide conjugate (M1) accounted for 19.9% of radioactivity, and two minor metabolites accounted for 4.47% (M2, a sulfate conjugate) and 4.64% (M12, formed by oxidation and sulfate conjugation) of the radioactivity in circulation. Additional radioactivity in the AUC plasma sample extract was not identified due to low percentage of radioactivity (<5%) or eluted in the column wash at the end of the HPLC method gradient. Only 50% of the radioactivity in plasma could be identified as imlunestrant and metabolites. The remainder consisted of minor components. In faeces, parent was the predominant component (61.8% of radioactive dose) followed by M2 (20.9% of dose). Other components in faeces were minor. Urine was not radio-profiled because urinary elimination of imlunestrant was negligible. Based on recovery in faeces, it was concluded that 21% of the dose was eliminated as a sulfate conjugate and that 13% was eliminated as oxidative metabolites. The amount undergoing glucuronidation cannot be estimated because in the intestinal tract, glucuronide that is converted back into parent compound mixes with parent compound that is not absorbed.

Figure 4 Proposed metabolic scheme for imlunestrant in healthy women after a single oral dose of 400 mg [^{14}C]-imlunestrant



Dose proportionality and time dependencies

In study JZLA, imlunestrant exposure increased approximately dose-proportionally at doses from 200 mg to 1200 mg.

The elimination half-life is approximately 30 hours. Steady state was estimated to be reached after 6 days of QD dosing. The accumulation ratio was 2.59 at the recommended dose of 400 mg/day.

Intra- and inter-individual variability

In patients (study JZLA), following a 400 mg single dose, inter-individual CV% was 71% for Cmax, 74% for $AUC_{0\text{-}inf}$ and 53% for $AUC_{0\text{-}24h}$. On day 15, following dosing at 400 mg/day, inter-individual CV% was 47% for Cmax and 46% for AUC_{tau}. In the population PK analysis, estimated inter-individual variability (CV%) was 51% for CL/F and 69% for Vc/F. Intra-individual variability was reflected in the residual variability (24.1%) and inter-occasion variability on the relative bioavailability (35.4%).

Pharmacokinetics in the target population

Patient population was a significant covariate in the population PK analysis. Based on pop PK, Vc/F was predicted to be lower in patients with mBC (47% lower) and in patients with EEC (64% lower) than in healthy subjects. This resulted in higher predicted imlunestrant concentrations in cancer patients than in healthy subjects. No therapeutic window was defined.

Special populations

No dedicated study was performed regarding renal impairment, because of the low contribution of renal excretion to the total elimination (0.3% of the dose and about 3% of imlunestrant-related radioactivity in plasma). Population PK analysis indicated no significant effect of mild (60 mL/min ≤ eGFR < 90 mL/min) or moderate (30 mL/min ≤ eGFR < 60 mL/min) renal impairment on imlunestrant clearance. There were limited data in patients with severe renal impairment. A higher AUCs was observed in these two subjects i.e. of 4410 ng*h/mL and 6630 ng*h/mL, compared to average steady state exposures of 2400 ng*h/mL.

A dedicated hepatic impairment study revealed no significant changes in AUC and Cmax in subjects with mild hepatic impairment, based on the Child-Pugh classification. Based on the NCI classification, increases were observed in AUC and Cmax up to approximately 1.5x. In subjects with moderate hepatic impairment, significant increases (2x based on Child-Pugh and 3x based on NCI) compared to subjects with normal hepatic function) were observed in AUC. Increases in Cmax were statistically significant only if based on the NCI classification (up to 1.7x). In subjects with severe hepatic impairment, based on the Child-Pugh classification, significant increases (3x based on total imlunestrant but 2x based on unbound fraction) compared to subjects with normal hepatic function were observed in AUC. No significant change was observed on Cmax. Based on the NCI classification, there was only 1 subject with severe hepatic impairment. Population PK analysis, which used the NCI classification, showed no effect of mild hepatic impairment on clearance. There were no or insufficient subjects in the database with moderate or severe hepatic impairment.

The number of male subjects in the clinical studies was very low (7 in total, <1%). Limited PK-data in males indicates that there is no gender effect.

In the population PK analysis there was no significant effect of race or ethnicity on the PK of imlunestrant. In a study in Chinese patients with a limited number of subjects (8-9 per group), exposure was somewhat higher compared to the patients in study JZLA (at 400 mg QD on day 17, AUC_{0-24} was 3270 ng.h/mL compared to 2480 ng.h/mL on day 15 in study JZLA and Cmax was 235 ng/mL compared to 164 ng/mL on day 15 in study JZLA).

Body weight was a significant covariate in the population PK model, with lower predicted imlunestrant concentrations at higher body weight.

The median age in the PK population was 60 years, ranging from 28 to 95 years. Population PK analysis showed no statistically significant effect of age on the PK of imlunestrant. Age ranges studied in the PK trials are shown in Table 11.

Table 11 Age ranges studied in the elderly population

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials JZLA, JZLB, JZLC, JZLD	272	94	14

Pharmacokinetic interaction studies

Imlunestrant as a victim

Imlunestrant is a substrate of CYP3A4 and UGT1A1 and UGT1A8, and to a lesser extent UGT1A3, UGT1A9, and UGT1A10 in vitro.

In vitro, imlunestrant is a substrate of P-gp and not a substrate of BCRP. The effect of P-gp inhibition was investigated clinically. Imlunestrant is not a substrate of OCT1, OATP1B1, or OATP1B3 in vitro. Human renal transporters have not been studied given the negligible renal clearance of imlunestrant.

In study JZLD, co-administration of a proton pump inhibitor, omeprazole, with a 400 mg oral dose of imlunestrant did not result in statistically significant changes in imlunestrant AUC(0-tlast) and C_{max}. Based on these results, imlunestrant may be co-administered with a gastric acid-reducing agent.

In study JZLI, quinidine (P-gp inhibitor) decreased the AUC of imlunestrant by approximately 13% and had no effect on imlunestrant C_{max}. Therefore, no clinically relevant effect of P-gp inhibitors on the PK of imlunestrant is expected.

In vivo studies revealed no effect of co-administration of omeprazole (proton pump inhibitor) or quinidine (P-gp inhibitor) on the exposure to imlunestrant. After co-administration with CYP3A inhibitor itraconazole, AUC_{inf} increased 2.11-fold and Cmax 1.87-fold. Co-administration with CYP3A inducer carbamazepine reduced AUC_{inf} by 42% and Cmax by 29%. See Table 17.

Imlunestrant as a perpetrator

In vitro, no reversible inhibition by imlunestrant was observed of the CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A (data not shown). A potential for time- plus NADPH-dependent inhibition was observed of CYP3A, CYP2C19, CYP2C9 and CYP2C8. Follow-up in vitro studies showed no time-dependent inhibition of CYP2C8 and CYP3A (data not shown).

Inhibition of CYP2C19, CYP2C8, CYP2D6 and CYP3A was investigated clinically.

No clinically relevant increases were observed there, so no relevant time-dependent inhibition is expected for CYP2C19 and CYP3A. Potential for time-dependent inhibition was not further studied for CYP2C9. Inhibition of CYP3A could not be investigated up to the cut-off value for the intestinal concentration (305 µM) because the solubility of imlunestrant in the test system was determined as maximally 20 µM.

Imlunestrant was not an inducer of CYP1A2, CYP2B6 and CYP3A4. Also no induction of CYP enzymes 2C8, 2C9, 2D6, 3A5 and 2C19 was observed.

Imlunestrant was not an inhibitor of the transporters OCT1, OCT2, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, MATE1, and MATE2K. Imlunestrant inhibited P-gp. BCRP and P-gp were not studied up to the cut-off level for intestinal concentration due to solubility limitations, but were investigated clinically.

In study JZLI, imlunestrant increased the AUC and C_{max} of rosuvastatin (BCRP substrate) by approximately 49% and 65%, respectively, demonstrating the inhibitory effect of imlunestrant on BCRP activity. Therefore, caution should be advised when co-administering imlunestrant with BCRP substrates for which a small increase in concentration leads to significant AEs.

In study JZLI, imlunestrant increased the AUC and C_{max} of digoxin (P-gp substrate) by approximately 39% and 60%, respectively, demonstrating the inhibitory effect of imlunestrant on P-gp activity. Therefore, caution should be advised when co-administering imlunestrant with P-gp substrates for which a small increase in concentration leads to significant AEs.

In study J2J-MC-JZLK, imlunestrant had no effect on the AUC and C_{max} of midazolam (CYP3A4 substrate). Therefore, no clinically relevant effect of imlunestrant on the PK of CYP3A4 substrates is expected.

In study J2J-MC-JZLI (JZLI), imlunestrant increased the AUC and C_{max} of dextromethorphan (CYP2D6 substrate) by approximately 33% and 43%, respectively, demonstrating the inhibitory effect of imlunestrant on CYP2D6 activity. Therefore, caution should be advised when co-administering imlunestrant with CYP2D6 substrates for which a small increase in concentration leads to significant AEs.

Imlunestrant had no effect on the AUC and C_{max} of repaglinide (CYP2C8 substrate) and increased the C_{max} of omeprazole (CYP2C19 substrate) by 28% but did not increase its AUC. Therefore, no clinically relevant effect of imlunestrant on the PK of CYP2C8 and CYP2C19 substrates is expected.

In vivo DDI studies are shown in Table 12.

Table 12 Summary of clinical DDI studies

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{inf}	
Victim			
Effect of co-administration with itraconazole (CYP3A inhibition) (study JZLD)	187 (162, 217)	211 (177, 253)	Reduce dose by half (not proposed by Applicant)
Effect of co-administration with carbamazepine (CYP3A induction) (study JZLD)	71 (60, 85)	58 (49, 69)	Increase dose by 200 mg QD (as proposed by Applicant)
Effect of co-administration with omeprazole (proton pump inhibitor) (study JZLD)	85 (65, 111)	105 * (85, 129)	No adjustment
Effect of co-administration with quinidine (P-gp inhibition) (study JZLI)	87 (72, 106)	87 (76, 100)	No adjustment
Perpetrator			
Effect on repaglinide (CYP2C8 substrate) (study JZLI)	93 (79, 110)	102 (97, 108)	No adjustment
Effect on omeprazole (CYP2C19 substrate) (study JZLI)	128 (105, 157)	110 (97, 124)	No adjustment
Effect on dextromethorphan (CYP2D6 substrate) (study JZLI)	143 (124, 165)	133 (122, 146)	Warning in section 4.5 of SmPC (as proposed by Applicant)
Effect on midazolam (CYP3A substrate) (study JZLK)	107 (99, 116)	93 (85, 102)	No adjustment
Effect on rosuvastatin (BCRP substrate) (study JZLI)	165 (128, 213)	149 (114, 197)	Warning in section 4.5 of SmPC (as proposed by Applicant)
Effect on digoxin (P-gp substrate) (study JZLI)	160 (134, 191)	139 (122, 159)	Warning in section 4.5 of SmPC (as proposed by Applicant)

* $AUC_{0\text{-tlast}}$

No formal DDI study was performed with the combination of imlunestrant and abemaciclib. Population PK analysis indicates no effect of the presence of abemaciclib on imlunestrant clearance. In study JZLC, imlunestrant concentrations at approximate Cmax and at Ctrough were comparable in the presence and absence of abemaciclib (see Table 13).

Table 13 Summary of imlunestrant concentrations at 400 mg QD in EMBER-3 (study JZLC)

	Approximate Sampling Times	Number of Samples	Geometric Mean (CV%) Imlunestrant Plasma Concentration (ng/mL)
Arm A (Imlunestrant Monotherapy)			
Cycle 1 Day 1	2–4 hr postdose	276	45.7 (123)
Cycle 2 Day 1	Predose	269	76.0 (76)
Cycle 3 Day 1	3 hr postdose	219	141 (70)
	5 hr postdose	209	136 (69)
Cycle 4 Day 1	Predose	178	85.2 (69)
Arm C (Imlunestrant + Abemaciclib)			
Cycle 1 Day 1	2–4 hr postdose	189	56.5 (122)
Cycle 2 Day 1	Predose	140	64.9 (103)
Cycle 3 Day 1	3 hr postdose	125	144 (73)
	5 hr postdose	123	146 (69)
Cycle 4 Day 1	Predose	105	63.0 (97)

Abbreviations: CV = coefficient of variation; QD = once daily.

Pharmacokinetics using human biomaterials

The potential of imlunestrant to be a substrate for P-gp and BCRP was assessed in study 20ELIP19. Bidirectional permeability assessment for imlunestrant (5 µM and 10 µM) and the positive control, digoxin, was conducted with MDR1-MDCK cell monolayers in the absence and presence of a P-gp inhibitor (10 µM). Bidirectional permeability assessment for imlunestrant (5 µM and 10 µM) and the positive control, cladribine, was conducted with BCRP-MDCK cell monolayers in the absence and presence of a BCRP inhibitor (0.5 µM Ko143). Imlunestrant was a substrate of P-gp and not a substrate of BCRP in this test. The positive controls and inhibitors functioned as expected.

A substrate depletion approach using human recombinant CYP enzymes was used to identify CYPs metabolizing imlunestrant and to predict the relative contributions of these CYPs to hepatic CYP-mediated clearance (study 191311_KAB5334214). No quantifiable depletion was observed for the following rCYPs: CYP12, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2E1, rCYP2J2, and rCYP3A5. CYP2D6 and CYP3A4 were responsible for <1% and 99.7%, respectively, of the hepatic CYP-mediated clearance of imlunestrant.

The UGT enzymes involved in the glucuronidation of imlunestrant to glucuronide metabolite M1 were investigated using microsomes from human intestine, liver and kidney. UGT1A1 and UGT1A8, and to a lesser extent UGT1A3, UGT1A9, and UGT1A10 were responsible for the O-glucuronidation based on the unbound intrinsic clearance per milligram of total protein (CLint,u was 4163, 2028, 857, 203 and 429 µL/min/mg protein respectively).

The potential to inhibit CYP enzymes was investigated in human liver microsomes (study XT195069). For all enzymes, Ki for direct inhibition was above the cut-off value for systemic exposure of 0.13 µM. Follow-up studies for time-dependent inhibition were performed for CYP2C8 (in human liver microsomes) and for CYP3A (in human hepatocytes). No time-dependent inhibition was observed.

The potential to induce CYP enzymes was investigated in human hepatocytes (study 1905242). The potential to induce CYPs 1A2, 2B6 and 3A4 was assessed by mRNA and activity. Furthermore, the potential to induce CYPs 2C8, 2C9, 2D6 and 3A5 was investigated (mRNA only) as well as 2C19 (activity only). No significant enzyme induction was observed.

Potential for transporter inhibition was investigated in inside-out membrane vesicles from HEK cells over-expressing MDR1 (P-gp) and in inside-out membrane vesicles from Sf9 insect cells expressing human BCRP (study LY3484356-2021TP-BCRP-Pgp-In) and in transfected HEK293 cells (OCT1, OCT2, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, MATE1, and MATE2K) (study 20ELIP20). Inhibition was observed only for P-gp.

Additional analyses performed as part of the Clinical Study Data Pilot

As part of the Clinical Study Data Pilot, analyses were performed in support of the clinical pharmacology assessment. Using the raw data, the results presented by the Applicant in the dossier were reproduced and were concluded to be consistent. Additionally, the replicated evaluation of the population PK analyses indicated that the evaluations as conducted by the Applicant were fit for purpose. Additional simulations for the identified covariates, i.e. body weight and patient population, indicated that breast- and endometrial/endometroid cancer patients have more variability in concentrations at steady state, while the plasma exposure does not differ to a relevant degree. On the other hand, patients with a lower body weight have a substantially higher exposure compared to patients with a higher body weight, which is consistent with the data provided by the Applicant and triggered questions on the consequences of this phenomenon for safety and efficacy.

2.6.2.2. Pharmacodynamics

Mechanism of action

Imlunestrant is an orally bioavailable potent selective degrader and pure antagonist of wild-type and mutant ERα. In in vitro studies, imlunestrant antagonized and degraded wild-type and mutant ERα, leading to inhibition of ER-dependent gene transcription and cellular proliferation in ER+ breast cancer cells. Imlunestrant demonstrated anti-tumour activity in multiple ER+ breast cancer xenograft models, including models with *ESR1* mutations, and models with resistance to fulvestrant and CDK4/6i.

Primary and Secondary pharmacology

Primary pharmacology: Study EMBER-2 (JZLB) was a Phase 1, open-label, randomized preoperative window study of imlunestrant in postmenopausal women with Stage I to Stage III oestrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer who are scheduled for surgery with curative intent. Patients gave consent to provide tumour samples obtained at the time of diagnosis and at the time of scheduled surgery or repeat biopsy for the purpose of biomarker analyses. Prior to Study Amendment (b), patients were randomly assigned to 1 of 2 dose level cohorts either 400 mg (Cohort A) or 800 mg (Cohort B) of imlunestrant. For the third dose level cohort (Cohort C, added in Amendment b), patients were directly assigned to 200 mg of imlunestrant. All patients received treatment for approximately 15 days, up to and including the day of scheduled surgery or repeat biopsy (if neoadjuvant therapy was subsequently planned). The primary objective was to determine the change in ER=expression (as measured by IHC and quantified by H-score) between pre- and on-treatment tumour samples at each dose level of imlunestrant.

Start date of the study was 21-04-2021, study was completed 11-11-2022. A total of 87 patients were enrolled of which 30 patients treated in the 400-mg imlunestrant treatment arm, 29 patients treated in the 800-mg imlunestrant treatment arm, and 28 patients treated in the 200-mg imlunestrant treatment arm. A total of 83 patients completed treatment. The majority of patients had Stage I (n = 47, 54.7%) or Stage II (n = 35, 40.7%) breast cancer, a histopathological G1 (n = 18, 20.9%) or G2 (n = 57, 66.3%) at initial diagnosis, and a baseline Eastern Cooperative Oncology Group score of 0 (n = 79, 91.9%).

After receiving treatment with imlunestrant, the geometric mean reduction in ER levels were 88.9% (90% CI: -95.6, -71.9), -81.5% (90% CI: -91.3, -60.5), and -70.1% (90% CI: -78.4, -58.8) for the 200 mg, 400 mg and 800 mg dose of imlunestrant, respectively. There was no dose-dependent effect observed when comparing randomized cohorts 400 mg and 800 mg.

Table 14 Analysis of percent change from baseline to day 15 biomarker-evaluable population study J2J-MC-JZLB

	Imlunestrant 200 mg	Imlunestrant 400 mg	Imlunestrant 800 mg	Total
ER (N = 75)				
n (%)	22 (29.33)	27 (36.00)	26 (34.67)	75 (100.0)
Geometric mean percent change[a] (90% CI)	-88.89 (-95.62, -71.85)	-81.50 (-91.34, -60.47)	-70.13 (-78.38, -58.75)	-81.20 (-87.31, -72.14)
Geometric mean ratio[b] (90% CI)	1.60 (0.69, 3.68)			
PR (N = 72)				
n (%)	20 (27.78)	26 (36.11)	26 (36.11)	72 (100.0)
Geometric mean percent change[a] (90% CI)	-85.44 (-96.61, -37.36)	-75.56 (-90.33, -38.20)	-82.01 (-91.98, -59.66)	-81.05 (-89.35, -66.29)
Geometric mean ratio[b] (90% CI)	0.72 (0.21, 2.44)			
Ki-67 (N = 63)				
n (%)	21 (33.33)	22 (34.92)	20 (31.75)	63 (100.0)
Geometric mean percent change[a] (90% CI)	-68.56 (-78.81, -53.59)	-70.61 (-80.04, -56.73)	-72.28 (-81.22, -59.09)	-70.49 (-76.18, -63.45)
Geometric mean ratio[b] (90% CI)	0.95 (0.55, 1.64)			
Ki-67 with baseline >5% (N = 59)				
n (%)	20 (33.9)	22 (37.29)	17 (28.81)	59 (100.0)
Geometric mean percent change[a] (90% CI)	-70.37 (-80.06, -55.97)	-70.61 (-80.04, -56.73)	-78.20 (-84.23, -69.87)	-72.96 (-78.07, -66.66)
Geometric mean ratio[b] (90% CI)	0.75 (0.45, 1.26)			

Abbreviations: CI = confidence interval; ER = estrogen receptor; n = number of patients in the specified category; N = number of biomarker-evaluable patients; PR = progesterone receptor; QD = once daily.

[a] Geometric mean percent changes based on t-statistic, assuming a normal distribution.

[b] Comparing the ratios of on-treatment and baseline biomarker results between 800-mg and 400-mg cohorts based on a linear model with treatment (400 mg and 800 mg) and histology as fixed effects.

Secondary pharmacology: In study EMBER (2J-MC-JZLA) concentration-QTcF analyses were conducted in 79 patients with matching PK and QTcF samples from Phase 1a and 1b EMBER monotherapy patients with ER+, HER2- mBC (Cohorts E3) and patients with ER+ EEC (Cohort E8). Results showed no effect of imlunestrant concentrations across the 200- to 1200-mg dose range on QTc interval, with the upper bound of the 90% CI of the mean delta QTc less than 10 ms at Cmax of 400 mg (change from baseline of 1.72 msec; 90% CI: - 0.43, 3.87).

Please refer to section *2.6.8.4. Laboratory findings* for ECG data from the EMBER-3 study.

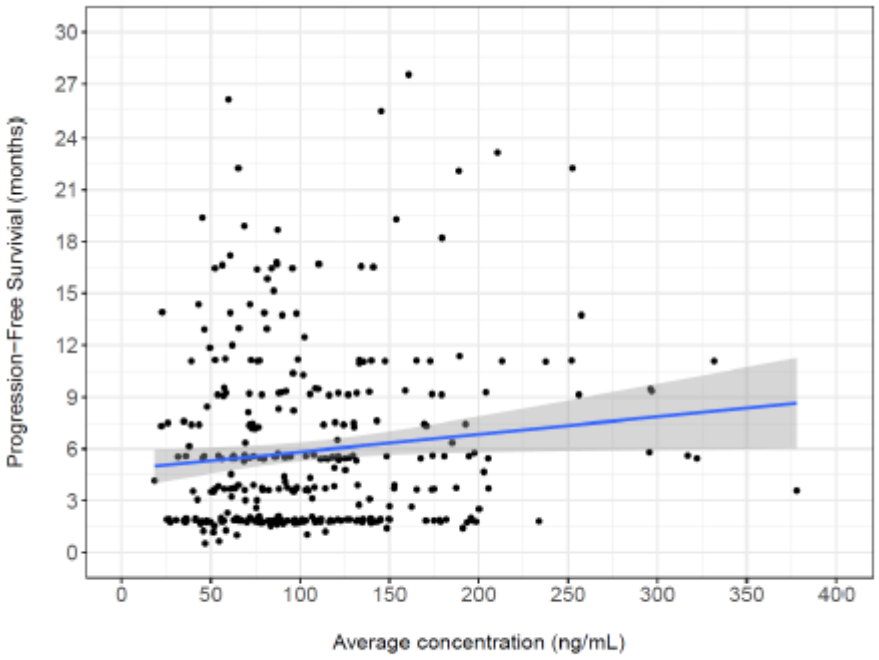
Pharmacokinetics/pharmacodynamics

Exposure-response analysis efficacy

The efficacy exposure-response analysis was based on study JZLC (EMBER-3). The relationships between average imlunestrant plasma concentration and PFS (progression-free survival) or CBR (clinical benefit rate) were analysed. A time to event model was used to describe the relationship with PFS and a logistic regression model to describe the relationship with CBR.

There was no relevant exposure-response relationship with PFS at the investigated exposures (see figure below).

Figure 5 Exposure-response plot of PFS against imlunestrant concentration



Abbreviation: PFS = progression-free survival.
Note: Black dots represent observations, blue line is linear regression line as visual aid and grey area is 95% confidence interval around linear regression.

Median predicted PFS at 400 mg QD was 5.5 months. In combination with abemaciclib this was 7.4 months. Imlunestrant exposure did not have a significant effect on PFS. Other statistically significant covariates identified in the exposure-PFS relationship included prior CDK4/6i therapy (associated with a decrease in median PFS of approximately 2 months), and presence of visceral metastases (associated with a decrease in PFS of approximately 2 months).

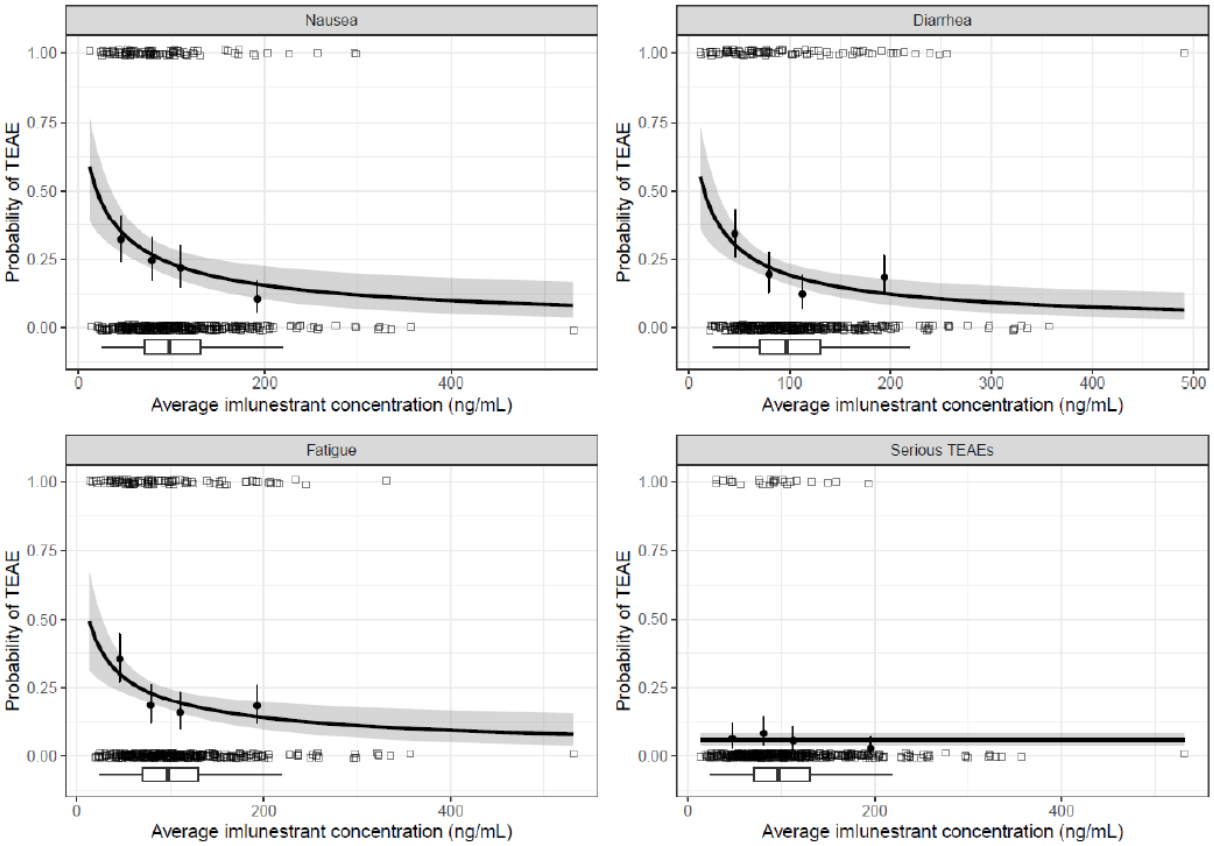
The relationship between imlunestrant average concentration and CBR was not statistically significant.

Exposure-response analysis safety

The safety exposure-response analysis was based on studies JZLA and JZLC. The relationships between imlunestrant exposure (PK metrics were average concentration and maximum concentration) and TEAEs (SAEs, nausea, diarrhea, and fatigue) were analysed. A logistic regression model was used to describe the exposure-response relationships regarding the safety endpoints.

Increasing average concentrations were associated with decreasing occurrence of TEAEs (see figure below).

Figure 6 Exposure-response relationships for safety endpoints using the average concentration of imlunestrant up to the day of TEAE for participants in monotherapy arms of Studies JZLA (EMBER) and JZLC (EMBER-3).



Abbreviations: CI = confidence interval; TEAE = treatment-emergent adverse event.
Note: Solid black lines and grey shaded area are the logistic regressions and 95% CIs of the predicted probability of TEAE. Black open squares reflect the individual observed TEAEs in imlunestrant patients. The observed response rate (black circles) and 95% CI (black error bars) of each exposure quartile are plotted versus imlunestrant concentration. Box plots represent the 25th, 50th, and 75th percentiles of predicted average imlunestrant concentration for a 400-mg dose. Whiskers represent 1.5 times the interquartile range.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetic studies provided were adequate. Imlunestrant was analysed in plasma with LC/MS/MS methods which were sufficiently validated. Analysis of samples in the clinical studies was performed in accordance with the ICH Guideline M10 on bioanalytical method validation and study sample analysis.

Population PK analysis

The population PK model was fit for purpose to characterize the PK of imlunestrant in the patient population, to estimate covariate effects and derive exposure metrics for PK/PD analyses. Unexplained interindividual variability in MTT, CL/F and Vc/F was moderate to high (48 – 69%). The prediction-corrected VPC and goodness-of-fit plots indicate that the model describes the PK data sufficiently. Shrinkage was not too high (13 – 24%). Simulated PK parameters matched measured values well.

The final model was evaluated by bootstrap (n=1000) providing the 95% CI of final parameters.

Absorption

A food effect study was performed, in which the effect of a low-fat meal on the PK of imlunestrant was investigated. The low-fat meal is reported to be relevant for the population of oncology patients. The exposure was higher in the fed state than in the fasted state (AUC is approximately 2-fold and Cmax is nearly 4-fold). In the product information, it is recommended to take Inluriyo on an empty stomach at least 2 hours before or 1 hour after food. This advice is given because the increase in Cmax was beyond the exposure range studied in clinical development of imlunestrant. These were also the conditions under which EMBER, EMBER 2, and EMBER 3 were carried out. Given the size of the food effect, i.e. a nearly 4-fold increase in Cmax when given with a low-fat meal, there may be consequences for safety in case patients would take imlunestrant with food inadvertently. A warning in the SmPC that Inluriyo should be taken in the fasted state as higher exposures may occur with food, has been included.

No bioequivalence studies were performed. This is acceptable because population PK analysis showed no statistically significant effect of formulation on the bioavailability and the absorption rate of imlunestrant.

Pharmacokinetics in the target population

In the clinical studies, conflicting results were obtained regarding the exposure in cancer patients compared to healthy subjects: exposure in cancer patients (AUC0-∞ was 2250 ng.h/mL, Cmax was 81 ng/mL) was lower than in healthy subjects from one study (AUC0-∞ was 3130 ng.h/mL, Cmax was 108 ng/mL in study JZLE part 1) and higher than healthy subjects from two other studies (studies JZLE part 2 and JZLD fasted state, AUC0-∞ was 1810 ng.h/mL in both studies, Cmax was 33.1 ng/mL and 37.2 ng/mL).

Patient population was a significant covariate in the population PK analysis. Based on pop PK, Vc/F was predicted to be lower in patients with mBC (47% lower) and in patients with EEC (64% lower) than in healthy subjects. This resulted in higher predicted imlunestrant concentrations in cancer patients than in healthy subjects. However, analysis in the raw data showed that when steady state was simulated for the healthy subjects (who actually had received a single dose only), no relevant difference in exposure was observed between healthy subjects and patients.

Special populations

According to the pop PK model, C_{max} and C_{min} in body weight quartile 1 (36 – 59 kg) to quartile 4 (80 – 145 kg) groups are comparable to the values at steady state at 400 mg. $AUC_{0\text{-}24h,ss}$ values in body

weight quartile 1 to quartile 4 groups are comparable to the values at 400 mg (2070-2610 ng.h/mL) or slightly above but still below exposure levels at 600 mg (3060-3390 ng.h/mL). Patients in the lowest body weight group possibly have a slightly higher risk of some gastrointestinal adverse events. However, this cannot be fully confirmed with the current study data, also considering the fact that no dose between 400 mg and 600 mg was investigated. The effect of gender on PK has not been fully investigated. It is justified by the indication breast cancer, that the investigation of PK in males is limited.

Pharmacokinetic interaction studies

Imlunestrant as a victim

Imlunestrant was metabolised by sulfation (21% of dose), oxidation (13% of dose) and glucuronidation. Among CYP enzymes, imlunestrant was primarily metabolised by CYP3A4. Effect of CYP3A inhibition and induction was investigated clinically. Effect on UGT enzymes was not investigated clinically. The amount undergoing glucuronidation cannot be estimated because in the intestinal tract, glucuronide that is converted back into parent compound mixes with parent compound that is not absorbed. M1 was not found in the faeces, suggesting that in the intestinal tract, glucuronide hydrolyzes back to parent drug immediately. Multiple UGTs are involved in the glucuronidation of imlunestrant. Based on intrinsic clearance of UGT1A1, UGT1A8, UGT1A3, UGT1A9, and UGT1A10 (CLint,u was 4163, 2028, 857, 203 and 429 µL/min/mg protein respectively), and considering that elimination by sulfation and oxidation together comprise 34% of dose, a significant part of the elimination of imlunestrant may occur by UGT1A1. However, retrospective pharmacogenetic analysis (samples from patients and healthy volunteers) showed not a higher but a slightly lower exposure to imlunestrant in poor UGT1A1 metabolizers, indicating that inhibition of UGT1A1 is not likely to be clinically relevant. Co-administration with CYP3A inhibitor itraconazole increased AUC_{inf} 2.11-fold and Cmax 1.87-fold. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose should be decreased to 200 mg once daily.

Co-administration with CYP3A inducer carbamazepine reduced AUC_{inf} by 42% and Cmax by 29%. The dose should be increased by 200 mg once daily if concomitant use with strong CYP3A inducers cannot be avoided.

Imlunestrant as a perpetrator

In one of the in vitro DDI studies, investigating the potential of imlunestrant to inhibit transporters (study 20ELIP20), actual imlunestrant concentrations were often considerably lower than intended concentrations, which was ascribed to non-specific binding. In this study, measured imlunestrant concentrations were therefore used for IC_{50} calculations to account for non-specific binding. The fact that measuring non-specific binding was not possible for the other in vitro DDI studies is not expected to have influenced the results, for various reasons. In CYP induction assays, assessed recovery of imlunestrant was 70 – 205% of nominal concentrations, which is acceptable. Inhibition of CYP enzymes 2C8, 2C19, 2D6 and 3A was investigated clinically and therefore assessment of inhibition of these enzymes does not rely on the in vitro studies. For the remaining CYP enzymes which were not investigated clinically, it is not expected that non-specific binding would change the conclusion to a significant extent, because Ki values were > 100-fold higher than the cut-off value for systemic exposure.

It was investigated if imlunestrant inhibits UGT1A1. Bilirubin (Endogenous UGT1A1 biomarker) data from EMBER-3 study indicates that imlunestrant likely is not a clinically relevant UGT1A1 inhibitor. This was further supported by mechanistic static modelling, in which a Ki-value in the calculation was assumed from the Km-value. This has been updated with an in vitro Ki-value (1.075 uM) that is half

the measured IC_{50} value (2.15 uM) determined in vitro (study KC255108). Overall, it is considered that clinically relevant perpetrator interaction for imlunestrant with UGT1A1 is not to be expected.

CYP2C9 was one of the enzymes for which it was concluded that the screen for time- plus NADPH-dependent inhibition was positive and that a follow-up study may be warranted. No follow-up study was provided. However, since imlunestrant was a stronger inhibitor of CYP2C8 than CYP2C9 in vitro and no inhibition of CYP2C8 was observed in vivo, significant inhibition of CYP2C9 is considered unlikely and a follow-up study regarding CYP2C9 is considered not necessary. There was no clinically relevant effect of imlunestrant on CYP2C8 substrate repaglinide, on CYP2C19 substrate omeprazole and on CYP3A substrate midazolam. Imlunestrant increased CYP2D6 substrate dextromethorphan AUC_{inf} 1.33-fold and Cmax 1.43-fold, BCRP substrate rosuvastatin AUC_{inf} 1.49-fold and Cmax 1.65-fold and P-gp substrate digoxin AUC_{inf} 1.39-fold and Cmax 1.60-fold. Information on interactions with other medicinal products is included in section 4.5 of the SmPC. In the study regarding the effect of imlunestrant on dextromethorphan, sampling for dextromethorphan was performed up to 24 h following a single dose on day 1 and up to 48 h following the combination of imlunestrant + dextromethorphan on day 3. The $t_{1/2}$ of dextromethorphan can be up to 45 h in slow metabolisers (2-4 h in fast metabolisers). In this study, mean $t_{1/2}$ of dextromethorphan was 11.4 h (range 6.79 – 24.1 h). Therefore, the elimination phase of dextromethorphan was not complete, at least after the dose on day 1. However, only 2 out of 26 subjects had extrapolated AUC greater than 20%. Mean $t_{1/2}$ (geometric mean) for dextromethorphan was 11.4 h. When 2 subjects with extrapolated AUC greater than 20% were excluded, median $t_{1/2}$ was also 11.4 h. Even though this is a median instead of a geometric mean, it is clear that sampling up to 24 h did not have a large impact on PK parameters of dextromethorphan and a reliable exposure was estimated for the comparison in this DDI study. The information regarding the pharmacokinetic interactions is reflected adequately in the SmPC.

Special populations

Regarding renal impairment, the SmPC states that no dose adjustment is necessary in patients with mild or moderate renal impairment. This is agreed, considering that population PK analysis indicated no significant effect of mild or moderate renal impairment on imlunestrant clearance and considering the low contribution of renal excretion to the total elimination (0.3% of dose and 3% of imlunestrant-related radioactivity in plasma). Limited data indicates that exposure could potentially be increased in severe RI, therefore a caution of the use imlunestrant in patients with severe renal impairment has been included in the SmPC. No dose adjustment is necessary in patients with mild or moderate renal impairment. Limited data indicates that the exposure of imlunestrant may be increased in patients with severe renal impairment, end stage renal disease, or in patients on dialysis. Inluriyo should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity.

Imlunestrant is metabolised by the liver. No clinical data is available in patients with severe hepatic impairment. The recommended dose of 200 mg QD daily in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is based on a PK hepatic impairment study. Regarding hepatic impairment, no dose adjustment is recommended for patients with mild hepatic impairment (based on Child-Pugh classification). For patients with moderate and severe hepatic impairment it is advised to reduce the dose to 200 mg/day. This advice is acceptable, since a dedicated hepatic impairment study showed increases in exposure of approximately 2x, for the unbound fraction and based on the Child-Pugh classification.

Regarding use by the elderly, it is stated that no dose adjustment is required on the basis of patient age. This is agreed. Investigated age range was 28 to 95 years. Limited data are available in the patient group ≥ 75 years of age.

Exposure-response relationships

There was no relevant exposure-response relationship between imlunestrant average concentration and efficacy endpoints PFS and CBR.

An inverse relationship was observed between average imlunestrant concentration and safety endpoints. The Applicant concluded that increasing imlunestrant exposures did not lead to increase in incidence of TEAEs of SAE, nausea, diarrhoea, and fatigue. The exact cause of the inverse relationship is not clear. Nevertheless, it can be concluded that there is no clear relationship between imlunestrant concentration and safety endpoints.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of imlunestrant have been adequately described.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

EMBER: A phase 1a/1b study of imlunestrant administered as monotherapy and in combination with anticancer therapies for patients with ER+ locally advanced or metastatic breast cancer and other select non-breast cancers (J2J-MC-JZLA)

Study design

EMBER was a first-in-human global, open-label, phase 1a/1b study of imlunestrant for adults with recurrent or persistent ER+ ABC or metastatic ER+ endometrioid endometrial cancer (EEC) with dose escalation followed by dose expansions of imlunestrant as monotherapy and in combination with other targeted therapeutic agents. Combinations included abemaciclib with or without AIs (anastrozole, exemestane, or letrozole), alpelisib, everolimus, or trastuzumab (with or without abemaciclib or pertuzumab).

The primary objective was to determine the recommended phase 2 dose (RP2D) of imlunestrant in the ER+ breast and endometrial cancer landscape. The secondary objectives were to determine the tolerability and safety, the pharmacokinetics, and the antitumour activity of imlunestrant alone and in combination treatment. Efficacy in both *ESR1* mutant and *ESR1* wild-type BC was an exploratory endpoint.

Phase 1a: A dose range of 200 – 1200 mg imlunestrant monotherapy was investigated in the escalation phase 1a. Dose escalation utilized a standard 3+3 design from the initial dose level cohort with 5 dose levels (200 mg to 1200 mg) evaluated. Approximately 20 patients per dose level were enrolled with the exception of the 1200-mg daily dose level, which was voluntarily stopped once 3 patients had been enrolled and assessed for safety. The 1200 mg dose level was not explored further based on PK data while also considering the patient experience and pill burden.

Phase 1b: The dose-expansion phase 1b of the EMBER study enrolled a total of 304 patients, 297 of whom were treated with imlunestrant plus or without various targeted therapies (Cohort E1 – Cohort E10). Relevant cohorts in support of the claimed indication are Cohort E1, including patients with HR+ HER2- advanced/metastatic BC to be treated with imlunestrant + abemaciclib and no prior CDK4/6i

use, and Cohort E3 in the same disease setting and in which patients with prior CDK4/6i use received imlunestrant monotherapy.

Results

Efficacy

Phase 1a dose escalation: Of the 81 patients treated, 56 patients had measurable disease at baseline and antitumour activity is shown below (see table below).

Table 15 Summary of best overall response by investigator in patients with measurable disease (phase 1a) – ORR Evaluable population.

	PART A-A - 200mg (N=14)	PART A-A - 400mg (N=14)	PART A-A - 600mg (N=12)	PART A-A - 800mg (N=14)	PART A-A - 1200mg (N=2)	Total (N=56)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Best Overall Response						
Complete Response (CR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Partial Response (PR)	0 (0)	3 (21.4)	0 (0)	0 (0)	1 (50.0)	4 (7.1)
Stable Disease (SD)	4 (28.6)	9 (64.3)	6 (50.0)	7 (50.0)	0 (0)	26 (46.4)
SD Persistent for >= 24 (weeks)	2 (14.3)	6 (42.9)	2 (16.7)	5 (35.7)	0 (0)	15 (26.8)
Progressive Disease (PD)	9 (64.3)	2 (14.3)	6 (50.0)	6 (42.9)	1 (50.0)	24 (42.9)
Non Evaluable	1 (7.1)	0 (0)	0 (0)	1 (7.1)	0 (0)	2 (3.6)
Overall Response Rate (CR/PR)	0 (0)	3 (21.4)	0 (0)	0 (0)	1 (50.0)	4 (7.1)
Disease Control Rate (CR, PR, SD)	4 (28.6)	12 (85.7)	6 (50.0)	7 (50.0)	1 (50.0)	30 (53.6)
Clinical Benefit Rate (CR or PR, or SD Persistent for >= 24 (weeks))	2 (14.3)	9 (64.3)	2 (16.7)	5 (35.7)	1 (50.0)	19 (33.9)

Abbreviations: N = number of subjects in population; n = number of subjects.
Response criteria used was RECIST 1.1
Data Cutoff date is 2023-03-09.
ORR evaluable: Patients who had at least 1 post-baseline tumor assessment or discontinued prior to 1st tumor assessment.

Phase 1b dose expansion: As for the RP2D of 400 mg daily, the ORR was 32.1% for Cohort E1 (n=28, imlunestrant + abemaciclib) and 11.1% for Cohort E3 (n=27, imlunestrant monotherapy) for patients with measurable disease at baseline. The clinical benefit rate (CBR) based on all patients treated was 71.4% and 52.5% in Cohort E1 and E3, respectively.

Combining the results for the RP2D of 400 mg imlunestrant monotherapy daily from phase 1a and 1b for all patients with HR+, HER2- MBC (n=51), the ORR was 11.8% (n=34 evaluable patients) and CBR was 54.9%. Median treatment duration was 6.5 months (range: 0.3-25.9).

Responses were observed in both the *ESR1*m-detected and *ESR1*m-not-detected patients (data not shown).

Safety

Across all dose levels, 75 of 81 (92.6%) patients experienced treatment emergent adverse events (TEAEs). A majority of TEAEs were Grade 1 or 2, and no patients discontinued treatment due to an AE. No dose limiting toxicities (DLTs) were experienced at any dose level tested, and the maximum tolerated dose (MTD) was not reached. Overall, the most common TEAEs were nausea (n=31, 38.3%), diarrhoea (n=26, 32.1%) and fatigue (n=25, 30.9%). In total, 19 (23.5%) patients experienced Grade 3 or greater TEAEs; Grade 3 (n=18; 22.2%), Grade 4 (n=1; 1.2%, hyponatraemia). Overall, the most common Grade ⩾3 TEAEs were diarrhoea and hypotension (each n=2; 2.5%). No Grade 5 TEAE was experienced at any dose level. Serious adverse events (SAEs) occurred in 11.1% (n=9) of the patients and the incidence of SAEs was not dose dependent. Each SAE was reported in 1 patient. Dose reductions due to TEAEs were low and occurred in 3 of 81 (3.7%) patients, including 2 out of the 20 (10.0%) patients who received the RP2D 400-mg daily dose. There were no treatment discontinuations due to TEAE.

2.6.5.2. Main study

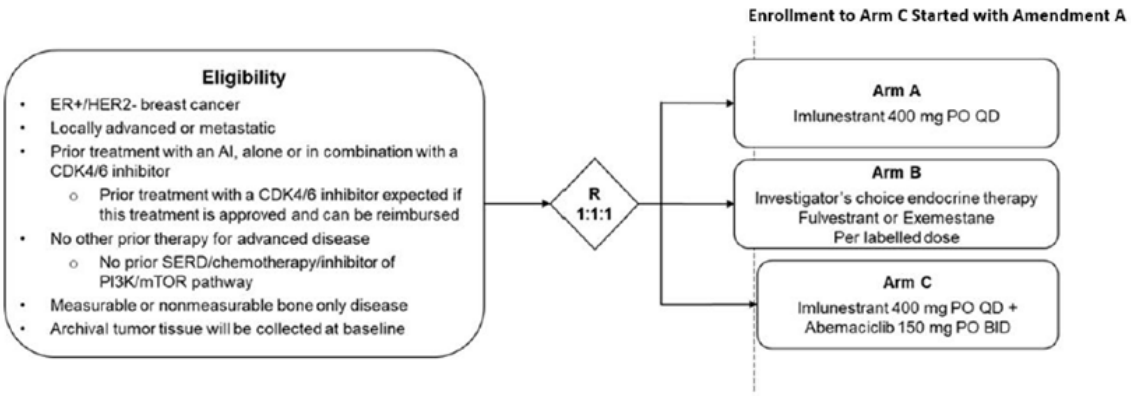
EMBER-3: A phase 3, randomized, open-label study of imlunestrant, investigator's choice of endocrine therapy, and imlunestrant plus abemaciclib in patients with oestrogen receptor positive, HER2 negative locally advanced or metastatic breast cancer previously treated with endocrine therapy

The information provided below on the study design is based on the most recent versions of the protocol (Amendment (d), Approved on 31 July 2023) and the Statistical Analysis Plan (version 5, Approved on 24 August 2023). For details on relevant amendments please refer to the section on the conduct of the study.

Methods

Study J2J-OX-JZLC is a phase 3, randomized, open-label 3-arm study in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor (see figure below). Eligible patients were randomized to either imlunestrant monotherapy (Arm A), investigator's choice of endocrine therapy (fulvestrant or exemestane; Arm B), or imlunestrant plus abemaciclib (Arm C). Patients were initially randomized 1:1 between Arm A and Arm B, Arm C was added as part of amendment (a) and enrolment to Arm C began in March 2022 at which point 122 patients had been randomized across Arm A and Arm B. Randomization was stratified by previous treatment with CDK4/6i (yes vs no), presence of visceral metastases (yes vs no), and region (East Asia vs North America/Western Europe vs Others).

Figure 7 Study schema EMBER-3 (J2J-OX-JZLC)



Abbreviations: AI = aromatase inhibitor; BID = twice daily; CDK4/6 = cyclin-dependent kinase 4/6; ER+ = estrogen receptor positive; HER2- = human epidermal growth factor receptor 2 negative; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide 3-kinase; PO = orally; QD = once daily; R = randomization; SERD = selective estrogen receptor degrader.

- **Study Participants**

Key inclusion criteria:

- Participant must be at least 18 years of age.
- Have a diagnosis of ER+, HER2- breast cancer:

- to fulfil the requirement for ER+ disease, a breast cancer must express the ER by immunohistochemistry, as defined in the relevant ASCO/CAP Guidelines (Allison et al. 2020)
- to fulfil the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either immunohistochemistry (IHC) or in-situ hybridization as defined in the relevant ASCO/CAP Guidelines (Wolff et al. 2018).

- Have locally advanced (not amenable to curative treatment by surgery) or metastatic disease and fulfil 1 of the following criteria (3a-c) below. *Note 1*: Patients are expected to have received prior treatment with a CDK4/6 inhibitor if this treatment is approved and can be reimbursed. *Note 2*: During the course of the trial, the Sponsor may elect to limit the enrolment of participants **who have NOT received prior treatment with a CDK4/6 inhibitor.**
  - relapsed with evidence of progression while on or within 12 months of completion of (neo)adjuvant aromatase inhibitor (AI), alone or in combination with a CDK4/6 inhibitor, with no treatment for advanced disease.
  - relapsed with evidence of progression >12 months from completion of (neo)adjuvant ET (ET, tamoxifen, or AI), with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor.
  - presented de novo with metastatic disease, with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor.
- Must be deemed appropriate for treatment with ET.
- If female, have a postmenopausal status due either to surgical/natural menopause or ovarian function suppression (OFS) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin or leuprolide (received monthly and initiated at least 28 days prior to Cycle 1 Day 1).
- If male, must agree to use hormone suppression (initiated at least 28 days prior to Cycle 1 Day 1) with a gonadotropin-releasing hormone agonist such as goserelin or leuprolide.
- Have one of the following as defined by RECIST v1.1 (Eisenhauer et al. 2009):
  - Measurable disease
  - Non-measurable bone-only disease. Non-measurable bone-only disease may include any of the following:

    i. Blastic bone lesions (also known as sclerotic bone lesions)

    ii. Lytic bone lesions without a measurable soft tissue component

    iii. Mixed lytic-blastic bone lesions without a measurable soft tissue component
  - Have a Performance Status of 0 or 1 on the Eastern Cooperative Oncology Group scale (Oken et al. 1982)

Key exclusion criteria:

- Have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, any investigational-ER-directed therapy (including SERDs and non-SERDs), any PI3K-, mTOR-, or AKT-inhibitor. Patients who have progressed on prior exemestane treatment must not receive exemestane if randomized to the control arm.
- Known pathogenic germline mutations appropriate for treatment with a PARP inhibitor, in regions where these therapies are approved and available.

- Have inflammatory breast cancer.
- Have visceral crisis, lymphangitic spread within the lung, or any evidence of leptomeningeal disease.
- Have symptomatic or untreated brain metastasis. Patients with treated brain metastases are eligible for this study if they completed prior therapy (including radiation and/or surgery) ≥28 days prior to first dose of study treatment and are not receiving corticosteroids and/or anticonvulsants for at least 14 days prior to first dose of study treatment, and their disease is asymptomatic and radiographically stable for at least 28 days prior to randomization by repeat imaging (repeat imaging should be performed during study screening).
- Have had wide-field radiotherapy ≤4 weeks (defined as involving ≥25% of the bone marrow), or limited field radiation for palliation ≤1 week prior to randomization. Patients must also have recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).
- Have a serious cardiac condition, such as congestive heart failure, New York Heart Association Class III/IV heart disease, unstable angina pectoris, myocardial infarction (MI) or cerebrovascular accident (stroke) within the last 3 months, a mean QT interval corrected for heart rate of ≥470 msec on screening ECG.
- Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, pre-existing medical condition of ILD/pneumonitis, severe dyspnoea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhoea).

- **Treatments**

The trial interventions are described in the below figure. Patients were treated until disease progression, development of unacceptable toxicity, withdrawal of informed consent, or other discontinuation criteria as outlined in the protocol. Patients should not consume any food at least 1 hour before and at least 2 hours after administration of imlunestrant.

Figure 8 Study interventions administered

	Arm A Imlunestrant	Arm B Investigator's Choice Endocrine Therapy[a] (Fulvestrant or Exemestane)		Arm C Imlunestrant + Abemaciclib	
Treatment	Imlunestrant	Fulvestrant	Exemestane	Imlunestrant	Abemaciclib
Dose	400 mg	500 mg	25 mg	400 mg	150 mg
Schedule	QD in 28-day continuous cycles	500 mg on C1D1 and C1D15 and then on Day 1 of a 28-day cycle starting at Cycle 2	QD in 28-day continuous cycles	QD in 28-day continuous cycles	BID in 28-day continuous cycles
Route	Oral[b]	Two 250 mg intramuscular injections	Oral	Oral[b]	Oral
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Not authorized in EU	Authorized and used according to EU authorization

Abbreviations: BID = twice daily; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; QD = once every day.

[a] Per local label.

[b] Patients were instructed not to consume any food at least 1 hour before and at least 2 hours after administration.

Dose interruptions and dose reduction to 200 mg QD were allowed in case of toxicity. If patients tolerated the reduced dose for ≥2 weeks, a re-escalation was allowed.

Patients with documented progressive disease (PD) as determined by the investigator may be allowed to continue study treatment if the patient is tolerating study drug and, in the opinion of the investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

Tumour Assessments: All enrolled patients were assessed for tumour response using RECISTv1.1 that included measurement of visible lesions, by CT or MRI scan of the chest, abdomen, and pelvis, scheduled at baseline and then every 8 weeks (±4 days) for the first 12 months and then every 12 weeks thereafter. Radiological imaging occurred at baseline and then at regular intervals thereafter until radiographic disease progression, death, start of a new anti-cancer therapy or study completion, whichever occurred first.

- **Objectives**

Three primary objectives were defined:

- To show superiority of imlunestrant (Arm A) to SOC (Arm B) by assessment of investigator-assessed progression-free survival (PFS) in the intention to treat (ITT) population
- To show superiority of imlunestrant (Arm A) to SOC (Arm B) by assessment of investigator-assessed progression-free survival (PFS) in the *ESR1*m-detected population
- To show superiority of imlunestrant plus abemaciclib (Arm C) to imlunestrant monotherapy (Arm A) by assessment of investigator-assessed progression-free survival (PFS) in the concurrent ITT population.

- **Outcomes/endpoints**

Table 16 Objectives and endpoints for EMBER-3

Objectives	Endpoints
Primary	
• To compare the PFS of imlunestrant (Arm A) to the standard comparator of Investigator's Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B) in the ITT population. • To compare the PFS of Arm A to Arm B in the *ESR1*-mutation detected population. • To compare the PFS of imlunestrant plus abemaciclib (Arm C) to imlunestrant (Arm A) in the ITT population.	• Investigator-assessed PFS (between Arm A and Arm B) in the ITT population. • Investigator-assessed PFS (between Arm A and Arm B) in the *ESR1*-mutation detected population. • Investigator-assessed PFS (between Arm C and Arm A) in the ITT population.
Secondary	
• To compare OS of Arm A to Arm B in the ITT population. • To compare OS of Arm A to Arm B in the *ESR1*-mutation detected population. • To compare OS of Arm C to Arm A in the ITT population. • To compare other efficacy objectives of Arm A to Arm B, and Arm C to Arm A.	• OS between Arm A and Arm B in the ITT population (*key secondary endpoint*). • OS between Arm A and Arm B in the *ESR1*-mutation detected population (*key secondary endpoint*). • OS between Arm C and Arm A in the ITT population *(key secondary endpoint*). • Investigator-assessed ORR, DoR, and CBR • PFS by blinded Independent Review Committee (BIRC).
• To assess the safety and tolerability of each treatment arm.	• Including but not limited to AEs, serious AEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0.
• To evaluate the effectiveness of Arm A compared to Arm B and Arm C compared to Arm A based on PROs of pain using the Worst Pain NRS.	• Time to sustained worsening of the "worst pain" as measured by Worst Pain NRS.
• To assess the PK of imlunestrant (Arm A and Arm C). • To assess the PK of abemaciclib and its metabolites (Arm C).	• Plasma concentrations of imlunestrant and abemaciclib.

Abbreviations: AE = adverse event; BIRC = blinded Independent Review Committee; CBR = clinical benefit rate; CFS = chemotherapy-free survival; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; ESR1 = oestrogen receptor 1; ITT = intention to treat; NCI = National Cancer Institute; NRS = numeric rating scale; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics.

The comparison of efficacy parameters between combination treatment and SOC were included as exploratory objectives.

- **Sample size**

The primary analysis of PFS for Arm A versus Arm B in the ITT population was to be performed after approximately 480 investigator-assessed events were observed in Arm A and Arm B. Assuming a PFS hazard ratio of 0.74, a total of 480 events yields at least 76% power to detect superiority of imlunestrant Arm A over Arm B with the 1-sided log-rank test at the significance level of 0.005. If this comparison (H1) could be tested at the full alpha level of 0.025 after recycling per the graphical approach, the same number of events could yield at least 91% power with the 1-sided log-rank test. The median PFS of Arm B was assumed to be 4.3 months, and the hazard ratio of 0.74 amounts to an approximate 1.5-month improvement in median PFS under the assumption of exponential survival distribution. The assumed median PFS of Arm B was estimated based on an unpublished meta-analysis of historical controls.

The analysis population for the second primary hypothesis (H2; PFS for Arm A versus Arm B in the *ESR1*-mutation detected population) was defined as the *ESR1*-mutation detected subset in Arm A and Arm B. The primary analysis of PFS was to be performed after approximately 192 investigator-assessed events had been observed in the *ESR1*-mutation detected subset. Assuming a PFS hazard ratio of 0.57, a total of 192 events yields approximately 97% power to detect superiority of Arm A over Arm B with the 1-sided log-rank test at the significance level of 0.02. Assuming the median PFS of Arm B in the subset is 3.6 months, the hazard ratio of 0.57 amounts to an approximate 2.7-month improvement in median PFS under the assumption of exponential survival distribution.

The power and sample size for PFS for Arm C versus Arm A in the ITT population (H3) was based on the 1-sided alpha level of 0.025 assuming that both H1 and H2 were rejected. The analysis population for H3 was to be the participants concurrently randomized to Arm A and Arm C. The primary analysis of PFS was to be performed after approximately 248 investigator-assessed events had been observed in this analysis population. Assuming a PFS hazard ratio of 0.7, a total of 248 events yields at least 80% power to detect superiority of Arm C over Arm A with the 1-sided log-rank test at the significance level of 0.025. If the median PFS of Arm A is assumed to be 5.8 months (i.e. assuming the target HR for Arm A versus Arm B in the ITT population is met), the hazard ratio of 0.7 then amounts to an approximate 2.5-month improvement in median PFS under the assumption of exponential survival distribution. Per the enrolment assumptions, it was estimated that 220 participants were to be enrolled in Arm C. Thus approximately 440 participants will be concurrently randomized to Arm A and Arm C.

Under these assumptions, it was estimated that a total number of 860 participants would be enrolled to this study. Specifically, approximately 320 participants will be enrolled in Arms A and B respectively, and approximately 220 participants in Arm C.

- **Randomisation and Blinding (masking)**

EMBER-3 was designed as a randomised, open-label study. Participants who met all criteria for enrolment were randomly assigned to the treatment arm through the interactive web response system (IWRS). Assignment to treatment groups was determined by a computer-generated random sequence using the IWRS. Initially patients were randomized 1:1 to Arm A and Arm B, and thereafter 1:1:1 to Arm A, Arm B and Arm C.

Randomisation was stratified by:

- Previous treatment with CDK4/6i (yes vs no)
- Presence of visceral metastases (yes vs no)
- Geographic region (East Asia vs North America/Western Europe vs Others).

Participants and investigative site staff were aware of treatment assignment. Investigative site staff and Lilly as sponsor were blinded to aggregate data. Access to data was strictly controlled and documented prior to final analyses. Access to the electronic data capture system was limited to those who required this information for their role. Interim analyses for safety and futility were conducted under the guidance of an independent data monitoring committee (DMC) who reviewed unblinded data prepared by the independent Statistical Analysis Centre.

- **Statistical methods**

Analysis sets

ITT: All participants randomly assigned to study treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants were to be analysed according to

the treatment group to which they were assigned. The ITT was used as the primary population to compare imlunestrant monotherapy versus SOC (Arm A vs Arm B).

ESR1m-detected population: The subset of participants with *ESR1* mutation detected in the ITT population used for the comparison of imlunestrant monotherapy versus SOC.

Concurrent ITT: Subset of ITT of patients concurrently randomized to Arm A, Arm B, and Arm C. This population was used as the primary population for the comparison of combination treatment versus imlunestrant monotherapy (Arm C vs Arm A).

Safety population: All participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the study treatment they actually received.

Endpoints and Estimands

Plain language description of the primary estimand for PFS, Imlunestrant monotherapy vs SOC, full population: In adults with advanced/metastatic HR+, HER2- breast cancer who have progressed or relapsed on prior treatment with an AI, alone or in combination with a CDK4/6 inhibitor, what is the difference between Imlunestrant monotherapy and SOC (physician's choice of Fulvestrant or Exemestane) in time to investigator-assessed progression or death, in the situation where alternative anti-cancer therapies are not available and regardless of treatment discontinuation?

Plain language description of the primary estimand for PFS, Imlunestrant monotherapy vs SOC, *ESR1*-m population: In adults with advanced/metastatic HR+, HER2- breast cancer with a detected *ESR1*-mutation, who have progressed or relapsed after on prior treatment with an AI, alone or in combination with a CDK4/6 inhibitor, what is the difference between Imlunestrant monotherapy and SOC (physician's choice of Fulvestrant or Exemestane) in time to investigator-assessed progression or death, in the situation where alternative anti-cancer therapies are not available and regardless of treatment discontinuation?

Plain language description of the primary estimand for PFS, imlunestrant plus abemaciclib vs Imlunestrant monotherapy, full population: In adults with advanced/metastatic HR+, HER2- breast cancer who have progressed or relapsed on prior treatment with an AI, alone or in combination with a CDK4/6 inhibitor, what is the difference between imlunestrant plus abemaciclib and Imlunestrant monotherapy in time to investigator-assessed progression or death, in the situation where alternative anti-cancer therapies are not available and regardless of treatment discontinuation?

Progression-free survival was defined as the time from randomization to the date of first documented progression of disease or death from any cause in the absence of disease progression using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Progression-free survival was assessed by investigator assessment for the primary analysis. A sensitivity analysis of PFS by BIRC was also planned.

Patients that received new systemic anticancer therapy prior to tumour progression or death were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. If the patient progressed or died immediately after two or more consecutive missed visits, the patient was censored at the time of the latest evaluable RECIST v1.1 assessment prior to the two missed visits. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

Overall survival is defined as the time from randomization until death was alive or lost to follow-up at the time of analysis, OS data was censored on the last date the participant was known to be alive.

Adjustment for multiplicity

To adjust for multiplicity and control the overall family-wise type I error rate at 0.025 (1-sided), the graphical approach (Bretz et al. 2009; Mauer and Bretz et al. 2013) was used to test the 3 PFS primary hypotheses and the 3 OS key secondary hypotheses. The corresponding hypotheses were defined as follows.

Primary hypotheses:

H1: PFS between Arm A and Arm B in the ITT population

H2: PFS between Arm A and Arm B in the *ESR1*-mutation detected population

H3: PFS between Arm C and Arm A in the [concurrently randomised] ITT population.

Key secondary hypotheses:

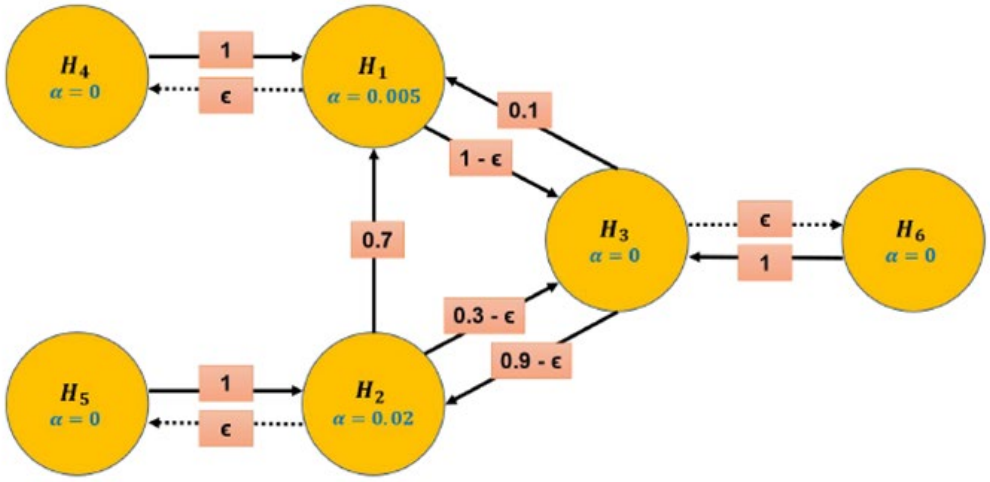
H4: OS between Arm A and Arm B in the ITT population

H5: OS between Arm A and Arm B in the *ESR1*-mutation detected population

H6: OS between Arm C and Arm A in the [concurrently randomised] ITT population.

Initially, the overall 1-sided significance level of α = 0.025 was to be split between H1 and H2, with H1 tested at the 1-sided significance level of α = 0.005, and H2 tested at the 1-sided significance level of α = 0.02. No significance level (α = 0) was to be initially assigned to H3, H4, H5 and H6. The below figure represents the graph with initially allocated significance levels at each node, and the associated weights for each directed edge from these respective nodes.

Figure 9 Initial graphical representation of testing scheme. Small edge weights are represented by dotted lines. ϵ denotes an infinitesimally small number (ϵ = 10−4)



The other secondary endpoints were not included as part of the graphical approach and were included as supportive endpoints.

Interim analyses for PFS

Arm A vs Arm B: One interim analysis was planned for the primary endpoint of PFS between Arm A and Arm B, when approximately 192 of the 480 events (40% information fractions, respectively) had been observed in the ITT analyses set. The purpose of this interim was to allow the trial to stop early due to futility. The DMC was to recommend stopping the trial (for the comparison between Arm A versus Arm B) for futility if the hazard ratio was above 1.128. There were no plans to stop for superiority at the time of this interim analysis.

Arm A vs Arm B, *ESR1*-mutation: For PFS between Arm A and Arm B in the *ESR1*-mutation detected population, if approximately 192 events had been observed in this subset at the time of final PFS analysis in the ITT population, the final PFS analysis for the *ESR1*-mutation detected population was to be conducted at the 1-sided alpha level of 0.02 (assuming the initial alpha level based on the graphical approach). If the target number of events in this subset had not been reached at this time, 1 interim analysis for efficacy may be conducted in the subset at this time if deemed appropriate. The Lan-DeMets spending function (O'Brien-Fleming type) was to be used to determine the boundaries at the interim and final analyses for PFS in the *ESR1*-mutation detected population. If the number of events in the subset was close enough to the target number of events then the final analysis for PFS in the subset may have been performed at this time.

Arm C vs Arm A: One interim analysis was planned for the primary endpoint of PFS between Arm C and Arm A after approximately 100 of the 248 events (40% information fraction) had been observed in the concurrent ITT analysis set. The purpose of the interim was to allow the trial comparison for Arm C versus Arm A to stop early (stop the enrolment to Arm C if not completed) due to futility. The DMC was to recommend stopping the trial (for Arm C versus Arm A) for futility if the hazard ratio was above 1.126. There were no plans to stop for superiority at the time of this interim analysis.

Interim analyses for OS

For OS between Arm A and Arm B in the ITT population, the following analyses were planned:

- OS look 1 At the time of final analysis of PFS between Arm A vs Arm B in the ITT population
- OS look 2 Approximately 255 OS events
- OS look 3 Approximately 330 OS events
- Final OS Approximately 390 OS events (estimated to be 3 years after the final analysis of PFS).

According to the graphical approach, if PFS (H1) was not significant after the final analysis, OS (H4) would not be statistically evaluated.

For OS between Arm A and Arm B in the *ESR1*-mutation detected population (H5), the following analyses were planned assuming that the final analysis for Arm A versus Arm B in the ITT population and the final analysis for Arm A versus Arm B in the *ESR1*-mutation detected population occurred at the same time.

- OS look 1 At the time of final analysis of PFS between Arm A vs Arm B in the ITT population
- OS look 2 At the time of OS look 2 in ITT
- OS look 3 At the time of OS look 3 in ITT
- Final OS Approximately 155 OS events (estimated to be 3 years after the final analysis of PFS).

Multiple looks were also planned for the OS endpoint between Arm C and Arm A in the ITT population (H6).

Statistical analyses

Estimation of the primary endpoint, PFS

The Kaplan-Meier method was used to estimate the PFS curves. Median PFS and PFS rates at various time points with 95% CIs were estimated for each arm. The comparison of PFS curves between treatment arms was conducted by a stratified log-rank test as the primary analysis, stratified by the randomisation strata. The treatment effect was estimated by hazard ratio with its corresponding 95%

CIs using the stratified Cox proportional hazard model with treatment as the only covariate, stratified by the randomisation strata.

For the PFS analyses related to the *ESR1*-mutated population, region was excluded as a stratification factor to reduce the number of strata from 12 to 4.

For the primary analysis, censoring rules were applied in line with the primary estimand, with a patient's followed-up time censored at the date of last adequate tumour assessment that was taken prior to start of new therapy or date of randomization (whichever is later) if a patient received new anticancer therapy before progression. Patients' follow up times were censored at randomisation if there was no post-baseline assessment available. If a patient missed two or more assessment visits then their follow up time was also censored at the last adequate assessment or baseline, regardless of whether there was a progression or death recorded later.

Estimation of the key secondary endpoint, OS

OS curves, median OS, and OS rates at 1 year, 2 years, and 3 years with 95% CI for each treatment arm were planned to be estimated using the Kaplan-Meier method. OS was to be compared between treatment arms using a log-rank test stratified by the same factors as PFS, as the primary analysis for OS. The corresponding hazard ratio between treatment arms was to be estimated using the stratified Cox regression model. The inferential analysis of OS was to be based on the stratified analyses.

Estimation of the supportive secondary endpoints

All supportive secondary endpoint analyses were to be conducted for each comparison (Arm A versus Arm B, and Arm C versus Arm A) per the prespecified analysis population for each comparison.

Progression-free survival by blinded independent review committee (BIRC) was defined the same way as the primary endpoint of PFS. For BIRC analysis, scans were to be collected and reviewed in all randomized participants based on RECIST version 1.1. PFS as assessed by BIRC was intended to evaluate the reliability of the treatment effect based on the investigator-assessed PFS. Discordance rates (i.e. differences in assessment of progression between investigator and BIRC) were to be summarized for each arm. Specifically, differential discordance was to be described using early discrepancy rate (EDR)and late discrepancy rate (LRD) differences.

Objective response rate (ORR) was defined as the proportion of participants who achieve a confirmed best overall response of CR or PR. The ORR with 95% CI was to be summarized for each treatment arm and compared between treatment arms using the Cochran-Mantel-Haenszel test adjusting for the randomisation strata. The analysis of ORR was conducted in the ORR evaluable population. The Mantel-Haenszel estimate of the common risk difference of ORR with 95% CI between 2 arms was also estimated.

Clinical benefit rate (CBR) is defined as the number of participants who achieve a best overall response of CR, PR, or SD $\geq$ 24 weeks divided by the total number of participants randomised to the corresponding treatment arm. The CBR with 95% CI will be summarized for each treatment arm and compared between treatment arms using the Cochran-Mantel-Haenszel test adjusting for the randomization strata. The Mantel-Haenszel estimate of the common risk difference of CBR with 95% CI between 2 arms will also be estimated.

Duration of response (DoR) was defined as the time from the date that measurement criteria for complete response (CR) or partial response (PR) (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. The DoR was to be censored according to the same scheme as the main scheme for PFS. Median DoR with 95% CI and curves for each treatment arm was be estimated using the Kaplan-Meier

method. The analysis of DoR was to be based on the participants who achieve an objective response (CR or PR).

PFS and OS were to be compared between Arm C and Arm B using the stratified log-rank test. The treatment effect was to be estimated by hazard ratio with its corresponding 95% CIs using the stratified Cox proportional hazard model. The analysis population for Arm C versus Arm B was defined as all concurrently randomized participants between two arms. Subgroup analyses (e.g. based on stratification factors) were to be conducted if deemed appropriate. Other efficacy endpoints may also be compared between Arm C and Arm B if deemed appropriate.

Supplementary and sensitivity analyses for PFS

Multiple sensitivity analyses for the primary PFS analysis were planned to be conducted as defined below:

- Using different rules for censoring including following up for progression or death regardless of missed visits, regardless of use of new anticancer therapy (i.e. treatment policy strategy), or regardless of both
- Using an unstratified log-rank test and unstratified Cox model
- Using stratification factors based on the case report form (CRF) data if available
- For PFS comparing Arm A versus Arm B in the *ESR1*-mutation detected population, in addition to the preplanned analyses above, PFS analysis in the *ESR1*-mutation not detected population will also be conducted.
- For PFS comparing Arm C versus Arm A in the ITT population, using the full ITT population (i.e., all participants randomized to both arms will be used).

Results

- **Participant flow**

A total of 1172 patients were screened, of which 874 were randomized. Of the 298 patients who were screened but not randomized, most were screen fail patients who did not meet the eligibility criteria (n=260, primarily due to disease-stage requirements n=95, 36.5%). Other reasons included withdrawal by patient (n=32), physicians' decision (n=5), and death (n=1).

Few randomized patients (1.7%) were not treated. At the time of data cut-off (DCO) 24 June 2024), 261/331 (78.5%) patients in Arm A, 281/330 (85.2%) of patients in Arm B, and 134/213 (62.9%) patients in Arm C were off treatment, predominantly due to progressive disease. Discontinuation due to AEs occurred at a rate of ≤5% in all arms. Patient disposition for the ITT and concurrent ITT is shown in Table 22 and Table 23, respectively.

Table 17 Summary of patient disposition in the ITT population

Category, n (%)	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213
Enrolled (randomized)			
Treated	326 (98.5)	324 (98.2)	209 (98.1)
Never treated	5 (1.5)	6 (1.8)	4 (1.9)
Discontinuation of all study treatment			
Progressive disease	239 (72.2)	258 (78.2)	113 (53.1)
Adverse event	9 (2.7)	0	11 (5.2)
Withdrawal by subject	4 (1.2)	11 (3.3)	5 (2.3)
Death	7 (2.1)	6 (1.8)	4 (1.9)
Physician decision	0	3 (0.9)	1 (0.5)
Protocol deviation	2 (0.6)	3 (0.9)	0
On post treatment discontinuation follow up	158 (47.7)	161 (48.8)	77 (36.2)
Off post treatment discontinuation follow up	95 (28.7)	108 (32.7)	48 (22.5)
Death	55 (16.6)	84 (25.5)	32 (15.0)
Lost to follow up	11 (3.3)	4 (1.2)	5 (2.3)
Withdrawal by subject	29 (8.8)	20 (6.1)	11 (5.2)

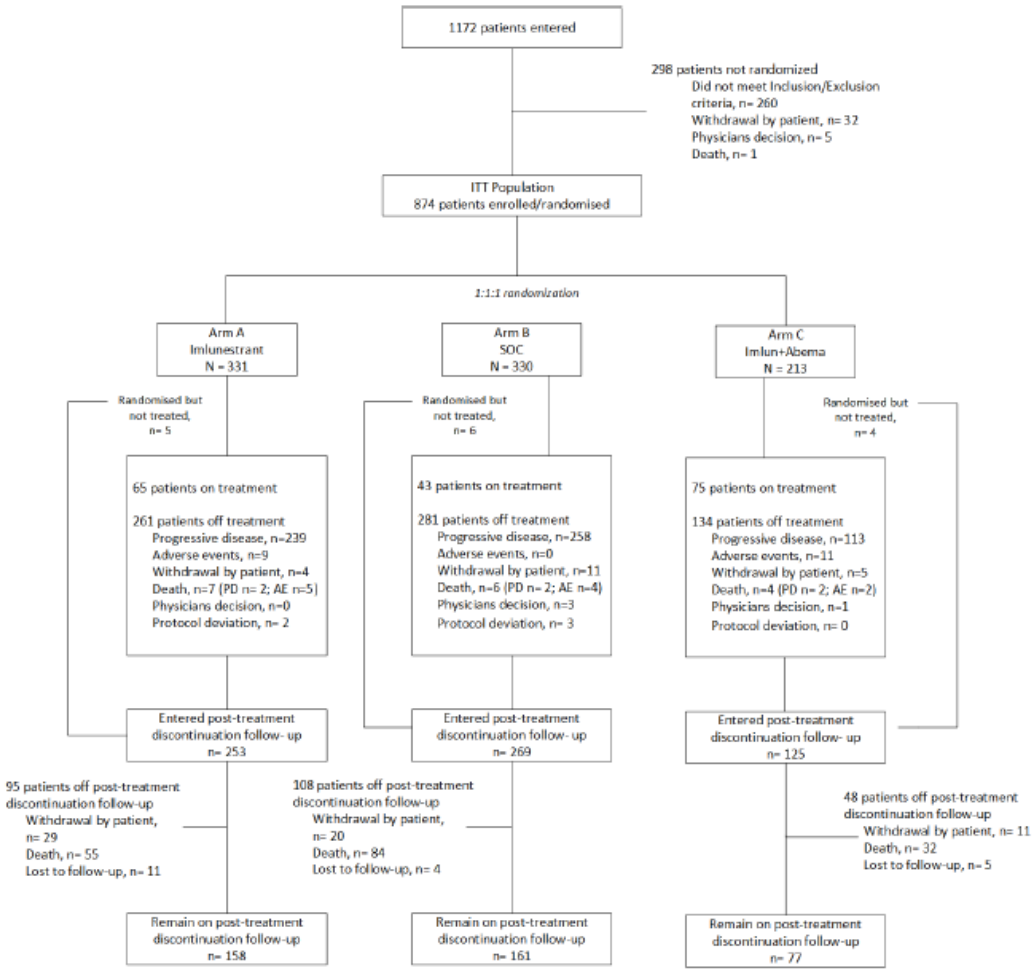
Abbreviations: Abema = abemaciclib; Imlun = imlunestrant; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Table 18 Summary of patient disposition concurrent ITT population

Category, n (%)	Arm A Imlun N=213	Arm B SOC N=213	Arm C Imlun+Abema N=213
Enrolled (randomised)			
Treated	209 (98.1)	207 (97.2)	209 (98.1)
Never Treated	4 (1.9)	6 (2.8)	4 (1.9)
Discontinuation of all study treatment			
Progressive disease	148 (69.5)	166 (77.9)	113 (53.1)
Adverse event	7 (3.3)	0	11 (5.2)
Physician decision	0	2 (0.9)	1 (0.5)
Withdrawal by subject	3 (1.4)	8 (3.8)	5 (2.3)
Death	2 (0.9)	3 (1.4)	4 (1.9)
Protocol deviation	0	1 (0.5)	0
On post-treatment-discontinuation follow-up[a]	115 (54.0)	126 (59.2)	77 (36.2)
Off post-treatment-discontinuation follow-up[a]	41 (19.2)	46 (21.6)	48 (22.5)
Death	26 (12.2)	37 (17.4)	32 (15.0)
Lost to follow-up	4 (1.9)	1 (0.5)	5 (2.3)
Withdrawal by subject	11 (5.2)	8 (3.8)	11 (5.2)

Abbreviations: Abema = abemaciclib; Imlun = imlunestrant; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; n = number of subjects within category; N = number of subjects in Concurrent ITT Population; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
a Includes patients who were off treatment as well as the patients who were Enrolled/Randomised,but never treated. Data cutoff date is 24 June 2024.

Figure 10 Patient disposition



Abbreviations: Abema = abemaciclib; Imlun = imlunestrant; n = number of patients in the specific category; N = number of patients; ITT = intention-to-treat; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] 1:1:1 randomization occurred after implementation of Arm C.

- **Recruitment**

The study initiation date was 04 October 2021, and the first patient entering treatment was on 15 October 2021. Enrolment to Arm C began in March 2022 at which point 122 patients had been randomized across Arm A and Arm B. The Enrolment end date was 01 November 2023. The data cut-off (DCO) date for the Clinical Study Report was 24 June 2024.

Patients were randomized across 195 sites in 22 countries worldwide.

Median follow-up time at DCO was 16.1 months in Arm A, 16.9 months in Arm B and 13.7 months in Arm C.

- **Conduct of the study**

The original study protocol (1 March 2021) was amended four times. Relevant amendments concerned the inclusion of a third treatment arm (amendment a), addition of a new primary endpoint for the comparison of the *ESR1*-mutation detected population (amendment b), and altering the alpha allocation in the graphical approach to assign greater alpha to the *ESR1* mutated subgroup and lower alpha to the comparison in the ITT (amendment d).

All 3 arms remained open until the target enrolment for Arm A and Arm B was met. At end of enrolment, 426 patients had been concurrently randomised between Arm A and Arm C.

Table 19 Summary of protocol amendments

Protocol amendment	Date	Key Reasons for Amendment
EMBER-3	15-Mar-2021	NA
EMBER-3 amendment (a)	08-Oct-2021	Addition of: • A new treatment arm (Arm C). • Inclusion criteria #3 where patients were expected to have received prior treatment with a CDK4/6 inhibitor if approved and reimbursed.
EMBER-3 amendment (b)	17-Aug-2022	• Primary and secondary endpoints were updated. ○ The comparison of PFS between Arm A and B in the *ESR1*-mutation detected population was elevated to a primary objective. • Inclusion criteria #3 revised to allow the Sponsor to limit the number of participants who had not received a prior CDK4/6 inhibitor.

EMBER-3 amendment (c)	11-Nov-2022	• Projected PFS hazard ratios were updated based on Phase 3 results for other oral SERDs. The updated projections necessitated an increase in the estimated total study enrollment.
		  ○ The sample size for Arms A and B increased from approximately 500 to 640 patients (320 in each arm).
		  ○ Added that Arm C was expected to enroll approximately 220 patients and would complete at the same time as Arms A and B.
		• Added exploratory analyses to assess PFS and OS of Arm C compared to Arm B.

EMBER-3 amendment (d)	31-Jul-2023	The initial alpha allocation for the PFS primary endpoint analysis between Arms A and B for ITT and the *ESR1* subgroup was changed with greater alpha assigned to the later. This was based on new external data of oral SERDs in breast cancer.

Abbreviations: CDK4/6 = cyclin-dependent kinase 4/6; *ESR1*m = estrogen receptor 1-mutation; ITT = intention-to-treat; NA = not applicable; OS = overall survival; PFS = progression-free survival; SERD = selective estrogen receptor degrader.

The SAP amendments followed the protocol amendments, in response to the specification of the three dual primary endpoints, the multiple testing procedure moved from hierarchical in SAP version 3 (24 March 2022) to a graphical approach in SAP version 4 (approval date 6 December 2022), with SAP version 5 (approval data 24 August 2023) reflecting the decision to change the initial alpha allocation in protocol amendment (d).

Important protocol deviations were reported for about 30% of patients. Most violations were related to visit schedule criteria, inclusion criteria, and treatment assignment/randomization.

Table 20 Summary of important protocol deviations for the ITT population

Important protocol deviation	Number (%) of patients			
	Arm A (N=331) n (%)	Arm B (N= 330) n(%)	Arm C (N=213) n(%)	Total (N=874) n(%)
Subjects with ≥1 important protocol deviation	105 (31.7)	107 (32.4)	60 (2.8)	272 (31.1)
Visit Schedule Criteria	36 (10.9)	35 (10.6)	24 (11.3)	95 (10.9)

Important protocol deviation	Number (%) of patients Arm A (N=331) n (%)	Arm B (N= 330) n(%)	Arm C (N=213) n(%)	Total (N=874) n(%)
Eligibility Criteria	41 (12.4)	33 (10.0)	14 (6.6)	88 (10.1)
Inclusion criteria #1-14[a]	33 (10.0)	19 (5.8)	10 (4.7)	62 (7.1)
#2 (Have a diagnosis of ER+, HER2- breast cancer)	0 (0.0)	1 (0.3)	2 (0.9)	3 (0.3)
#3 (Have a locally-advanced – not amenable to curative treatment by surgery – or metastatic disease and fulfil 1 of 3 criterion)	17 (5.1)	10 (3.0)	5 (2.3)	32 (3.7)
#5 (Must be postmenopausal due to surgery, natural menopause, or ovarian function suppression with a GnRH agonist)	3 (0.9)	1 (0.3)	1 (0.5)	5 (0.6)
#6 (Females must have a negative pregnancy test at baseline and use effective birth control during the study and for 6 months (2 years for fulvestrant) following last dose)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
#7 (If male, must agree to hormone suppression and highly effective methods of birth control)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
#8 (Must have measurable disease or specific types of nonmeasurable bone-only disease)	11 (3.3)	5 (1.5)	3 (1.4)	19 (2.2)
#10 (Have adequate organ function)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
#11 (Discontinued previous therapies for cancer prior to receiving study drug, and recovered from the acute effects of therapy to at least Grade 1, except for residual alopecia and peripheral neuropathy, therapy washout periods required.)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Exclusion Criteria #15-30[a]	13 (3.9)	14 (4.2)	4 (1.9)	31 (3.5)
#15 (Prior treatment with chemotherapy excluding neoadjuvant/adjuvant, fulvestrant, any ER-directed therapy, PI3K, m-TOR or AKT-inhibitor, progression on prior exemestane treatment must not receive this if randomised to control arm)	0 (0.0)	1 (0.3)	1 (0.5)	2 (0.2)
#19 (Have visceral crisis, lymphangitic spread within lung or any evidence of leptomeningeal disease)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
#20 (Have symptomatic or untreated brain metastasis)	9 (2.7)	8 (2.4)	4 (1.9)	21 (2.4)
#22 (Have had wide-field radiotherapy ≤4 weeks, or limited field radiation for palliation ≤1 week prior to randomisation.)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
#23 (Have a serious cardiac condition)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
#27 (Have active bacterial or fungal infection, or detectable viral infection)	1 (0.3)	3 (0.9)	0 (0.0)	4 (0.5)
#29 (Have initiated bisphosphonates or approved RANK-L targeted agents <7 days prior to randomisation)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Treatment Assignment/Randomisation	35 (10.6)	29 (8.8)	13 (6.1)	77 (8.8)
Safety Reporting	9 (2.7)	14 (4.2)	8 (3.8)	31 (3.5)
Study Procedure Compliance	10 (3.0)	6 (1.8)	11 (5.2)	27 (3.1)
Informed Consent	3 (0.9)	6 (1.8)	1 (0.5)	10 (1.1)
Investigational Medicinal Product and/or Investigational Device	1 (0.3)	1 (0.3)	5 (2.3)	7 (0.8)
Discontinuation Criteria	1 (0.3)	2 (0.6)	1 (0.5)	4 (0.5)
Concomitant Medication	1 (0.3)	2 (0.6)	0 (0.0)	3 (0.3)

Abbreviations: AKT = protein kinase B; ER = oestrogen receptor; ER+ = oestrogen receptor-positive; ET = endocrine therapy; GnRH = gonadotropin-releasing hormone; HER2- = human epidermal growth factor receptor 2-negative; m-TOR = mammalian target of rapamycin; N = number of subjects in intention-to-treatment population; n = number of subjects in the specified category; PI3K = phosphoinositide 3-kinase; RANK = receptor activator of nuclear factor κ B; RANK-L = RANK ligand.
a Full definition of inclusion and exclusion criteria are outlined in Section 5.1 of Study JZLC protocol amendment D. Data cutoff date is 24 June 2024.

Table 21 Comparison of Stratification Errors - IWRS versus eCRF Arm A (Imlun), Arm B (SOC) and Arm C (Imlun+Abema) ITT Population

	Arm A (Imlun) N=331 n/N (%)	**Arm B (SOC) N=330 n/N (%)**	**Arm C (Imlun +Abema) N=213 n/N (%)**

Visceral Metastases (Inconsistent between eCRF and IWRS)	**32/331 (9.7)**	**25/330 (7.6)**	**13/213 (6.1)**
Prior CDK4/6 Inhibitor (Inconsistent between eCRF and IWRS)	**4/331 (1.2)**	**4/330 (1.2)**	**1/213 (0.5)**

Abbreviations: Abema = abemaciclib; CDK4/6 = cyclin-dependent kinase 4 and 6; eCRF = electronic case report form; Imlun = imlunestrant; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; IWRS = interactive web report system; n = number of subjects with an event in the subgroup; N = total number of subjects in the population within the treatment group; SOC = investigator's choice of endocrine therapy of fulvestrant or exemestane.
Data cutoff date is 24 June 2024.

Ten investigator's sites were subject to an independent audit.

- **Baseline data**

About 70% of patients had one line of prior ET and 32% in the adjuvant setting only, whereas about 60% had received prior CDK4/6i mainly in the advanced/metastatic setting. Less than 5% received prior abemaciclib.

Overall, 37% of patients had an *ESR1*-m-detected, with the lowest percentage in the imlun+abema arm (31.5%) and highest in the imlunestrant arm (41.7%). A limited number of patients (<10%) had a BRCA mutation, in line with the exclusion criteria. Overall, 40% of patients had a mutation in the AKT pathway and 32% had PIK3CA mutation only, for which targeted therapies might have been more appropriate.

Within the *ESR1*m-detected patient population, the known baseline characteristics were generally balanced between the monotherapy arms. For the combination treatment, patients were generally older (≥65 yrs), had higher frequencies (>5%) of prior CDK4/6i treatment, a mutation in the AKT pathway, and disease with 1 organ involved. Further, patients were more frequently from North America/Western Europe.

The concurrent ITT population largely resembles the ITT population and baseline characteristics were generally balanced among treatment arms.

Details on patient characteristics, disease characteristics and prior treatment are given in the following tables.

Table 22 Summary of patient demographics ITT population

Category	ITT Population			
	Arm A Imlunestrant N=331	**Arm B SOC N=330**	**Arm C Imlun+Abema N=213**	**Total N=874**
Age (years)				
Median	61.0	62.0	62.0	61.0
Range	28-87	27-89	36-87	27-89
< 65	211 (63.7)	197 (59.7)	122 (57.3)	530 (60.6)
≥65	120 (36.3)	133 (40.3)	91 (42.7)	344 (39.4)
65-74	82 (24.8)	83 (25.2)	64 (30.0)	229 (26.2)
75-84	32 (9.7)	44 (13.3)	23 (10.8)	99 (11.3)
≥85	6 (1.8)	6 (1.8)	4 (1.9)	16 (1.8)
Sex, n (%)				
Female	327 (98.8)	329 (99.7)	211 (99.1)	867 (99.2)
Male	4 (1.2)	1 (0.3)	2 (0.9)	7 (0.8)
Weight, kg				
Median	66.95	67.45	65.30	66.60
Range	37.0-142.7	38.0-129.1	38.9-122.1	37.0-142.7
Race, n (%)				

Category	ITT Population			
	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213	Total N=874
White	186 (56.2)	191 (57.9)	111 (52.1)	488 (55.8)
Black or African American	11 (3.3)	7 (2.1)	8 (3.8)	26 (3.0)
Asian	92 (27.8)	96 (29.1)	72 (33.8)	260 (29.7)
American Indian or Alaska native	23 (6.9)	16 (4.8)	3 (1.4)	42 (4.8)
Multiple	2 (0.6)	7 (2.1)	3 (1.4)	12 (1.4)
Missing	17 (5.1)	13 (3.9)	16 (7.5)	46 (5.3)
Ethnicity, n (%)				
Hispanic or Latino	79 (23.9)	80 (24.2)	37 (17.4)	196 (22.4)
Not Hispanic or Latino	218 (65.9)	216 (65.5)	148 (69.5)	582 (66.6)
Not Reported	33 (10.0)	34 (10.3)	27 (12.7)	94 (10.8)
Region, n (%)				
East Asia	83 (25.1)	84 (25.5)	66 (31.0)	233 (26.7)
North America/Western Europe	127 (38.4)	127 (38.5)	95 (44.6)	349 (39.9)
Other	121 (36.6)	119 (36.1)	52 (24.4)	292 (33.4)

Abbreviations: Abema = abemaciclib; *ESR1*m = oestrogen receptor 1 mutation; Imlun = imlunestrant; ITT = intention-to-treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Table 23 Summary of patient demographics *ESR1*m-detected Population

Category	*ESR1*m-detected Population			
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm C Imlun+Abema N=67	Total
Age (years)				
Median	61.0	59.5	63.0	61.0
Range	28-85	33-85	37-80	28-85
<65	91 (65.9)	78 (66.1)	38 (56.7)	207 (64.1)
≥65	47 (34.1)	40 (33.9)	29 (43.3)	116 (35.9)
65-74	31 (22.5)	24 (20.3)	21 (31.3)	76 (23.5)
75-84	14 (10.1)	15 (12.7)	8 (11.9)	37 (11.5)
≥85	2 (1.4)	1 (0.8)	0	3 (0.9)
Sex, n (%)				
Female	138 (100)	118 (100)	67 (100)	323 (100.0)
Male	0	0	0	0
Weight, kg				
Median	69.40	69.80	65.90	69.05
Range	42.5-111.0	38.0-127.3	47.0-114.8	38.0 – 127.3
Race, n (%)				
White	80 (58.0)	76 (64.4)	42 (62.7)	198 (61.3)
Black or African American	7 (5.1)	3 (2.5)	1 (1.5)	11 (3.4)
Asian	35 (25.4)	31 (26.3)	18 (26.9)	84 (26.0)
American Indian or Alaska native	7 (5.1)	3 (2.5)	0	10 (3.1)
Multiple	1 (0.7)	1 (0.8)	0	2 (0.6)
Missing	8 (5.8)	4 (3.4)	6 (9.0)	18 (5.6)
Ethnicity, n (%)				

Category	*ESR1*m-detected Population			
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm C Imlun+Abema N=67	Total
Hispanic or Latino	25 (18.1)	23 (19.5)	9 (13.4)	57 (17.6)
Not Hispanic or Latino	98 (71.0)	83 (70.3)	48 (71.6)	229 (70.9)
Not Reported	14 (10.1)	12 (10.2)	9 (13.4)	35 (10.8)
Region, n (%)				
East Asia	30 (21.7)	26 (22.0)	17 (25.4)	73 (22.6)
North America/Western Europe	63 (45.7)	54 (45.8)	36 (53.7)	153 (47.4)
Other	45 (32.6)	38 (32.2)	14 (20.9)	97 (30.0)

Abbreviations: Abema = abemaciclib; Imlun = imlunestrant; ITT = intention-to-treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Table 24 Summary of patient demographics – Concurrent ITT population

Category	Concurrent ITT Population			
	Arm A Imlunestrant N=213	Arm B SOC N=213	Arm C Imlun+Abema N=213	Total N=639
Age (years)				
Median	61.0	63.0	62.0	62.0
Range	31-87	27-87	36-87	27-87
<65	134 (62.9)	117 (54.9)	122 (57.3)	373 (58.4)
≥65	79 (37.1)	96 (45.1)	91 (42.7)	266 (41.6)
65-74	54 (25.4)	61 (28.6)	64 (30.0)	179 (28.0)
75-84	21 (9.9)	31 (14.6)	23 (10.8)	75 (11.7)
≥85	4 (1.9)	4 (1.9)	4 (1.9)	12 (1.9)
Sex, n (%)				
Female	210 (98.6)	212 (99.5)	211 (99.1)	633 (99.1)
Male	3 (1.4)	1 (0.5)	2 (0.9)	6 (0.9)
Weight, kg				
Median	67.20	66.40	65.30	66.50
Range	40.0-142.7	38.0-129.1	38.9-122.1	38.0-142.7
Race, n (%)				
White	113 (53.1)	115 (54.0)	111 (52.1)	339 (53.1)
Black or African American	11 (5.2)	7 (3.3)	8 (3.8)	26 (4.1)
Asian	72 (33.8)	71 (33.3)	72 (33.8)	215 (33.6)
American Indian or Alaska native	1 (0.5)	4 (1.9)	3 (1.4)	8 (1.3)
Multiple	2 (0.9)	5 (2.3)	3 (1.4)	10 (1.6)
Missing	14 (6.6)	11 (5.2)	16 (7.5)	41 (6.4)
Ethnicity, n (%)				
Hispanic or Latino	31 (14.6)	35 (16.4)	37 (17.4)	103 (16.1)
Not Hispanic or Latino	154 (72.3)	151 (70.9)	148 (69.5)	453 (70.9)
Not Reported	27 (12.7)	27 (12.7)	27 (12.7)	81 (12.7)
Region, n (%)				
East Asia	67 (31.5)	66 (31.0)	66 (31.0)	199 (31.1)
North America/Western Europe	92 (43.2)	94 (44.1)	95 (44.6)	281 (44.0)
Other	54 (25.4)	53 (24.9)	52 (24.4)	159 (24.9)

Abbreviations: Abema = abemaciclib; Imlun = imlunestrant; ITT = intention-to-treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Table 25 Summary of key baseline disease characteristics

Category	ITT Population				*ESR1*m-detected Population			
	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213	Total N = 874	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm C Imlun+Abema N=67	Total N=323
Median duration of disease, months (Q1-Q3)	45 (24, 95)	46 (22, 103)	44 (25, 105)	45 (23, 102)	40 (24, 98)	46 (22, 128)	39 (25, 82)	41 (23, 105)
Initial pathological diagnosis type, n (%)								
Carcinoma Ductal Breast	235 (71.0)	229 (69.4)	141 (66.2)	605 (69.2)	103 (74.6)	87 (73.7)	46 (68.7)	236 (73.1)
Carcinoma Lobular Breast	32 (9.7)	34 (10.3)	30 (14.1)	96 (11.0)	11 (8.0)	12 (10.2)	7 (10.4)	30 (9.3)
Adenocarcinoma, Breast	1 (0.3)	1 (0.3)	0	2 (0.2)	0	0	0	0
Carcinoma, Breast	54 (16.3)	64 (19.4)	38 (17.8)	156 (17.8)	21 (15.2)	18 (15.3)	14 (20.9)	53 (16.4)
Other	9 (2.7)	2 (0.6)	4 (1.9)	15 (1.7)	3 (2.2)	1 (0.8)	0	4 (1.2)
Disease stage at study entry, n (%)								
I	0	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0	0
IIIB/IIIC	14 (4.2)	9 (2.7)	4 (1.9)	27 (3.1)	4 (2.9)	1 (0.8)	2 (3.0)	7 (2.2)
IV	317 (95.8)	321 (97.3)	209 (98.1)	847 (96.9)	134 (97.1)	117 (99.2)	65 (97.0)	316 (97.8)
Initial Histopathological diagnosis: Grade, n (%)								
1	30 (9.1)	26 (7.9)	18 (8.5)	74(8.5)	11 (8.0)	5 (4.2)	6 (9.0)	22 (6.8)
2	159 (48.0)	180 (54.5)	125 (58.7)	464(53.1)	68 (49.3)	69 (58.5)	36 (53.7)	173 (53.6)
3	77 (23.3)	68 (20.6)	33 (15.5)	178(20.4)	34 (24.6)	26 (22.0)	14 (20.9)	74 (22.9)
Not assessed	54 (16.3)	46 (13.9)	28 (13.1)	128(14.6)	22 (15.9)	16 (13.6)	8 (11.9)	46 (14.2)
ECOG PS, n (%)								
0	219 (66.2)	208 (63.0)	142 (66.7)	569 (65.1)	85 (61.6)	77 (65.3)	44 (65.7)	206 (63.8)
1	112 (33.8)	122 (37.0)	71 (33.3)	305 (34.9)	53 (38.4)	41 (34.7)	23 (34.3)	117 (36.2)
Baseline Menopausal Status								
Post menopausal	278 (84.0)	284 (86.1)	184 (86.4)	746 (85.4)	122 (88.4)	105 (89.0)	60 (89.6)	287 (88.9)
Pre menopausal	49 (14.8)	45 (13.6)	27 (12.7)	121 (13.8)	16 (11.6)	13 (11.0)	7 (10.4)	36 (11.1)
Missing	4 (1.2)	1 (0.3)	2 (0.9)	7 (0.8)	0	0	0	0
ESR1 mutation status, n (%)								
Detected	138 (41.7)	118 (35.8)	67 (31.5)	323 (37.0)	138 (100)	118 (100)	67 (100)	67 (100)
Not detected	193 (58.3)	212 (64.2)	146 (68.6)	551 (63)	0	0	0	0
ER Status, n (%)								
Positive	331 (100)	330 (100)	213 (100)	874 (100)	138 (100)	118 (100)	67 (100)	323 (100)
Negative	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0
HER2 status per ASCO guidelines[a], n (%)								
Negative	331 (100)	330 (100)	212 (99.5)	873 (99.9)	138 (100)	118 (100)	66 (98.5)	322 (99.7)
Positive	0	0	0	0	0	0	0	0
Missing	0	0	1 (0.5)	1 (0.1)	0	0	1 (1.5)	1 (0.3)
HER2 IHC status[b], n (%)								
Negative (IHC 0)	143 (43.2)	159 (48.2)	82 (38.5)	384 (43.9)	55 (39.9)	59 (50.0)	23 (34.3)	137 (42.4)
Low (IHC 1+, IHC 2+/FISH-)	139 (42.0)	125 (37.9)	96 (45.1)	360 (41.2)	60 (43.5)	40 (33.9)	31 (46.3)	131 (40.6)
Unknown	5 (1.5)	2 (0.6)	3 (1.4)	10 (1.1)	2 (1.4)	1 (0.8)	2 (3.0)	5 (1.5)
Missing	44 (13.3)	44 (13.3)	32 (15.0)	120 (13.7)	21 (15.2)	18 (15.3)	11 (16.4)	50 (15.5)
PgR Status, n (%)								
Positive	257 (77.6)	260 (78.8)	158 (74.2)	675 (77.2)	109 (79.0)	97 (82.2)	58 (86.6)	264 (81.7)
Negative	70 (21.1)	67 (20.3)	53 (24.9)	190 (21.7)	26 (18.8)	21 (17.8)	9 (13.4)	56 (17.3)
Unknown	3 (0.9)	3 (0.9)	1 (0.5)	7 (0.8)	2 (1.4)	0	0	2 (0.6)
Missing	1 (0.3)	0	1 (0.5)	2 (0.2)	0	0	0	0
De Novo Metastatic n (%)								

Category	ITT Population				*ESR1*m-detected Population			
	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213	Total N = 874	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm C Imlun+Abema N=67	Total N=323
No	201 (60.7)	207 (62.7)	124 (58.2)	532 (60.9)	68 (49.3)	63 (53.4)	30 (44.8)	161 (49.8)
Yes	130 (39.3)	123 (37.3)	89 (41.8)	342 (39.1)	70 (50.7)	55 (46.6)	37 (55.2)	162 (50.2)
BRCA1/BRCA2 Mutation Status n (%)								
Detected	20 (6.0)	19 (5.8)	19 (8.9)	58 (6.6)	9 (6.5)	11 (9.3)	7 (10.4)	27 (8.4)
Germline	9 (2.7)	11 (3.3)	14 (6.6)	34 (3.9)	3 (2.2)	6 (5.1)	4 (6.0)	13 (4.0)
Somatic	11 (3.3)	10 (3.0)	6 (2.8)	27 (3.1)	6 (4.3)	6 (5.1)	3 (4.5)	15 (4.6)
Not detected	288 (87.0)	292 (88.5)	178 (83.6)	758 (86.7)	127 (92.0)	107 (90.7)	58 (86.6)	292 (90.4)
Not evaluable	23 (6.9)	19 (5.8)	16 (7.5)	58 (6.6)	2 (1.4)	0	2 (3.0)	4 (1.2)
AKT Pathway Mutation Status n (%)								
Detected	129 (39.0)	128 (38.8)	88 (41.3)	345 (39.5)	72 (52.2)	57 (48.3)	40 (59.7)	169 (52.3)
PIK3CA only	108 (32.6)	104 (31.5)	71 (33.3)	283 (32.4)	62 (44.9)	47 (39.8)	32 (47.8)	141 (43.7)
Not detected	179 (54.1)	183 (55.5)	109 (51.2)	471 (53.9)	64 (46.4)	61 (51.7)	25 (37.3)	150 (46.4)
Not evaluable	23 (6.9)	19 (5.8)	16 (7.5)	58 (6.6)	2 (1.4)	0	2 (3.0)	4 (1.2)
Renal Function n (%)								
Normal (GFR ≥90)	154 (46.5)	159 (48.2)	103 (48.4)	416 (47.6)	60 (43.5)	57 (48.3)	27 (40.3)	144 (44.6)
Mild impairment (GFR 60-<90)	142 (42.9)	136 (41.2)	86 (40.4)	364 (41.6)	61 (44.2)	51 (43.2)	28 (41.8)	140 (43.3)
Moderate impairment (GFR 30-<60)	31 (9.4)	27 (8.2)	21 (9.9)	79 (9.0)	15 (10.9)	8 (6.8)	11 (16.4)	34 (10.5)

Abbreviations: Abema = abemaciclib; AKT = protein kinase B; ASCO = American Society of Clinical Oncology; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ER = oestrogen receptor; ESR1m = oestrogen receptor 1 mutation; FISH = fluorescence in situ hybridization; GFR = glomerular filtration rate; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; Imlun = imlunestrant; ITT = intention-to-treat; n = number of patients in the specific category; N = number of patients; PgR = progesterone receptor; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; Q = quartile; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.
a As reported by investigators.
b Derived from IHC score when reported. A total of 130 patients had tumors with missing/unknown IHC scores.
Data cutoff date is 24 June 2024.

Table 26 Summary of disease burden at baseline ITT and ESR1m-detected population

Category	ITT			*ESR1*m-detected		
	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm C Imlun+Abema N=67
Measurable Disease, n (%)	262 (79.2)	251 (76.1)	167 (78.4)	112 (81.2)	91 (77.1)	54 (80.6)
Number of Organs Involved, n (%)						
1	109 (32.9)	115 (34.8)	76 (35.7)	35 (25.4)	35 (29.7)	23 (34.3)
2	105 (31.7)	98 (29.7)	57 (26.8)	45 (32.6)	39 (33.1)	19 (28.4)
3 or more	117 (35.3)	117 (35.5)	80 (37.6)	58 (42.0)	44 (37.3)	25 (37.3)
Visceral Metastasis, n (%)	189 (57.1)	177 (53.6)	119 (55.9)	84 (60.9)	67 (56.8)	38 (56.7)
Liver	107 (32.3)	98 (29.7)	57 (26.8)	57 (41.3)	47 (39.8)	25 (37.3)
Lung	92 (27.8)	88 (26.7)	58 (27.2)	32 (23.2)	28 (23.7)	15 (22.4)
Liver or lung	171 (51.7)	154 (46.7)	102 (47.9)	77 (55.8)	60 (50.8)	33 (49.3)
Bone-only, n (%)	72 (21.8)	86 (26.1)	51 (23.9)	27 (19.6)	30 (25.4)	16 (23.9)

Abbreviations: Abema = abemaciclib; *ESR1*m = estrogen receptor 1 mutation detected; Imlun = imlunestrant; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Table 27 Summary of key baseline disease characteristics – Concurrent ITT population

Category	Concurrent ITT Population			
	Arm A Imlunestrant N= 213	**Arm B SOC N= 213**	**Arm C Imlun+Abema N= 213**	**Total N = 639**
Median duration of disease, months (Q1-Q3)	46 (25, 105)	48 (22, 124)	44 (25, 105)	46 (24, 107)
Initial pathological diagnosis type, n (%)				
Carcinoma Ductal Breast	147 (69.0)	142 (66.7)	141 (66.2)	430 (67.3)
Carcinoma Lobular Breast	16 (7.5)	23 (10.8)	30 (14.1)	69 (10.8)
Adenocarcinoma, Breast	1 (0.5)	0	0	1 (0.2)
Carcinoma, Breast	40 (18.8)	46 (21.6)	38 (17.8)	124 (19.4)
Other	9 (4.2)	2 (0.9)	4 (1.9)	15 (2.3)
Disease stage at study entry, n (%)				
I	0	0	0	0
II	0	0	0	0
IIIB/IIIC	7 (3.3)	3 (1.4)	4 (1.9)	14 (2.2)
IV	206 (96.7)	210 (98.6)	209 (98.1)	625 (97.8)
Initial Histopathological diagnosis: Grade, n (%)				
1	19 (8.9)	19 (8.9)	18 (8.5)	56 (8.8)
2	92 (43.2)	117 (54.9)	125 (58.7)	334 (52.3)
3	57 (26.8)	41 (19.2)	33(15.5)	131 (20.5)
Not assessed	37 (17.4)	29 (13.6)	28 (13.1)	94 (14.7)
ECOG PS, n (%)				
0	149 (70.0)	145 (68.1)	142 (66.7)	436 (68.2)
1	64 (30.0)	68 (31.9)	71 (33.3)	203 (31.8)
Baseline Menopausal Status				
Post menopausal	178 (83.6)	178 (83.6)	184 (86.4)	540 (84.5)
Pre menopausal	32 (15.0)	34 (16.0)	27 (12.7)	93 (14.6)
Missing	3 (1.4)	1 (0.5)	2 (0.9)	6 (0.9)
ESR1 mutation status, n (%)				
Detected	92 (43.2)	76 (35.7)	67 (31.5)	235 (36.8)
Not detected	121 (56.8)	137 (64.3)	146 (68.6)	404 (63.2)
ER Status, n (%)				
Positive	213 (100)	213 (100)	213 (100)	639 (100)
Negative	0	0	0	0
Unknown	0	0	0	0
HER2 status per ASCO guidelines[a], n (%)				
Negative	213 (100)	213 (100)	212 (99.5)	638 (99.8)
Positive	0	0	0	0
Missing	0	0	1 (0.5)	1 (0.2)
HER2 IHC status[b], n (%)				
Negative (IHC 0)	82 (38.5)	88 (41.3)	82 (38.5)	252 (39.4)
Low (IHC 1+, IHC 2+/FISH-)	104 (48.8)	96 (45.1)	96 (45.1)	296 (46.3)
Unknown	2 (0.9)	1 (0.5)	3 (1.4)	6 (0.9)
Missing	25 (11.7)	28 (13.1)	32 (15.0)	85 (13.3)
PgR Status, n (%)				
Positive	159 (74.6)	165 (77.5)	158 (74.2)	482 (75.4)
Negative	53 (24.9)	46 (21.6)	53 (24.9)	152 (23.8)
Unknown	1 (0.5)	2 (0.9)	1 (0.5)	4 (0.6)
Missing	0	0	1 (0.5)	1 (0.2)

Category	Concurrent ITT Population			
	Arm A Imlunestrant N= 213	Arm B SOC N= 213	Arm C Imlun+Abema N= 213	Total N = 639
De Novo Metastatic n (%)				
No	124 (58.2)	128 (60.1)	124 (58.2)	376 (58.8)
Yes	89 (41.8)	85 (39.9)	89 (41.8)	263 (41.2)
BRCA1/BRCA2 Mutation Status n (%)				
Detected	15 (7.0)	9 (4.2)	19 (8.9)	43 (6.7)
Germline	6 (2.8)	4 (1.9)	14 (6.6)	24 (3.8)
Somatic	9 (4.2)	6 (2.8)	6 (2.8)	21 (3.3)
Not detected	181 (85.0)	188 (88.3)	178 (83.6)	547 (85.6)
Not evaluable	17 (8.0)	16 (7.5)	16 (7.5)	49 (7.7)
AKT Pathway Mutation Status n (%)				
Detected	84 (39.4)	79 (37.1)	88 (41.3)	251 (39.3)
PIK3CA only	72 (33.8)	64 (30.0)	71 (33.3)	207 (32.4)
Not detected	112 (52.6)	118 (55.4)	109 (51.2)	339 (53.1)
Not evaluable	17 (8.0)	16 (7.5)	16 (7.5)	49 (7.7)
Renal Function n (%)				
Normal (GFR ≥90)	96 (45.1)	103 (48.4)	103 (48.4)	302 (47.3)
Mild impairment (GFR 60- <90)	94 (44.1)	85 (39.9)	86 (40.4)	265 (41.5)
Moderate impairment (GFR 30- <60)	22 (10.3)	20 (9.4)	21 (9.9)	63 (9.9)

Abbreviations: Abema = abemaciclib; AKT = protein kinase B; ASCO = American Society of Clinical Oncology; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ER = oestrogen receptor; ESR1m = oestrogen receptor 1 mutation; FISH = fluorescence in situ hybridization; GFR = glomerular filtration rate; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; Imlun = imlunestrant; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; n = number of patients in the specific category; N = number of patients; PgR = progesterone receptor; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; Q = quartile; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.
a As reported by investigators.
b Derived from IHC score when reported.
Data cutoff date is 24 June 2024.

Table 28 Summary of disease burden at baseline – Concurrent ITT population

	Arm A (Imlun) (N=213)	Arm B (SOC) (N=213)	Arm C (Imlun + Abema) (N=213)	Total (N=639)
Measurable Disease n (%)				
Yes	169 (79.3)	162 (76.1)	167 (78.4)	498 (77.9)
No	44 (20.7)	51 (23.9)	46 (21.6)	141 (22.1)
Unknown	0	0	0	0
Number of Organs Involved n (%)				
1	65 (30.5)	80 (37.6)	76 (35.7)	221 (34.6)
2	74 (34.7)	63 (29.6)	57 (26.8)	194 (30.4)
3 or more	74 (34.7)	70 (32.9)	80 (37.6)	224 (35.1)
Unknown	0	0	0	0
Visceral Metastasis (CRF) n (%)				
Yes	120 (56.3)	113 (53.1)	119 (55.9)	352 (55.1)
No	93 (43.7)	100 (46.9)	94 (44.1)	287 (44.9)
Disease Site n (%)				
Bone	156 (73.2)	159 (74.6)	146 (68.5)	461 (72.1)
Liver or Lung	107 (50.2)	101 (47.4)	102 (47.9)	310 (48.5)
Lung	56 (26.3)	54 (25.4)	58 (27.2)	168 (26.3)
Bone only	46 (21.6)	59 (27.7)	51 (23.9)	156 (24.4)

Abbreviations: N = number of subjects in population; n = number of subjects; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane; Abema = abemaciclib.
Data cutoff date is 24-Jun-2024.

The majority of patients in the ITT were treated in the second-line advanced setting (67%) versus the first-line setting (33%). About 70% had received one line of prior ET and 60% had received a prior CDK4/6i. Less than 5% had received prior abemaciclib. Patient demographics for those with *ESR1*-mutated tumours were generally representative of the broader study population (Table 24). Frequencies of prior CDK4/6i were somewhat higher for arm C (ITT) and for the *ESR1*m-detected population. It is noted that patients in Arm C were less frequently from Mexico/Other region compared to other arms in the ITT population (Table 29 - Table 32).

Table 29 Summary of prior cancer therapies in the ITT population

Category, n (%)	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213
Prior anti-cancer therapy			
Surgical procedure	232 (70.1)	231 (70.0)	152 (71.4)
Radiotherapy	185 (55.9)	200 (60.6)	124 (58.2)
Systemic therapy	330 (99.7)[a]	330 (100)	213 (100)
Chemotherapy in (neo)adjuvant setting	136 (41.1)	138 (41.8)	90 (42.3)
Line of therapy in advanced setting			
First-line	109 (32.9)	113 (34.2)	63 (29.6)
Second-line	220 (66.5)	217 (65.8)	149 (70.0)
Prior ET in any setting			
Disease recurrence on or <12 months after completing adjuvant AI for EBC (prior ET in adjuvant setting only)	106 (32.0)	113 (34.2)	63 (29.6)
Disease recurrence >12 months after completing adjuvant ET for EBC and after AI ± CDK4/6i for ABC (prior ET in both adjuvant and metastatic setting)	76 (23.0)	76 (23.0)	53 (24.9)
Disease progression on AI with or without CDK4/6i for de novo MBC (prior ET in metastatic setting only)	132 (39.9)	132 (40.0)	92 (43.2)

Prior lines of ET in any setting			
0	1 (0.3)	1 (0.3)	0
1	230 (69.5)	238 (72.1)	147 (69.0)
≥2	100 (30.2)	91 (27.6)	66 (31.0)
Types of prior ET in any setting			
AI	237 (71.6)	255 (77.3)	161 (75.6)
Tamoxifen	1 (0.3)	0	0
AI and Tamoxifen	92 (27.8)	74 (22.4)	52 (24.4)
Endocrine resistance [b]			
Primary	25 (7.6)	36 (10.9)	16 (7.5)
1st exposure to ET as ET alone	17 (5.1)	26 (7.9)	12 (5.6)
1st exposure to ET as ET+CDK4/6i	8 (2.4)	10 (3.0)	4 (1.9)
Secondary	305 (92.1)	293 (88.8)	197 (92.5)
1st exposure to ET as ET alone	186 (56.2)	179 (54.2)	112 (52.6)
1st exposure to ET as ET+CDK4/6i	119 (36.0)	114 (34.5)	85 (39.9)
Prior CDK4/6i in any setting	195 (58.9)	189 (57.3)	139 (65.3)
Adjuvant	14 (4.2)	15 (4.5)	7 (3.3)
Recurrence during CDK4/6i therapy	7 (2.1)	6 (1.8)	4 (1.9)
Recurrence after CDK4/6i therapy	6 (1.8)	9 (2.7)	3 (1.4)
ABC	181 (54.7)	174 (52.7)	132 (62.0)
Duration <12 months	50 (15.1)	41 (12.4)	40 (18.8)
0-6 months	19 (5.7)	13 (3.9)	19 (8.9)
6-12 months	31 (9.4)	28 (8.5)	21 (9.9)
Duration ≥12 months	131 (39.6)	133 (40.3)	92 (43.2)
12-18 months	32 (9.7)	25 (7.6)	20 (9.4)
≥18 months	99 (29.9)	108 (32.7)	72 (33.8)
Type of prior CDK4/6i in ABC			
Palbociclib	112 (33.8)	121 (36.7)	86 (40.4)
Ribociclib	54 (16.3)	47 (14.2)	34 (16.0)
Abemaciclib	15 (4.5)	5 (1.5)	10 (4.7)
Dalpiciclib	0	1 (0.3)	1 (0.5)
Median prior CDK4/6i duration in ABC, months (range)			
Palbociclib	22.3 (0.7-108.0)	23.9 (2.6-83.1)	23.2 (0.0-69.7)
Ribociclib	17.3 (1.9-67.5)	21.1 (1.0-69.1)	16.5 (1.8-67.2)
Abemaciclib	11.0 (5.8-48.1)	10.8 (4.1-20.2)	20.2 (3.0-40.2)

Abbreviations: ABC = locally advanced/metastatic breast cancer; Abema = abemaciclib; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EBC = early breast cancer; ESMO = European Society for Medical Oncology; *ESR1*m = estrogen receptor 1 mutation detected; ET = endocrine therapy; Imlun = imlunestrant; ITT = intention to treat; MBC = metastatic breast cancer; n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] 1 patient in the **imlunestrant** arm did not receive any prior systemic therapy (protocol deviation).

[b] Derived for the patients who have received previous endocrine therapy using the ESMO criteria (Cardoso et al. 2024).

Table 30 Summary of prior cancer therapies in the *ESR1*m-detected population

Category, n (%)	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm C Imlun+Abema N=67
Prior anti-cancer therapy			
Surgical procedure	89 (64.5)	76 (64.4)	47 (70.1)
Radiotherapy	72 (52.2)	75 (63.6)	39 (58.2)
Systemic therapy	138 (100)	118 (100)	67 (100)
Chemotherapy in (neo)adjuvant setting	42 (30.4)	40 (33.9)	20 (29.9)
Line of therapy in advanced setting			
First-line	30 (21.7)	23 (19.5)	15 (22.4)
Second-line	106 (76.8)	95 (80.5)	52 (77.6)
Prior ET in any setting			
Disease recurrence on or <12-months after completing adjuvant AI for EBC (Prior ET in adjuvant setting only)	29 (21.0)	23 (19.5)	15 (22.4)
Disease recurrence >12-months after completing adjuvant ET for EBC and after AI ± CDK4/6i for ABC (Prior ET in both adjuvant and metastatic setting)	30 (21.7)	32 (27.1)	14 (20.9)
Disease progression on AI with or without CDK4/6i for de novo MBC (Prior ET in metastatic setting only)	71 (51.4)	59 (50.0)	37 (55.2)
Prior lines of ET in any setting			
0	0	0	0
1	101 (73.2)	80 (67.8)	52 (77.6)
≥2	37 (26.8)	38 (32.2)	15 (22.4)
Types of prior ET in any setting			
AI	106 (76.8)	85 (72.0)	55 (82.1)
Tamoxifen	1 (0.7)	0	0
AI and Tamoxifen	31 (22.5)	33 (28.0)	12 (17.9)
Endocrine resistance[a]			
Primary	0	0	0
1st exposure to ET as ET alone	0	0	0
1st exposure to ET as ET+CDK4/6i	0	0	0
Secondary	138 (100)	118 (100)	67 (100)
1st exposure to ET as ET alone	73 (52.9)	64 (54.2)	28 (41.8)
1st exposure to ET as ET+CDK4/6i	65 (47.1)	54 (45.8)	39 (58.2)
Prior CDK4/6i in any setting	93 (67.4)	85 (72.0)	53 (79.1)
Adjuvant	3 (2.2)	3 (2.5)	4 (6.0)
Recurrence during CDK4/6i therapy	2 (1.4)	1 (0.8)	2 (3.0)
Recurrence after CDK4/6i therapy	1 (0.7)	2 (1.7)	2 (3.0)
ABC	90 (65.2)	82 (69.5)	49 (73.1)
Duration <12 months	14 (10.1)	16 (13.6)	13 (19.4)
0-6 months	2 (1.4)	4 (3.4)	5 (7.5)
6-12 months	12 (8.7)	12 (10.2)	8 (11.9)
Duration ≥12 months	76 (55.1)	66 (55.9)	36 (53.7)
12-18 months	18 (13.0)	11 (9.3)	8 (11.9)
≥18 months	58 (42.0)	55 (46.6)	28 (41.8)
Type of prior CDK4/6i in ABC			
Palbociclib	63 (45.7)	58 (49.2)	28 (41.8)
Ribociclib	22 (15.9)	22 (18.6)	16 (23.9)
Abemaciclib	5 (3.6)	2 (1.7)	4 (6.0)
Dalpiciclib	0	0	0
Median prior CDK4/6i duration in ABC, months (range)			
Palbociclib	23.3 (0.7-85.1)	24.0 (4.4-83.1)	23.7 (5.0-65.3)
Ribociclib	27.8 (7.4-67.5)	21.4 (1.0-58.0)	16.5 (1.8-55.7)
Abemaciclib	10.7 (8.3-21.4)	14.4 (10.8-17.9)	20.2 (14.4-29.2)

Abbreviations: ABC = advanced breast cancer; Abema = abemaciclib; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EBC = early breast cancer; ESMO = European Society for Medical Oncology; *ESR1*m = estrogen receptor 1 mutation detected; ET = endocrine therapy; Imlun = imlunestrant; MBC = metastatic breast cancer; n = number of patients in the specific category; N = number of patients; NA = not applicable; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] Derived for the patients who have received previous endocrine therapy using the ESMO criteria (Cardoso et al. 2024).

Table 31 Summary of prior cancer therapies in the concurrent ITT population

	Arm A (Imlun) (N=213)	Arm B (SOC) (N=213)	Arm C (Imlun + Abema) (N=213)	Total (N=639)
Endocrine resistance*a n(%)				
Primary	12 (5.6)	19 (8.9)	16 (7.5)	47 (7.4)
1st Exposure to ET as ET alone	7 (3.3)	12 (5.6)	12 (5.6)	31 (4.9)
1st Exposure to ET as ET+CDK4/6i	5 (2.3)	7 (3.3)	4 (1.9)	16 (2.5)
Secondary	201 (94.4)	194 (91.1)	197 (92.5)	592 (92.6)
1st Exposure to ET as ET alone	114 (53.5)	110 (51.6)	112 (52.6)	336 (52.6)
1st Exposure to ET as ET+CDK4/6i	87 (40.8)	84 (39.4)	85 (39.9)	256 (40.1)
Line of therapy in advanced setting				
First-Line	61 (28.6)	65 (30.5)	63 (29.6)	189 (29.6)
Second-Line	150 (70.4)	148 (69.5)	149 (70.0)	447 (70.0)
Inclusion Criterion 3 n(%)				
3a (Prior ET in adjuvant setting only)	61 (28.6)	65 (30.5)	63 (29.6)	189 (29.6)
Received prior CDK4/6i	11 (5.2)	12 (5.6)	7 (3.3)	30 (4.7)
3b (Prior ET in both adjuvant and metastatic setting)	58 (27.2)	55 (25.8)	53 (24.9)	166 (26.0)
Received prior CDK4/6i	45 (21.1)	45 (21.1)	45 (21.1)	135 (21.1)
3c (Prior ET in metastatic setting only)	89 (41.8)	90 (42.3)	92 (43.2)	271 (42.4)
Received prior CDK4/6i	79 (37.1)	78 (36.6)	82 (38.5)	239 (37.4)
3b + 3c (Prior ET in metastatic setting)	147 (69.0)	145 (68.1)	145 (68.1)	437 (68.4)
Received prior CDK4/6i	124 (58.2)	123 (57.7)	127 (59.6)	374 (58.5)
Other *b	5 (2.3)	3 (1.4)	5 (2.3)	13 (2.0)
Prior lines of ET in any setting n(%)				
0	0	0	0	0
1	144 (67.6)	146 (68.5)	147 (69.0)	437 (68.4)
2+	69 (32.4)	67 (31.5)	66 (31.0)	202 (31.6)
Type of prior ET in any setting n(%)				
AI	154 (72.3)	161 (75.6)	161 (75.6)	476 (74.5)
Tamoxifen	0	0	0	0
AI and Tamoxifen	59 (27.7)	52 (24.4)	52 (24.4)	163 (25.5)
Prior CDK4/6i in any setting*c n(%)	140 (65.7)	138 (64.8)	139 (65.3)	417 (65.3)
Adjuvant	11 (5.2)	12 (5.6)	7 (3.3)	30 (4.7)
Recurrence during prior CDK4/6i	6 (2.8)	5 (2.3)	4 (1.9)	15 (2.3)
Recurrence after prior CDK4/6i	4 (1.9)	7 (3.3)	3 (1.4)	14 (2.2)
Locally-advanced/metastatic	129 (60.6)	126 (59.2)	132 (62.0)	387 (60.6)
Duration>=18 months	77 (36.2)	79 (37.1)	72 (33.8)	228 (35.7)
Duration>=12 months and <18 months	20 (9.4)	21 (9.9)	20 (9.4)	61 (9.5)
Duration>=6 months and <12 months	19 (8.9)	18 (8.5)	21 (9.9)	58 (9.1)
Duration<6 months	13 (6.1)	8 (3.8)	19 (8.9)	40 (6.3)
Duration of prior CDK4/6i in any setting n(%)	139 (65.3)	138 (64.8)	139 (65.3)	416 (65.1)
>= 12 months or recurrence after completing CDK4/6i in adjuvant setting	101 (47.4)	107 (50.2)	95 (44.6)	303 (47.4)
< 12 months or recurrence during adjuvant CDK4/6i treatment	38 (17.8)	31 (14.6)	44 (20.7)	113 (17.7)
Duration of prior CDK4/6i in locally-advanced/metastatic setting n(%)	129 (60.6)	126 (59.2)	132 (62.0)	387 (60.6)
>= 12 months	97 (45.5)	100 (46.9)	92 (43.2)	289 (45.2)
< 12 months	32 (15.0)	26 (12.2)	40 (18.8)	98 (15.3)
Prior ET in any setting*c n(%)	213 (100.0)	213 (100.0)	213 (100.0)	639 (100.0)
Locally-advanced/metastatic	152 (71.4)	148 (69.5)	150 (70.4)	450 (70.4)
Adjuvant	120 (56.3)	122 (57.3)	120 (56.3)	362 (56.7)
Type of prior CDK4/6i in locally advanced/metastatic setting*d n(%)				
Palbociclib	82 (38.5)	86 (40.4)	86 (40.4)	254 (39.7)
Median (range) duration, (months)	23.5 (0.7-85.1)	23.6 (2.6-83.1)	23.2 (0.0-69.7)	23.3 (0.0-85.1)
Ribociclib	37 (17.4)	37 (17.4)	34 (16.0)	108 (16.9)
Median (range) duration, (months)	17.6 (1.9-67.5)	21.2 (2.0-69.1)	16.5 (1.8-67.2)	18.5 (1.8-69.1)
Abemaciclib	10 (4.7)	2 (0.9)	10 (4.7)	22 (3.4)
Median (range) duration, (months)	18.6 (5.8-37.9)	12.2 (4.1-20.2)	20.2 (3.0-40.2)	18.6 (3.0-40.2)
Dalpiciclib	0	1 (0.5)	1 (0.5)	2 (0.3)
Median (range) duration, (months)		31.1 (31.1-31.1)	22.4 (22.4-22.4)	26.7 (22.4-31.1)
Type of prior CDK4/6i in any setting*d n (%)				
Palbociclib	86 (40.4)	94 (44.1)	90 (42.3)	270 (42.3)
Ribociclib	39 (18.3)	39 (18.3)	37 (17.4)	115 (18.0)
Abemaciclib	13 (6.1)	3 (1.4)	10 (4.7)	26 (4.1)
Dalpiciclib	2 (0.9)	2 (0.9)	1 (0.5)	5 (0.8)
Prior chemotherapy in (neo)adjuvant setting n(%)	82 (38.5)	79 (37.1)	90 (42.3)	251 (39.3)

Abbreviations: N = number of subjects in population; n = number of subjects; ET = endocrine therapy; CDK 4/6i = cyclin-dependent kinase 4/6 inhibitor; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane; Abema = abemaciclib.
*a: Derived for the patients who have received previous endocrine therapy using ABC guidelines 6 and 7.
*b: Patients with protocol deviation for IE #3.
*c: Patients may fall into more than 1 category.
*d: Last prior CDK4/6i is used if patients received more than 1 prior CDK4/6i.
Data cutoff date is 24-Jun-2024.

Overall, most patients in the SOC arm received fulvestrant (ITT: 88%; *ESR1*m population: 94%; concurrent ITT: 90%). 292 received fulvestrant (90 %), and 32 received exemestane (10 %).

- **Numbers analysed**

Table 32 Summary of populations analysed

Category, n (%)	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm C Imlun+Abema N=213	Total N=874
ITT Population	331 (100)	330 (100)	213 (100)	874
Arm A vs. Arm B	331 (100)	330 (100)	0	661
Arm C vs. Arm A in the Concurrently Randomized	213 (64.4)	0	213 (100)	426
Arm C vs. Arm B in the Concurrently Randomized	0	213 (64.5)	213 (100)	426
***ESR1*m-detected population**	138 (41.7)	118 (35.8)	67 (31.5)	323
***ESR1*m-not-detected (ITT)**	193 (58.3)	212 (64.2)	146 (68.5)	551
Safety Population	327 (98.8) [a]	324 (98.2)	208 (97.7)	859
ORR Evaluable Population	262 (79.2)	251 (76.1)	167 (78.4)	680
Per-protocol	300 (90.6)	301 (91.2)	199 (93.4)	800
PRO Population	313 (94.6)	317 (96.1)	204 (95.8)	834
PK Population	324 (97.9)	0 (0)	206 (96.7)	530

Abbreviations: Abema = abemaciclib; *ESR1*m = estrogen receptor 1 mutation; Imlun = imlunestrant; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; ORR = objective response rate; PRO = patient-reported outcomes; PK = pharmacokinetics; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] One patient who was assigned to the **imlun+abema** arm did not receive abemaciclib and was included in the **imlunestrant** arm for safety analyses.

- **Outcomes and estimation**

Imlunestrant monotherapy versus SOC

ITT

Primary endpoint: Progression-free survival PFS (investigator assessment) in the ITT

At the time of DCO (24 June 2024) with a median follow-up time of approximately 17 months in both treatment arms, PFS events were observed in 71.6% of patients in the imlunestrant arm and 76.7% of patients in the SOC. EMBER-3 did not meet its primary endpoint in the ITT population, stratified HR: 0.867 (95% CI: 0.724, 1.039, stratified log-rank test p=0.1158) (see table and figure below).

Table 33 Investigator-assessed PFS ITT population Imlunestrant versus SOC

Category	Arm A Imlunestrant N=331	Arm B SOC N=330
Number of events, n (%)	237 (71.6)	253 (76.7)
Disease progression	231 (69.8)	244 (73.9)
Death without disease progression	6 (1.8)	9 (2.7)
Number of patients censored, n (%)	94 (28.4)	77 (23.3)
Progression-free survival (months)		
Median PFS, months (95% CI) [a,b]	5.55 (5.32, 7.26)	5.52 (4.60, 5.62)
HR (95% CI) stratified[c]	0.867 (0.724, 1.039)	
p-value (2 sided) Log-rank stratified[c]	0.1158	
Restricted Mean (95%CI) with restriction time = 27.66 month[d]		
Months (95% CI)	9.69 (8.61, 10.76)	8.33 (7.38, 9.27)
Difference (95% CI)	1.36 (-0.07, 2.79)	
Nominal p-value (2-sided)[e]	0.0629	
Duration of follow-up (months)		
Median, months (95% CI)	16.62 (13.77, 19.38)	16.76 (13.93, 22.08)
Rate (%) of progression-free survival [f]		
6 months (95% CI)	45.3 (39.7, 50.8)	42.6 (37.0, 48.2)
12 months (95% CI)	29.5 (24.2, 34.9)	21.5 (16.9, 26.5)

Abbreviations: CDK6/4i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; HR = hazard ratio; INV = investigator; ITT = intention to treat; IWRS = interactive web response system; n = number of patients in the specific category; N = total number of patients in the population within the treatment group; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

a Estimate based on the Kaplan-Meier method.

b 95% CI was calculated using the Brookmeyer and Crowley method.

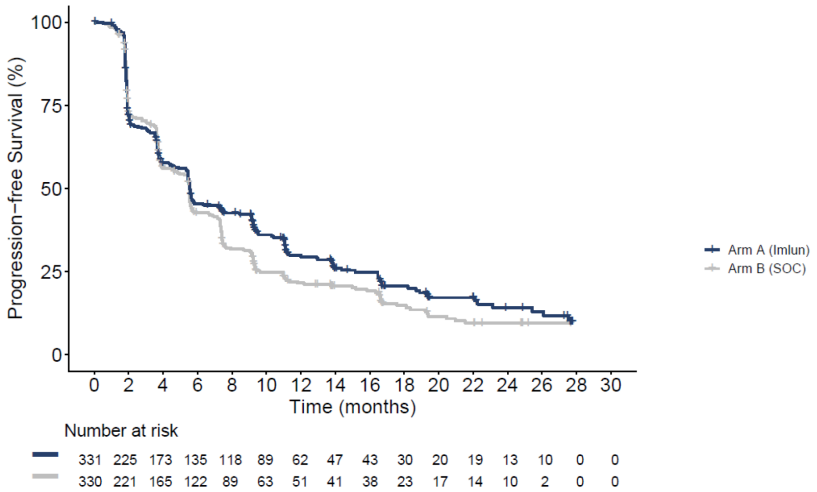
c Stratified by visceral metastases status from IWRS, prior CDK6/4i treatment from IWRS, region.

d Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075.

e 2-sided p-value based on normal approximation.

f 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

Figure 11 Kaplan-Meier plot of investigator-assessed PFS, ITT population Imlunestrant versus SOC



Abbreviations: Imlun = imlunestrant; INV = investigator; ITT = intention to treat; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Secondary endpoints in the ITT

The key secondary endpoint OS was immature at OS IA2 (cut-off date: 30 January 2025), with 222 events in total; mOS was 34.4 months in the imlunestrant arm versus mOS of 30.7 months in the SOC (exploratory analysis HR: 0.811; 95% CI: 0.620, 1.061). Given the non-significant PFS results for the comparison of Arm A vs Arm B in the ITT, OS can no longer be formally tested. ORR was numerically higher in the imlunestrant arm (12.2% versus 8.4% SOC, DCO: 24 June 2024).

ESR1m-detected population

Primary endpoint: Progression-free survival PFS (investigator assessment) in the *ESR1*m-detected population

In the imlunestrant arm and the SOC arm, 109 (79.0%) and 102 (86.4%) events were observed, mostly due to new lesions. A total of 29 (21.0%) and 16 (13.6%) of patients were censored, respectively. Treatment with imlunestrant showed a statistically significantly improvement in PFS, stratified HR:0.617 (95% CI: 0.464, 0.821, stratified log-rank test p=0.0008). Improvement in mPFS was 1.64 month, from 3.84 months (95% CI: 3.68, 5.52) for the SOC arm to 5.49 months (95% CI: 3.91, 7.39) for the imlunestrant arm.

Table 34 Investigator-assessed PFS *ESR1*m-detected population Imlunestrant versus SOC

Category	Arm A Imlunestrant N=138	Arm B SOC N=118
Number of events, n (%)	109 (79.0)	102 (86.4)
Disease progression	105 (76.1)	98 (83.1)
Death without disease progression	4 (2.9)	4 (3.4)
Number of patients censored, n (%)	29 (21.0)	16 (13.6)
Progression-free survival (months)		
Median PFS, months (95% CI) [a,b]	5.49 (3.91, 7.39)	3.84 (3.68, 5.52)
HR (95% CI) stratified[c]	0.617 (0.464, 0.821)	
p-value (2 sided) Log-rank stratified[c]	0.0008	
Restricted mean (95%CI) with restriction time = 19.38[d]		
Months (95% CI)	7.93 (6.81, 9.05)	5.37 (4.58, 6.15)
Difference (95% CI)	2.56 (1.19, 3.93)	
Nominal p-value (2-sided)[e]	0.0002	
Duration of follow-up (months)		
Median, months (95% CI)	16.69 (13.70, -)	13.80 (9.40, -)
Rate (%) of progression-free survival[f]		
6 months (95% CI)	44.1 (35.5, 52.4)	32.1 (23.4, 41.1)
12 months (95% CI)	24.5 (16.9, 32.9)	6.6 (2.7, 13.0)

Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; *ESR1*m = estrogen receptor 1 mutation; HR = hazard ratio; INV = investigator; IWRS = interactive web response system; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

a Estimate based on the Kaplan-Meier method.

b 95% CI was calculated using the Brookmeyer and Crowley method.

c Stratified by visceral metastases status from IWRS, prior CDK4/6i treatment from IWRS.

d Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075.

e 2-sided p-value based on normal approximation.

f 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

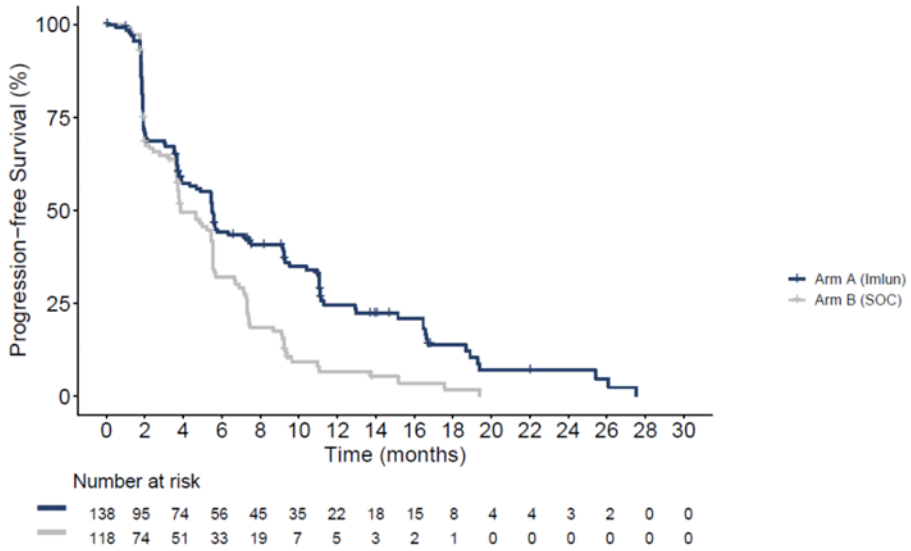
Data cut-off date 24 June 2024

Table 35 Summary of censoring for investigator-assessed PFS, *ESR1*m-detected population Imlunestrant versus SOC

Category	Arm A Imlunestrant N=138	Arm B SOC N=118
Number of patients censored, n (%)	29 (21.0)	16 (13.6)
Reason censored, n (%)		
No post-baseline tumor assessment	2 (1.4)	4 (3.4)
Start of new anti-cancer therapy	9 (6.5)	7 (5.9)
No documented PD with regular assessment	17 (12.3)	4 (3.4)
PD or death after two or more missed tumor assessments	0	1 (0.8)
Withdrawal by patient	1 (0.7)	0

Abbreviations: *ESR1*m = estrogen receptor 1 mutation; INV = investigator; n = number of patients in the specified category; N = number of patients; PD = progressive disease; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Figure 12 Kaplan-Meier plot of investigator-assessed PFS, *ESR1*m-detected population Imlunestrant versus SOC



Abbreviations: *ESR1*m = estrogen receptor 1 mutation; Imlun = imlunestrant; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane

Key secondary endpoint OS

Interim results of OS were based on OS look 1, which was planned at the time of the final PFS analysis for the Arm A vs Arm B ITT comparison. At the time of DCO for OS look 1, there were 32/138 (23.2%) deaths in the imlunestrant arm and 48/118 (40.7%) deaths in the SOC arm. According to the multiple testing procedure, only a small alpha was spent for the OS analysis at this data cut-off ($5.5x10^{-6}$) and the null hypothesis could not be rejected. Therefore, the results are exploratory only.

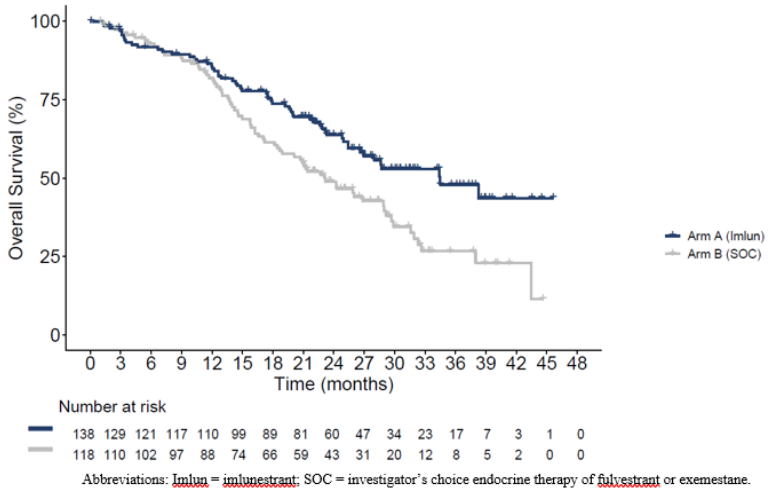
Updated OS results at OS IA3 (DCO: 18 August 2025) have been provided. While no formal conclusions can be made on OS, consistent with the primary analysis, a trend towards OS improvement at OS IA3 continues to be observed with imlunestrant in the *ESR1*m-detected population (see below table).

Table 36 Overall survival, *ESR1*m-detected population Imlunestrant versus SOC

Status	PO Data Cut-off: 24 Jun 2024		OS IA3 Data Cut-off: 18 Aug 2025	
	Arm A Imlunestrant N=138	Arm B SOC N=118	Arm A Imlunestrant N=138	Arm B SOC N=118
Survival status, n (%)				
Died	32 (23.2)	48 (40.7)	57 (41.3)	71 (60.2)
Censored	106 (76.8)	70 (59.3)	81 (58.7)	47 (39.8
Reason censored, n (%)				
Alive	91 (65.9)	63 (53.4)	62 (44.9)	39 (33.1
Lost to follow-up	5 (3.6)	0	4 (2.9)	0
Withdrawal	10 (7.2)	7 (5.9)	15 (10.9)	8 (6.8)
Overall survival (months)				
Median (95% CI)[a,b]	NR (23.20, -)	21.22 (16.23, 26.84)	34.45 (25.43, -)	23.1 (18.43, 28.94)
HR (95% CI) stratified[c]	0.546 (0.348, 0.856)		0.603 (0.425, 0.856)	
p-value (2-sided) Log-rank stratified[c]	0.0076		0.0043	
Duration of follow-up (months)				
Median, months (95% CI)	16.36 (14.42, 18.20)	17.41 (16.03, 19.38)	28.94 (26.78, 31.44))	29.74 (26.94, 33.35)
Rate (%) of overall survival				
12 months (95% CI)	86.6 (79.2, 91.4)	80.4 (71.1, 87.0)	85.7 (78.5, 90.6)	81.9 (73.4, 87.9)
24 months (95% CI)	57.4 (41.4, 70.5)	42.5 (29.5, 54.9)	63.8 (54.5, 71.6)	48.9 (39.1, 58.0)

Abbreviations: CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitor; CI = confidence interval; ESR1m = oestrogen receptor 1 mutation; HR = hazard ratio; IWRS = interactive web response system; n = number of patients in the specified category; N = number of patients; NR = not reached; OS IA3 = overall survival interim analysis 2; PO = primary outcome; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.
a. Estimate based on Kaplan-Meier method.
b. The 95% CI was calculated using the Brookmeyer and Crowley method.
c. Stratified by visceral metastases status from IWRS, prior CDK4/6i treatment from IWRS.
d. The 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

Figure 13 Kaplan-Meier plot of overall survival, *ESR1*m-detected population Imlunestrant versus SOC (OS IA3 DCO 18 Aug 2025)



Abbreviations: ESR1m = oestrogen receptor 1 mutation; Imlun = imlunestrant; ITT = intention-to-treat; OS = overall survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane. Data cutoff date is 18 August 2025.

Post-discontinuation therapies: Overall, surgical procedures were performed in 4.3% of the imlunestrant arm and 5.1% of the SOC, whereas 12.3% and 10.2% of patients received radiotherapy in the imlunestrant and SOC arm, respectively. A total of 63.8% patients in the imlunestrant arm and 74.6% patients in the SOC arm received subsequent systemic therapies.

Table 37 First subsequent post discontinuation systemic treatment *ESR1*m-detected population

	Arm A (Imlun) N =213 n (%)	Arm B (SOC) N=213 n (%)	Arm C (Imlun+Abema) N=213 n (%)	Total N=639 n (%)
Patients who were off treatment	121 (87.7)	114 (96.6)	42 (62.7)	277 (85.8)
Patients received first subsequent systemic therapy	88 (72.7)	88 (77.2)	25 (59.5)	201 (72.6)
Chemotherapy				
Chemotherapy alone	38 (31.4)	43 (37.7)	10 (23.8)	91 (32.9)
Chemotherapy + ET	1 (0.8)	1 (0.9)	1 (2.4)	3 (1.1)
Chemotherapy + Immunotherapy	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.4)
Chemotherapy + Other[a]	2 (1.7)	6 (5.3)	2 (4.8)	10 (3.6)
CDK4/6i-based Therapy				
CDK4/6i monotherapy	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.4)
CDK4/6i + ET	10 (8.3)	13 (11.4)	4 (9.5)	27 (9.7)
Endocrine Monotherapy	9 (7.4)	8 (7.0)	2 (4.8)	19 (6.9)
Endocrine-based combination therapy	16 (13.2)	10 (8.8)	4 (9.5)	30 (10.8)
Everolimus + ET	12 9.9)	6 (5.3)	4 (9.5)	22 (7.9)
PI3K inhibitor +ET	2 (1.7)	2 (1.8)	0 (0.0)	4 (1.4)
Other combinations with ET[a]	2 (1.7)	2 (1.8)	0 (0.0)	4 (1.4)
Other Therapy [a]	10 (8.3)	7 (6.1)	2 (4.8)	19 (6.9)

Abbreviations: Abema = abemaciclib; CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitor; Imlun = imlunestrant; ESR1m = oestrogen receptor 1 mutation; ET = endocrine therapy; Imlun+Abema = imlunestrant in combination with abemaciclib; n = number of subjects in the specified category; N = number of subjects in ESR1m-detected Population; PI3K = phosphoinositide 3-kinase; SOC = investigator choice endocrine therapy of fulvestrant or exemestane.
a The Other therapy category was detailed in Appendix 1, Table APP3
The percentages for post-discontinuation treatments are calculated based on the number of patients who discontinued study treatment.
Data cut-off date is 24 June 2024.

Other secondary endpoints (DCO: 24 June 2024)

BIRC-assessed PFS:

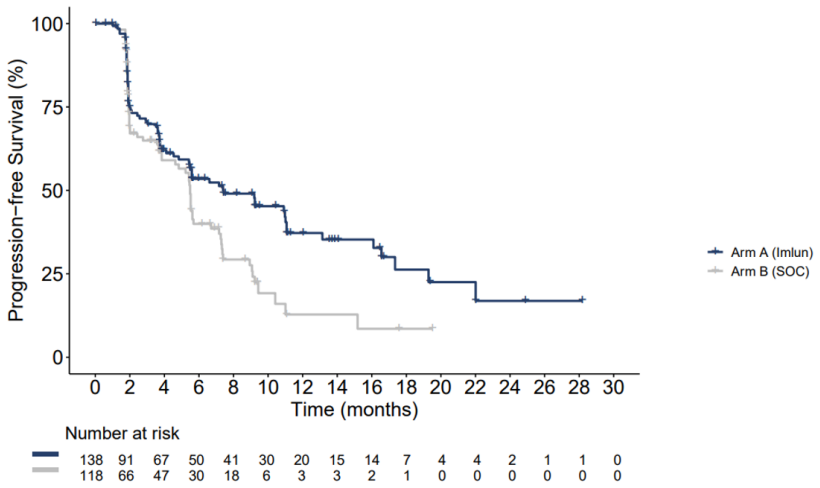
Based on BIRC-assessed PFs, mPFS was 7.43 months in the imlunestrant arm and 5.49 months in the SOC arm (see table below).

Table 38 BIRC-assessed PFS, *ESR1*m-detected population Imlunestrant versus SOC

Category	Arm A Imlun N=138	Arm B SOC N=118
Number of events, n (%)	74 (53.6)	71 (60.2)
Disease progression	69 (50.0)	65 (55.1)
Death without disease progression	5 (3.6)	6 (5.1)
Number of patients censored, n (%)	64 (46.4)	47 (39.8)
Progression-free survival (months)		
Median PFS, months (95% CI) [a,b]	7.43 (4.83, 11.07)	5.49 (3.84, 6.70)
HR (95% CI) stratified [c]	0.657 (0.469, 0.920)	
Nominal p-value (2 sided) Log-rank stratified[c]	0.0129	
Rate (%) of progression-free survival [d]		
6 months (95% CI)	53.4 (44.0, 62.0)	40.0 (29.6, 50.1)
12 months (95% CI)	37.2 (27.2, 47.2)	12.8 (5.0, 24.4)

Abbreviations: BIRC = blinded independent review committee; CDK6/4i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; ESR1m = oestrogen receptor 1 mutation; HR = hazard ratio; Imlun – imlunestrant; ITT = intention-to-treat; IWRS = interactive web response system; n = number of patients in the specific category; N = total number of patients in the population within the treatment group; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.
a Estimate based on the Kaplan-Meier method.
b 95% CI was calculated using the Brookmeyer and Crowley method.
c Stratified by visceral metastases status from IWRS, prior CDK6/4i treatment from IWRS
d 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.
Data cutoff date is 24 June 2024.

Figure 14 Kaplan−Meier plot of progression−free survival by BIRC Arm A (Imlun) vs. Arm B (SOC) *ESR1*m-detected Population.



Abbreviations: BIRC = blinded independent review committee; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
Data cutoff date is 24 June 2024.

The concordance rate (i.e. the combined number of agreed PFS events and agreed censored) between BIRC and Investigator assessments was 65.9% for the imlunestrant arm and 68.6 % for the SOC arm (see table below).

Table 39 Summary of concordance between INV and BIRC-assessed PFS, *ESR1*m-detected population Imlunestrant versus SOC

Category	Arm A Imlunestrant N=138	Arm B SOC N=118
PFS event by both Investigator and BIRC, n (%)	68 (49.3)	68 (57.6)
PFS event at the same time[a]	41 (29.7)	49 (41.5)
Investigator event date later than BIRC event date	20 (14.5)	16 (13.6)
Investigator event date earlier than BIRC event date	7 (5.1)	3 (2.5)
Censored by both Investigator and BIRC, n (%)	23 (16.7)	13 (11.0)
Event by Investigator but censored by BIRC, n (%)	41 (29.7)	34 (28.8)
Censored by Investigator but event by BIRC, n (%)	6 (4.3)	3 (2.5)
Early discordance rate[b], %	44.0	36.3
Differential discordance (EDR of imlunestrant-EDR of SOC)	7.8	
Late discordance rate[c], %	35.1	33.9
Differential discordance (LDR of imlunestrant -LDR of SOC)	1.2	

Abbreviations: BIRC = blinded independent review committee; EDR = early discordance rate; *ESR1*m = estrogen receptor 1 mutation; INV = investigator; LDR = late discordance rate; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] Absolute difference in progression call times between investigator and BIRC ≤3 days was considered concordant.

[b] EDR: early discrepancy rate quantifies the frequency with which the investigator assessment declares progression early relative to BIRC within each treatment arm.

[c] LDR: late discrepancy rate quantifies the frequency with which the investigator assessment declares progression later relative to BIRC within each treatment arm.

Tumour response:

Investigator-assessed ORR (based on confirmed response) was 14.3% in the imlunestrant arm and 7.7% in the SOC arm (see table below).

Table 40 Summary of investigator-assessed tumour response, *ESR1*m-detected population Imlunestrant versus SOC

	Arm A Imlunestrant N=138	Arm B SOC N=118
Number of ORR-evaluable patients[a]	112	91
ORR, n (%)	16 (14.3)	7 (7.7)
95% CI for ORR, %	7.8-20.8	2.2-13.2
Stratified risk difference, % (95% CI)[b]	6.3 (-2.3-14.9)	
Nominal p-value[c]	0.1811	
Median DoR, months (95% CI)	10.02 (3.98, 14.59)	5.59 (2.92, 7.79)
BOR in all patients, n (%)		
CR	1 (0.7)	0
PR	15 (10.9)	7 (5.9)
SD	54 (39.1)	47 (39.8)
Non-CR/Non-PD[d]	22 (15.9)	21 (17.8)
PD	40 (29)	35 (29.7)
NE	6 (4.3)	8 (6.8)
CBR (CR + PR + SD ≥24 weeks or Non-CR/Non-PD ≥24 weeks), n (%)	64 (46.4)	43 (36.4)

Abbreviations: BOR = best overall response; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CBR = clinical benefit rate; CR = complete response; DoR = duration of response; *ESR1*m = estrogen receptor 1 mutation;; Imlun = imlunestrant; INV = investigator; IWRS = interactive web response system; n = number of patients in the specified category; N = number of patients in the population; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] Per RECIST v1.1.

[b] Risk difference is defined as the incidence rate in Arm A (Imlun) minus that in Arm B (SOC), stratified by visceral metastases status from IWRS, prior CDK 4/6i treatment from IWRS.

[c] p-value is calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomization strata visceral metastases status from IWRS, prior CDK 4/6i treatment from IWRS.

[d] For patients without measurable disease at baseline.

Patient-reported Outcome

There was no clinically relevant changes in time to sustained worsening of "worst pain" between treatment arms (data not shown).

Imlunestrant + abemaciclib versus imlunestrant monotherapy

Primary endpoint: Progression-free survival PFS (investigator assessment) in the concurrent ITT population

In the imlunestrant + abemaciclib arm and the imlunestrant monotherapy arm, 114 (53.3%) and 149 (70.0%) events were observed, mostly due to new lesions. A total of 99 (46.5%) and 64 (30.0%) of patients were censored, respectively. Treatment with imlunestrant + abemaciclib showed a statistically significantly improvement in PFS, stratified HR:0.569 (95% CI: 0.441, 0.8733, stratified log-rank test p<0.0001). Improvement in mPFS was 3.88 month, from 5.49 months (95% CI: 3.78, 5.62) for the imlunestrant monotherapy arm to 9.36 months (95% CI: 7.49, 11.86) for the imlunestrant + abemaciclib arm.

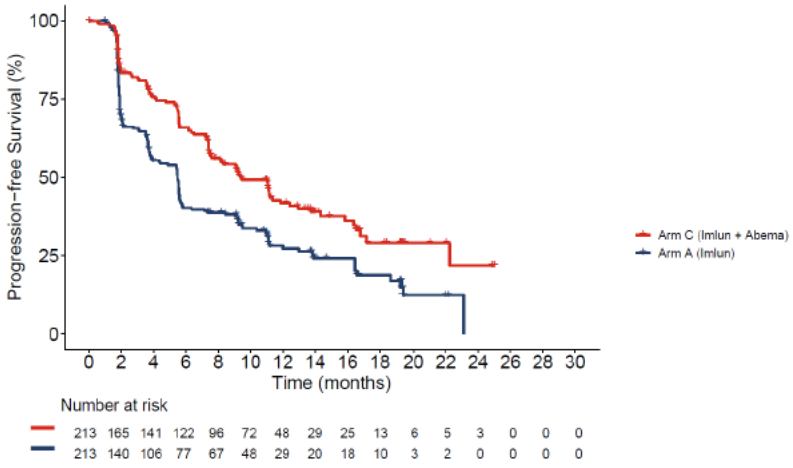
Table 41 Investigator-assessed PFS, concurrent ITT population imlun+abema versus imlunestrant

Category	ITT Population	
	Arm C Imlun+Abema N=213	Arm A imlunestrant N=213
Number of events, n (%)	114 (53.5)	149 (70.0)
Disease progression	105 (49.3)	148 (69.5)
Death without disease progression	9 (4.2)	1 (0.5)
Number of patients censored, n (%)	99 (46.5)	64 (30.0)
Progression-free survival (months)		
Median PFS, months (95% CI)[a,b]	9.36 (7.49, 11.86)	5.49 (3.78, 5.62)
HR (95% CI) stratified	0.569 (0.441, 0.733)	
p-value (2 sided) Log-rank stratified[c]	<0.0001	
Restricted Mean (95%CI) with restriction time = 19.25[d]		
Months (95% CI)	10.80 (9.78, 11.82)	8.02 (7.05, 8.99)
Difference (95% CI)	2.78 (1.37, 4.19)	
Nominal p-value (2-sided)[e]	0.0001	
Duration of follow-up (months)		
Median, months (95% CI)	13.54 (11.07, 13.86)	13.70 (11.07, 14.06)
Rate (%) of progression-free survival[f]		
6 months (95% CI)	65.9 (58.8, 72.2)	40.3 (33.4, 47.0)
12 months (95% CI)	41.8 (34.1, 49.3)	27.2 (20.7, 34.2)

Abbreviations: Abema = abemaciclib; CDK6/4i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; HR = hazard ratio; Imlun = imlunestrant; INV = investigator; ITT = intention to treat; IWRS = interactive web response system; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival.

a Estimate based on the Kaplan-Meier method.
b 95% CI was calculated using the Brookmeyer and Crowley method.
c Stratified by visceral metastases status from IWRS, prior CDK6/4i treatment from IWRS, region.
d Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075.
e 2-sided p-value based on normal approximation.
f 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

Figure 15 Kaplan-Meier plot of investigator-assessed PFS, concurrent ITT population imlun+abema versus imlunestrant



Abbreviations: Abema = abemaciclib; Imlun = imlunestrant; ITT = intention to treat; PFS = progression-free survival

Table 42 Summary of censoring for investigator-assessed PFS, concurrent ITT population imlun+abema versus imlunestrant

Category	Arm C Imlun+Abema N=213	Arm A Imlunestrant N=213
Number of patients censored, n (%)	99 (46.5)	64 (30.0)
Reason censored, n (%)		
No post- baseline tumor assessment	9 (4.2)	6 (2.8)
Start of new anti-cancer therapy	11 (5.2)	7 (3.3)
No documented PD with regular assessment	75 (35.2)	50 (23.5)
PD or death after two or more missed tumor assessments	2 (0.9)	0
Withdrawal by patient	2 (0.9)	1 (0.5)

Abbreviations: Abema = abemaciclib; INV = investigator; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; PD = progressive disease; PFS = progression-free survival.

Key secondary endpoint OS

Interim results of OS, based on the first OS look which coincided with the timing of the final PFS analysis for Arm C vs Arm A were immature at the time of DCO with 36/213 (16.9%) deaths in the imlunestrant + abemaciclib arm and 28/213 (13.1%) deaths in the imlunestrant monotherapy arm. According to the multiple testing procedure, only a small alpha was spent for the OS analysis at this data cut-off.

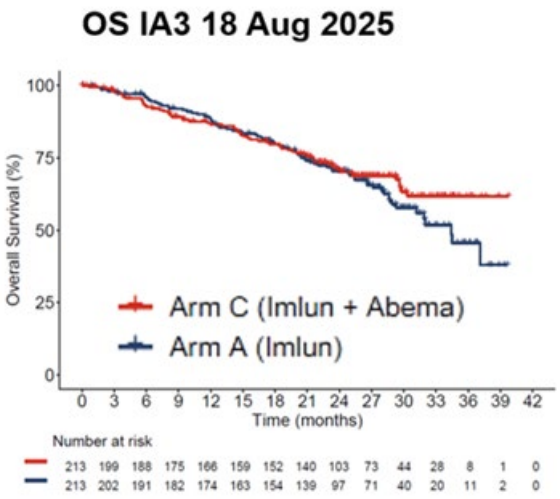
The Applicant presented updated OS results from OS IA3 (data cut-off 18 August 2025). OS results remain immature with 64 deaths (30.0%) and a censoring rate of 70.0% in the imlun+abema arm, and 76 deaths (35.7%) and a censoring rate of 64.3% in the imlunestrant arm.

Table 43 Overall survival at PO and OS IA3 concurrent ITT population imlun+abema versus imlunestrant

Status	PO Data Cutoff: 24 Jun 2024		OS IA3 Data Cutoff: 18 Aug 2025	
	Arm C Imlun+Abema N=213	Arm A Imlunestrant N=213	Arm C Imlun+Abema N=213	Arm A Imlunestrant N=213
Survival status, n (%)				
Died	36 (16.9)	28 (13.1)	64 (30.0)	76 (35.7)
Censored	177 (83.1)	185 (86.9)	149 (70.0	137 (64.3)
Overall survival (months)				
Median, months (95% CI)a,b	NR (- , -)	NR (23.29, -)	NR (-, -)	34.43(29.31, -)
HR (95% CI) stratified	1.337 (0.810, 2.208)		0.824 (0.588, 1.156)	
p-Value (2-sided) Log-rank stratifieda	0.2540		0.2622	
Duration of follow-up (months)				
Median, months (95% CI)	13.67 (12.65, 15.08)	13.70 (12.39, 14.32)	26.91 (25.79, 28.55)	27.10 (25.99, 28.12)
Rate (%) of overall survival				
12 months (95% CI)	86.5 (80.8, 90.7)	90.2 (84.8, 93.8)	not provided	not provided
24 months (95% CI)	69.7 (55.3, 80.2)	62.8 (34, 81.9)	not provided	not provided

Abbreviations: CI = confidence interval; HR = hazard ratio; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; n = number of patients in the specified category; N = number of patients; NR = not reached; OS IA2 = overall survival interim analysis 2; PO = primary outcome.

Figure 16 Kaplan-Meier plot of OS concurrent ITT population imlun+abema versus imlunestrant



Abbreviations: Imlun = imlunestrant; Imlun+Abema = imlunestrant in combination with abemaciclib; OS = overall survival; OS IA3 = overall survival interim analysis cut off 18 August 2025

Post-discontinuation therapies: Overall, surgical procedures were performed in 1.9% of the imlunestrant + abemaciclib arm and 5.1% of the imlunestrant monotherapy arm, whereas 7.0% and 13.1% of patients received radiotherapy in the imlunestrant + abemaciclib arm and imlunestrant monotherapy arm, respectively. A total of 43.2% patients in the imlunestrant + abemaciclib arm and 58.2% patients in the imlunestrant monotherapy arm received subsequent systemic therapies. Most frequently prescribed first subsequent systemic therapies were chemotherapy (about 50%) and endocrine therapy (about 44%) in both treatment arms. CDK4/6 inhibitors were more frequently prescribed in the imlunestrant monotherapy arm (see below table).

Table 44 First subsequent post-discontinuation systemic treatment concurrent ITT population

	Arm A (Imlun) N =213 n (%)	**Arm B (SOC) N=213 n (%)**	**Arm C (Imlun+Abema) N=213 n (%)**	**Total N=639 n (%)**
Patients who were off treatment	164 (77.0)	186 (87.3)	138 (64.8)	488 (76.4)
Patients received first subsequent systemic therapy	124 (75.6)	147 (79.0)	92 (66.7)	363 (74.4)
Chemotherapy				
Chemotherapy alone	54 (32.9)	57 (30.6)	40 (29.0)	151 (30.9)
Chemotherapy + ET	2 (1.2)	1 (0.5)	2 (1.4)	5 (1.0)
Chemotherapy + Immunotherapy	2 (1.2)	0 (0.0)	1 (0.7)	3 (0.6)
Chemotherapy + Other[a]	3 (1.8)	10 (5.4)	6 (4.3)	19 (3.9)
CDK4/6i-based Therapy				

CDK4/6i monotherapy	3 (1.8)	3 (1.6)	1 (0.7)	7 (1.4)
CDK4/6i + ET	25 (15.2)	24 (12.9)	8 (5.8)	57 (11.7)
Endocrine Monotherapy	9 (5.5)	17 (9.1)	16 (11.6)	42 (8.6)
Endocrine-based combination therapy	20 (12.2)	23 (12.4)	12 (8.7)	55 (11.3)
Everolimus + ET	16 (9.8)	14 (7.5)	11 (8.0)	41 (8.4)
PI3K inhibitor + ET	2 (1.2)	3 (1.6)	1 (0.7)	6 (1.2)
Other combinations with ET[a]	2 (1.2)	6 (3.2)	0 (0.0)	8 (1.6)
Other Therapy[a]	6 (3.7)	12 (6.5)	6 (4.3)	24 (4.9)

Abbreviations: Abema = abemaciclib; CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitor; ET = endocrine therapy; Imlun = imlunestrant; ITT = intention-to-treat; n = number of subjects in the specified category; N = number of subjects in concurrent-intention-to-treat population; PI3K = phosphoinositide 3-kinase; SOC = investigator choice endocrine therapy of fulvestrant or exemestane.

a The Other therapy category was detailed in Appendix 1, Table APP 2.

The percentages for post-discontinuation treatments are calculated based on the number of patients who discontinued study treatment.

Data cut-off date is 24 June 2024.

Other secondary endpoints (DCO: 24 June 2024)

BIRC-assessed PFS:

Based on BIRC assessment, the median PFS was 14.52 months in the imlunestrant + abemaciclib arm versus 9.23 months in the imlunestrant monotherapy arm (stratified HR: 0.617; 95% CI 0.453 0.84).

Table 45 Summary of Progression-Free Survival by BIRC Arm C (Imlun+Abema) vs. Arm A (Imlun)
Concurrent-Intention-to-Treat Population

Category	Arm C Imlun+Abema N=213	Arm A Imlun N=213
Number of events, n (%)	81 (38.0)	97 (45.5)
Disease progression	72 (33.8)	94 (44.1)
Death without disease progression	9 (4.2)	3 (1.4)
Number of patients censored, n (%)	132 (62.0)	116 (54.5)
Progression-free survival (months)		
Median PFS, months (95% CI) [a,b]	14.52 (11.37, -)	9.23 (5.49, 13.70)
HR (95% CI) stratified [c]	0.617 (0.453, 0.841)	
Nominal p-value (2 sided) Log-rank stratified[c]	0.0021	
Rate (%) of progression-free survival [d]		
6 months (95% CI)	69.5 (62.3, 75.7)	54.3 (46.6, 61.4)
12 months (95% CI)	57.2 (49.0, 64.5)	44.3 (35.8, 52.4)

Abbreviations: Abema = abemaciclib; BIRC = blinded independent review committee; CDK6/4i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; HR = hazard ratio; Imlun = Imlunestrant; Imlun+Abema = Imlunestrant in combination with abemaciclib; ITT = intention-to-treat; IWRS = interactive web response system; n = number of patients in the specific category; N = total number of patients in the population within the treatment group; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

a Estimate based on the Kaplan-Meier method.

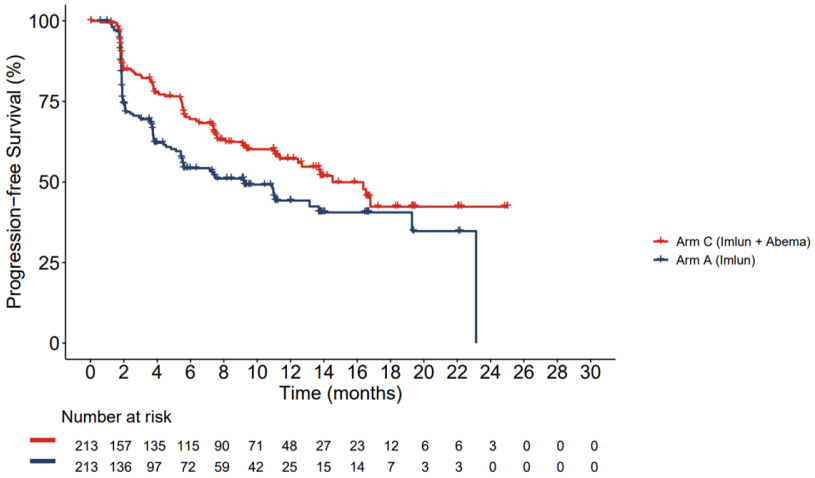
b 95% CI was calculated using the Brookmeyer and Crowley method.

c Stratified by visceral metastases status from IWRS, prior CDK6/4i treatment from IWRS, region.

d 95% CI and 2-sided p-value for the difference between rates were calculated based on normal approximation.

Data cutoff date is 24 June 2024.

Figure 17 Kaplan−Meier plot of progression−free survival by BIRC Arm C (Imlun + Abema) vs. Arm A (Imlun) Concurrent ITT Population Study



Abbreviations: Abema = abemaciclib; BIRC = blinded independent review committee; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
Data cutoff date is 24 Jun 2024

The concordance rate between BIRC and Investigator assessments was 79.8% for the imlun+abema arm and 69% for the imlunestrant arm (see table below).

Table 46 Summary of concordance between INV and BIRC-assessed PFS, concurrent ITT population imlunestrant +abemaciclib versus imlunestrant monotherapy

Category	Arm C imlun+abema N=213	Arm A imlunestrant N=213
PFS event by both Investigator and BIRC, n (%)	76 (35.7)	90 (42.3)
PFS event at the same time[a]	50 (23.5)	63 (29.6)
Investigator event date later than BIRC event date	22 (10.3)	22 (10.3)
Investigator event date earlier than BIRC event date	4 (1.9)	5 (2.3)
Censored by both Investigator and BIRC, n (%)	94 (44.1)	57 (26.8)
Event by Investigator but censored by BIRC, n (%)	38 (17.8)	59 (27.7)
Censored by Investigator but event by BIRC, n (%)	5 (2.3)	7 (3.3)
Early discordance rate[b], %	36.8	43.0
Differential discordance (EDR of imlun+abema-EDR of imlunestrant)	-6.1	
Late discordance rate[c], %	39.1	31.2
Differential discordance (LDR of imlun+abema -LDR of imlunestrant)	7.9	

Abbreviations: Abema = abemaciclib; BIRC = blinded independent review committee; EDR = early discordance rate; Imlun = imlunestrant; INV = investigator; ITT = intention to treat; LDR = late discordance rate; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival.

a Absolute difference in progression call times between investigator and BIRC ≤3 days was considered concordant.

b EDR: early discrepancy rate quantifies the frequency with which the investigator assessment declares progression early relative to BIRC within each treatment arm.

c LDR: late discrepancy rate quantifies the frequency with which the investigator assessment declares progression later relative to BIRC within each treatment arm.

Tumour response:

Investigator-assessed ORR (based on confirmed response) was 14.3% in the imlunestrant + abemaciclib arm and 7.7% in the imlunestrant monotherapy arm (see table below).

Table 47 Summary of investigator-assessed tumour response, concurrent ITT population imlun+abema versus imlunestrant

	Arm C Imlun+Abema N=213	Arm A Imlunestrant N=213
Number of ORR-evaluable patients[a], n	167	169
ORR, n (%)	45 (26.9)	20 (11.8)
95% CI for ORR, %	20.2-33.7	7.0-16.7
Stratified risk difference, % (95% CI)[b]	14.0 (5.9-22.2)	
Nominal p-value[c]	0.0011	
Median DoR, months (95% CI)	11.07 (9.13, -)	10.02 (6.57, 15.01)
BOR in all patients, n (%)		
CR	3 (1.4)	2 (0.9)
PR	42 (19.7)	18 (8.5)
SD	84 (39.4)	78 (36.6)
Non-CR/Non-PD[d]	38 (17.8)	37 (17.4)
PD	33 (15.5)	69 (32.4)
NE	13 (6.1)	9 (4.2)
CBR (CR + PR + SD ≥24 weeks or Non-CR/Non-PD ≥24 weeks), n (%)	134 (62.9)	94 (44.1)

Abbreviations: Abema = abemaciclib; BOR = best overall response; CBR = clinical benefit rate; CI = confidence interval; CDK6/4i = cyclin-dependent kinase 4/6 inhibitor;; CR = complete response; DoR = duration of response; Imlun = imlunestrant; INV = investigator; ITT = intention to treat; IWRS = interactive web response system; n = number of patients in the specified category; N = number of patients in the population; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease.

[a] Per RECIST v1.1.

[b] Risk difference is defined as the incidence rate in Arm C (Imlun+Abema) minus that in Arm A (Imlun), stratified by visceral metastases status from IWRS, prior CDK6/4i treatment from IWRS, region.

[c] p-value is calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomization strata visceral metastases status from IWRS, prior CDK 4/6i treatment from IWRS, region.

[d] For patients without measurable disease at baseline.

Patient-reported Outcome:

There was no clinically relevant changes in time to sustained worsening of "worst pain" between treatment arms (data not shown).

Exploratory analyses

- **Imlunestrant + Abemaciclib versus SOC**

A summary of efficacy endpoints comparing imlunestrant + abemaciclib versus SOC is shown below.

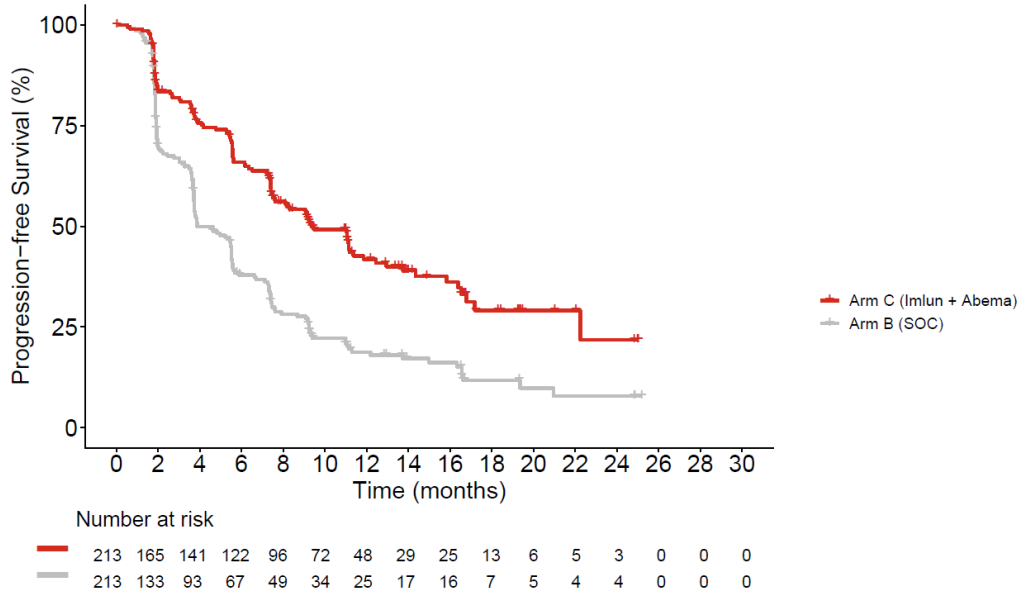
Table 48 Summary of primary and secondary endpoints concurrent ITT population imlunestrant + abemaciclib versus SOC

Endpoint	Arm C Imlun+Abema N=213	Arm B SOC N=213
Investigator-Assessed PFS		
Number of events, n (%)	114 (53.5)	160 (75.1)
Median, months (95% CI)	9.36 (7.49, 11.86)	3.88 (3.71, 5.52)
HR (95% CI)	0.464 (0.361, 0.597)	
Nominal p-value (2-sided)	<0.0001	
6-Month rate of PFS (95% CI)	65.9 (58.8, 72.2)	37.9 (31.0, 44.7)
12-Month rate of PFS (95% CI)	41.8 (34.1, 49.3)	18.8 (13.3, 24.9)
BIRC-Assessed PFS		
Number of events, n (%)	81 (38.0)	94 (44.1)
Median, months (95% CI)	14.52 (11.37, NR)	7.36 (5.49, 9.43)
HR (95% CI)	0.556 (0.408, 0.758)	
Nominal p-value (2-sided)	0.0002	
6-Month rate of PFS (95% CI)	69.5 (62.3, 75.7)	53.3 (45.1, 60.8)
12-Month rate of PFS (95% CI)	57.2 (49.0, 64.5)	37.2 (28.3, 46.0)
Interim OS		
Number of events, n (%)	36 (16.9)	40 (18.8)
Median, months (95% CI)	NR (NR, NR)	NR (22.70, NR)
HR (95% CI)	0.902 (0.572, 1.421)	
Nominal p-value (2 sided)	0.6548	
12-Month rate, % (95% CI)	86.5 (80.8, 90.7)	88.4 (82.7, 92.4)
24-Month rate, % (95% CI)	69.7 (55.3, 80.2)	60.6 (43.3, 74.1)
Median follow-up time, months	13.7	14.1
ORR[a]		
Measurable disease, N	167	162
ORR, % (n)	26.9 (45)	4.9 (8)
95% CI for ORR %	20.2, 33.7	1.6, 8.3
Clinical Benefit Rate		
% (n)	62.9 (134)	39.0 (83)
95% CI for CBR %	56.4, 69.4	32.4, 45.5

Abbreviations: BIRC = blinded independent review committee; CI = confidence interval; HR = hazard ratio; Imlun+Abema = imlunestrant plus abemaciclib; ITT = intent-to-treat; n = number of patients in the specified category; N = number of patients in the population; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SOC = standard of care.

[a] Per investigator assessment.

Figure 18 Kaplan-Meier plot of investigator-assessed PFS, concurrent ITT population imlunestrant + abemaciclib versus SOC



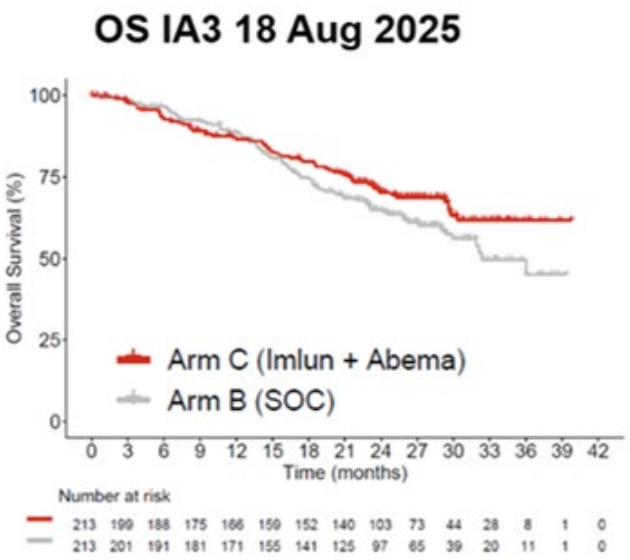
Updated results were provided for OS based on OS IA3.

Table 49 Updated results for OS

Status	PO Data Cutoff: 24 Jun 2024		OS IA3 Data Cutoff: 18 Aug 2025	
	Arm C Imlun+Abema N=213	**Arm B SOC N=213**	**Arm C Imlun+Abema N=213**	**Arm B SOC N=213**
Key Secondary Endpoint: OS				
Survival status, n (%)				
Died	36 (16.9)	40 (18.8)	64 (30.0)	80 (37.6)
Censored	177 (83.1)	173 (81.2)	149 (70.0)	133 (62.4)
Overall survival (months)				
Median, months (95% CI)	NR (- , -)	NR (22.70, -)	NR (-, -)	32.33 (29.34, -)
HR (95% CI) stratified[c]	0.902 (0.572, 1.421)		0.801 (0.573, 1.119)	
Nominal p-value (2-sided) Log-rank stratified[c]	0.6548		0.1928	
Duration of follow-up (months)				
Median, months (95% CI)	13.67 (12.65, 15.08)	14.13 (13.04, 14.82)	26.91 (25.79, 28.55)	27.04 (25.99, 28.39)
Rate (%) of overall survival				
12 months (95% CI)	86.5 (80.8, 90.7)	88.4 (82.7, 92.4)	not provided	not provided
24 months (95% CI)	69.7 (55.3, 80.2)	60.6 (43.3, 74.1)	not provided	not provided

Abbreviations: CI = confidence interval; HR = hazard ratio; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; n = number of patients in the specified category; N = number of patients; NR = not reached; OS = overall survival; OS IA2 = overall survival interim analysis 2; PO = primary outcome.

Figure 19 Kaplan-Meier plot overall survival, concurrent ITT imlunestrant + abemaciclib versus SOC



Abbreviations: Imlun+Abema = imlunestrant in combination with abemaciclib; OS = overall survival; OS IA3 = overall survival interim analysis 2; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

- **Ancillary analyses**
- **Imlunestrant monotherapy vs SOC**

Sensitivity analyses

Table 50 Prespecified sensitivity analyses for PFS, *ESR1*m-detected population Imlunestrant versus SOC

Analysis Description	Hazard Ratio (95% CI)
Progression-free survival per Investigator (primary)	0.617 (0.464, 0.821)
Progression-free survival per BIRC (secondary)	0.657 (0.469, 0.920)
Sensitivity analyses per different censoring rules[a]	
Ignoring new anticancer therapy prior to tumor progression or death[b]	0.611 (0.461, 0.809)
Ignoring absence of adequate postbaseline tumor assessment[c]	0.637 (0.481, 0.844)
Ignoring missing tumor assessments[d]	0.637 (0.481, 0.844)
Ignoring all censoring rules defined in the PFS Censoring Scheme tables[e]	0.623 (0.472, 0.822)
Unstratified analysis	0.605 (0.457, 0.801)
Stratified analysis based on CRF data	0.612 (0.460, 0.815)
Stratified analysis including randomization scheme as another stratification factor[f]	0.602 (0.450, 0.805)
Stratified analysis including the same stratification factors as in ITT analysis	0.623 (0.465, 0.833)
Multivariate Cox regression[g]	0.591 (0.445,0.784)
Progression-free survival based on the per-protocol population	0.532 (0.395, 0.716)

Abbreviations: BIRC = blinded independent review committee; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CDK = cyclin dependent kinase; CRF = case report form; *ESR1*m = estrogen receptor 1 mutation; ITT = intention to treat; n = number of patients in the specific category; N = number of patients; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] Stratified by Visceral Metastases Status from IWRS, Prior CDK 4/6 Inhibitor Treatment from IWRS.
[b] Disease progression or death occurred after the start date of the new therapy were counted as events.
[c] No postbaseline tumor assessment available, but deaths reported after 2-scan intervals were counted as events.
[d] Disease progression or death documented after 2 or more missing scan intervals following the last adequate tumor assessment were counted as events.
[e] All disease progression or death were counted as events, unless there was no baseline tumor assessment.
[f] Stratified analyses by including randomization scheme (patients randomized 1:1 under the original protocol versus 1:1:1 under amendment (a)).
[g] Multivariate Cox regression model adjusting for prior CDK4/6 inhibitor, age group, and bone-only metastasis.

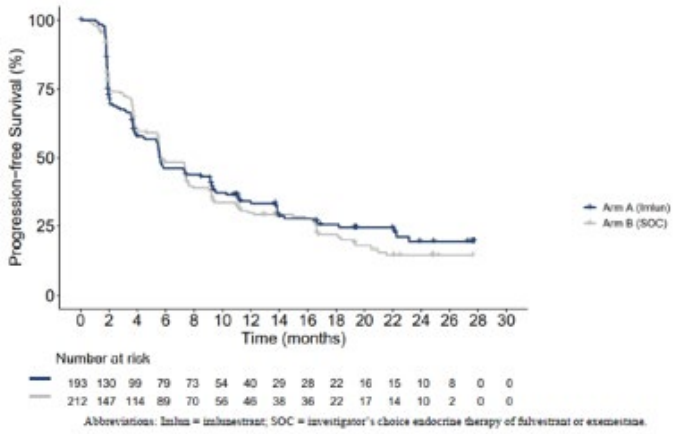
Important deviations of eligibility criteria to be excluded from the per-protocol analysis were pre-defined the in the SAP. In response to the GCP critical finding on eligibility criteria, it was concluded that overall n=88 patients were inadvertently enrolled. An additional sensitivity analyses was

performed excluding all inadvertently enrolled patients in the *ESR1*m-detected population (n=32), HR for PFS comparing imlunestrant versus SOC was 0.617 (95% CI: 0.464, 0.821) in the primary analysis and 0.541 (95% CI: 0.397, 0.739) in this additional sensitivity analysis.

Subgroup *ESR1*m-not detected (ITT including *ESR1* mutation unknown) population

In a prespecified subgroup analysis, PFS results were similar (hazard ratio=1.00 [95% CI: 0.79, 1.27]) between the imlunestrant arm and SOC arm in the *ESR1*m-not-detected subgroup of the ITT population. mPFS was 5.6 months vs 5.7 months in the imlunestrant and SOC arm, respectively (see figure below).

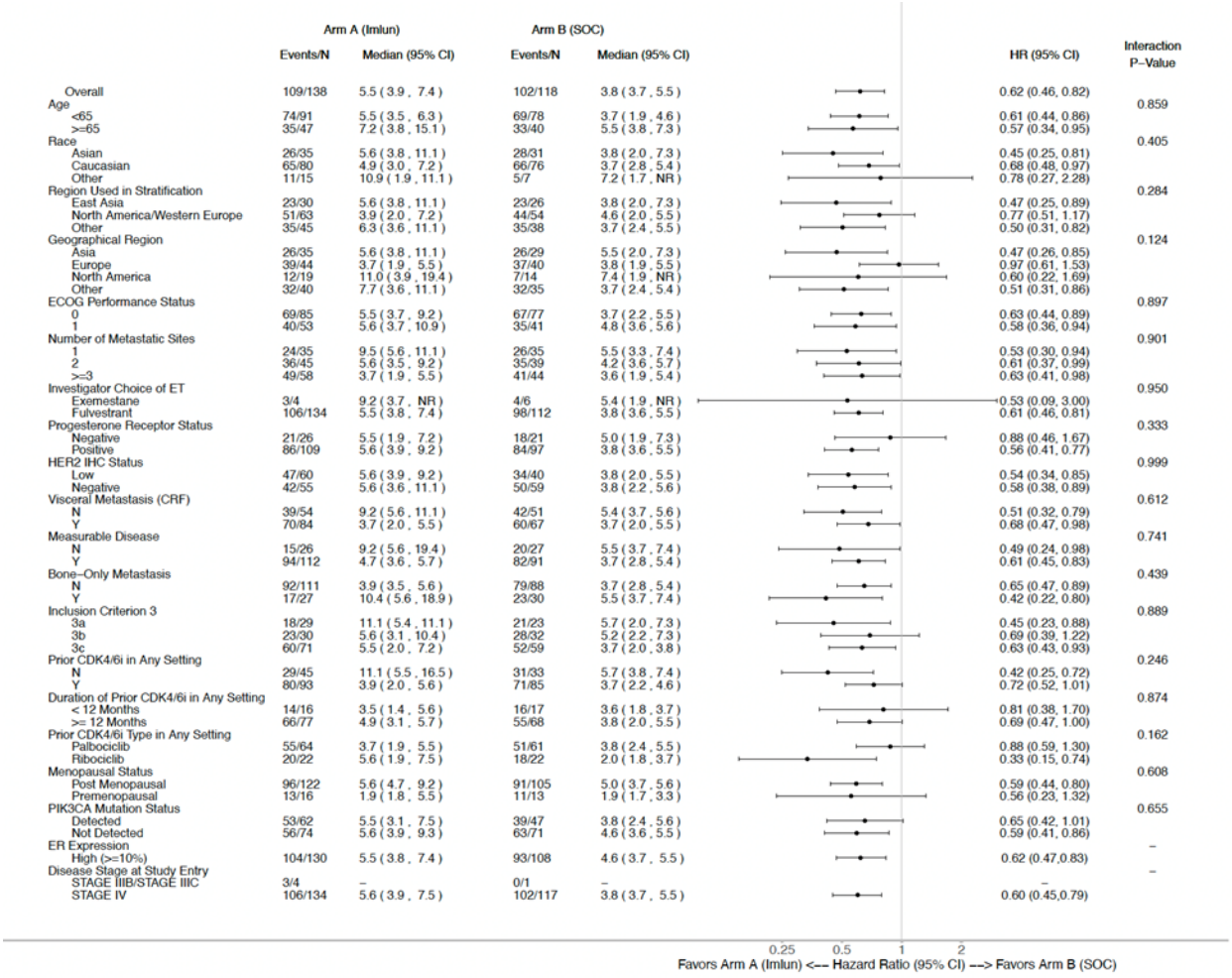
Figure 20 Kaplan-Meier plot of investigator's-Assessed progression-free survival, *ESR1*-mutation-not-detected (ITT including *ESR1* mutation unknown) population.



***ESR1*m-detected population**

Subgroup analyses for PFS are shown below (see figure below).

Figure 21 Forest plot of investigator-assessed PFS for SAP pre-defined subgroups, *ESR1*m-detected population imlunestrant versus SOC



Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CRF = Case Report Form; ER = oestrogen receptor; ESR1 = oestrogen receptor 1; ET = endocrine therapy; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IHC = immunohistochemistry; INV = investigator assessment; NR = not reported; PFS = progression-free survival; SOC = standard of care.
Note: Median PFS and HR (95% CI) were not calculated if the subgroup level had very small number of events. Interaction p-value was not calculated if one of the subgroup levels was not analysed.
Data cutoff: 24 June 2024

Subgroup analysis by prior CDK4/6i.

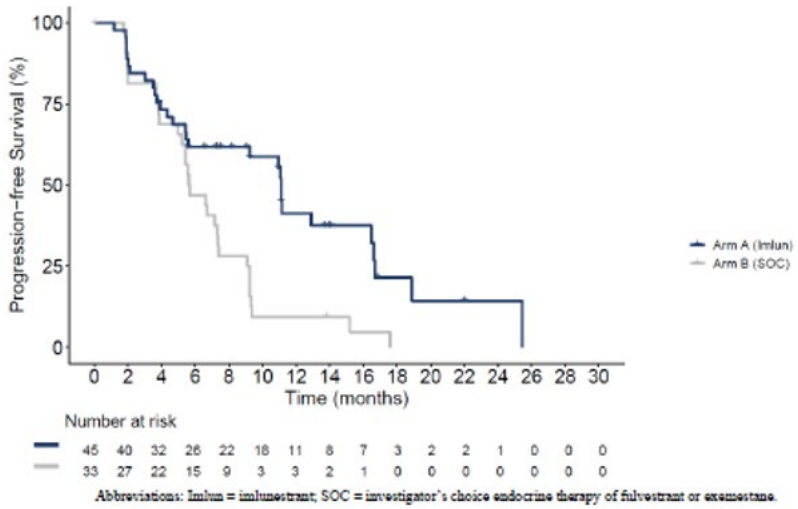
- ***CDK4/6i naïve subgroup ESR1m-detected population***

Table 51 Summary of investigator-assessed PFS for CDK4/6i naïve subgroup Arm A (imlun) versus Arm B (SOC) *ESR1*m-detected population

	Arm A (Imlun) (N=45)	Arm B (SOC) (N=33)	Arm A (Imlun) vs. Arm B (SOC) Treatment Effect /Difference /p-value*e
Number of Events, n (%)	29 (64.4)	31 (93.9)	
PD, n (%)	26 (57.8)	30 (90.9)	
Death without PD, n (%)	3 (6.7)	1 (3.0)	
Number of Patients Censored, n (%)	16 (35.6)	2 (6.1)	
Start of New Anti-Cancer Therapy, n (%)	5 (11.1)	0	
No documented PD with regular assessment, n (%)	10 (22.2)	1 (3.0)	
Death or PD after two or more missed tumor Assessments, n (%)	0	1 (3.0)	
Withdrawal by Subject, n (%)	1 (2.2)	0	
Progression-Free Survival summary			
Minimum *a, month	1.18	0.03+	
25th percentile (95% CI)	3.91(2.04, 5.59)	3.75(1.87, 5.42)	
Median (95% CI)	11.10(5.45, 16.46)	5.65(3.84, 7.36)	5.45
75th percentile (95% CI)	16.69(11.14, -)	9.17(6.70, 9.36)	
Maximum	25.43	17.58	
Restricted Mean (95% CI) with restriction time = 17.58 month *b	10.41(8.50, 12.32)	6.61(5.20, 8.02)	3.80(1.43, 6.17)
p-value (2-sided) - Log Rank Unstratified			p = 0.0012
Hazard Ratio (95% CI) - UnStratified			0.424(0.250, 0.721)
Follow-up time summary			
Minimum *a, month	1.18	0.03+	
25th percentile (95% CI)	9.07(6.57, 13.70)	13.80(13.80, -)	
Median (95% CI)	13.93(9.23, 22.01)	- (13.80, -)	-
75th percentile (95% CI)	22.01(14.06, -)	- (13.80, -)	
Maximum	25.43	17.58	
Progression-Free Survival Rate (%) with 95% CI *c			
2 - month	88.9 (75.3, 95.2)	84.4 (66.5, 93.2)	4.5 (-11.1, 20.1) p = 0.5700
4 - month	73.3 (57.7, 83.8)	68.8 (49.7, 81.8)	4.5 (-16.1, 25.1) p = 0.6679

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; - = not calculable; PD = progressive disease; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
Note: Quartiles and Progression-Free Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method.
*a - For minimum and maximum, + indicates a censored observation.
*b - Restriction time is defined by the latest time where the standard error of the survival estimates are <=0.075.
*c - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*d - 2-sided p-value based on normal approximation.
*e - Treatment Effect/Difference/p-values are computed based on comparator Arm B (SOC).
Data cutoff date is 24-Jun-2024.

Figure 22 KM-plot of investigator-assessed PFS for CDK4/6i naïve subgroup *ESR1*m-detected population imlunestrant versus SOC



Abbreviations: Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.

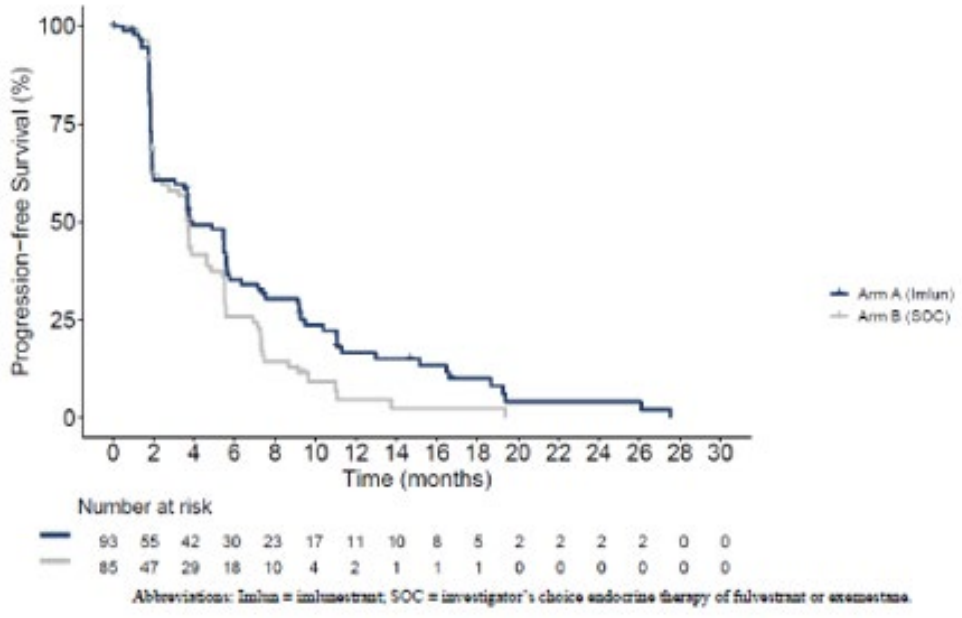
- ***CDK4/6i pretreated subgroup ESR1m-detected population***

Table 52 Summary of investigator-assessed PFS for CDK4/6i pretreated subgroup Arm A (imlun) versus Arm B (SOC) *ESR1*m-detected population

	Arm A (Imlun) (N=93)	Arm B (SOC) (N=85)	Arm A (Imlun) vs. Arm B (SOC) Treatment Effect /Difference /p-value*e
Number of Events, n (%)	80 (86.0)	71 (83.5)	
PD, n (%)	79 (84.9)	68 (80.0)	
Death without PD, n (%)	1 (1.1)	3 (3.5)	
Number of Patients Censored, n (%)	13 (14.0)	14 (16.5)	
No Post-Baseline Tumor Assessment, n (%)	2 (2.2)	4 (4.7)	
Start of New Anti-Cancer Therapy, n (%)	4 (4.3)	7 (8.2)	
No documented PD with regular assessment, n (%)	7 (7.5)	3 (3.5)	
Progression-Free Survival summary			
Minimum *a, month	0.03+	0.03+	
25th percentile (95% CI)	1.84(1.77, 1.91)	1.87(1.84, 1.94)	
Median (95% CI)	3.91(2.00, 5.59)	3.68(2.23, 4.63)	0.23
75th percentile (95% CI)	9.26(6.34, 12.98)	6.90(5.52, 7.46)	
Maximum	27.53	19.38	
Restricted Mean (95% CI) with restriction time = 19.38 month *b	6.54(5.30, 7.78)	4.79(3.90, 5.68)	1.75(0.22, 3.28) p = 0.0247*d
p-value (2-sided) - Log Rank Unstratified			p = 0.0551
Hazard Ratio (95% CI) - UnStratified			0.723(0.519, 1.006)
Follow-up time summary			
Minimum *a, month	0.03+	0.03+	
25th percentile (95% CI)	11.07(7.43, -)	9.23(3.68, 9.43)	
Median (95% CI)	- (14.69, -)	- (9.23, -)	-
75th percentile (95% CI)	- (- , -)	- (9.43, -)	
Maximum	27.53	19.38	
Progression-Free Survival Rate (%) with 95% CI *c			
2 - month	61.8 (50.9, 71.0)	62.0 (50.3, 71.7)	-0.2 (-14.9, 14.6) p = 0.9814
4 - month	49.2 (38.4, 59.1)	41.6 (30.4, 52.4)	7.6 (-7.6, 22.9) p = 0.3281
6 - month	35.1 (25.3, 45.1)	25.8 (16.4, 36.2)	9.3 (-4.9, 23.5)

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; - = not calculable; PD = progressive disease; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
Note: Quartiles and Progression-Free Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method.
*a - For minimum and maximum, + indicates a censored observation.
*b - Restriction time is defined by the latest time where the standard error of the survival estimates are <=0.075.
*c - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*d - 2-sided p-value based on normal approximation.
*e - Treatment Effect/Difference/p-values are computed based on comparator Arm B (SOC).
Data cutoff date is 24-Jun-2024.

Figure 23 KM-plot investigator's assessed PFS for CDK4/6i pretreated subgroup *ESR1*m-detected population imlunestrant versus SOC



Abbreviations: Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.

Subgroup analysis on PFS by type of *ESR1*-mutation:

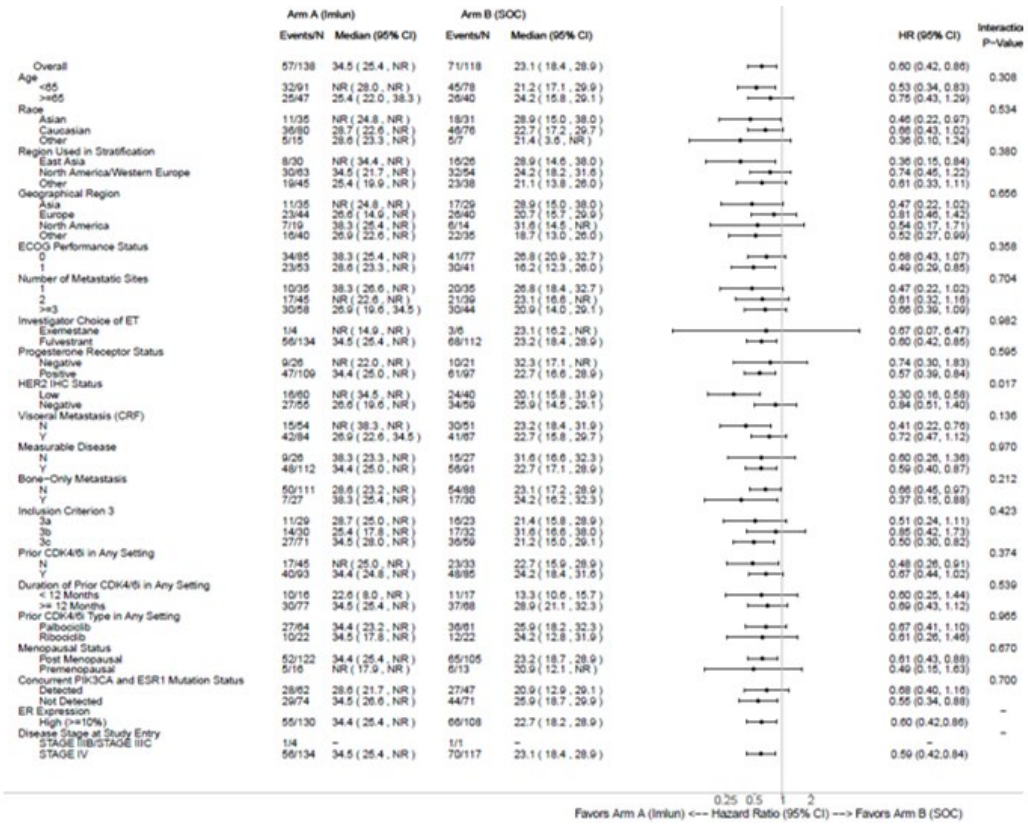
Table 53 Subgroup Analysis of Progression-free Survival *ESR1*m-detected Biomarker Subpopulations Imlunestrant versus SOC

ESR1m subpopulation	Arm A Imlunestrant Events/N (%)	Arm B SOC Events/N (%)	HR (95%CI)
Single *ESR1* mutation detected	72/95 (75.8)	64/73 (87.7)	0.563 (0.398, 0.795)
Multiple *ESR1* mutations detected	37/43 (86.1)	38/45 (84.4)	0.702 (0.429, 1.149)
D538G detected (No Y537S)	53/66 (80.3)	42/49 (85.7)	0.541 (0.351, 0.834)
Y537S detected (No D538G)	19/22 (86.4)	24/29 (82.8)	0.864 (0.466, 1.602)
Y537S and D538G detected	15/19 (79.0)	15/17 (88.2)	0.755 (0.358, 1.594)
Neither Y537S or D538G detected	22/31 (71.0)	21/23 (91.3)	0.563 (0.305, 1.038)

Abbreviations: CI = confidence interval; *ESR1*m = estrogen receptor 1 mutation; HR = hazard ratio; N= total number of patients in the population within the treatment group; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Subgroup analysis on OS in the *ESR1*m-detected population at OS IA3 (DCO 18 August 2025)

Figure 24 Forest plot of OS imlunestrant versus SOC *ESR1*m-detected population (DCO: 18 August 2025)



Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CRF = Case Report Form; ECOG = Eastern Cooperative Oncology Group; ET = endocrine therapy; ER = oestrogen receptor; ESR1 = oestrogen receptor 1; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IHC = immunohistochemistry; Imlun = imlunestrant; NR = not reached; OS = overall survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

Data cutoff date is 18−Aug−2025.

- **Imlunestrant + abemaciclib vs Imlunestrant monotherapy (concurrent ITT)**

Sensitivity analyses

Table 54 Prespecified sensitivity analyses for investigator-assessed PFS Concurrent ITT population imlun+abema versus imlunestrant

Analysis Description	Hazard Ratio (95% CI)
Progression-free survival per Investigator (primary)	0.569 (0.441, 0.733)
Progression-free survival per BIRC (secondary)	0.617 (0.453, 0.841)
Sensitivity analyses per different censoring rules[a]	
Ignoring new anticancer therapy prior to tumor progression or death[b]	0.578 (0.449, 0.744)
Ignoring absence of adequate postbaseline tumor assessment[c]	0.569 (0.441, 0.733)
Ignoring missing tumor assessments[d]	0.566 (0.439, 0.729)
Ignoring all censoring rules defined in the PFS Censoring Scheme tables[e]	0.588 (0.459, 0.754)
Unstratified analysis	0.602 (0.471, 0.769)
Stratified analysis based on CRF data	0.561 (0.435, 0.723)
Stratified analysis including randomization scheme as another stratification factor[f]	0.572 (0.444, 0.737)
Multivariate Cox regression[g]	0.570 (0.444, 0.731)
Progression-free survival based on the per-protocol population	0.613 (0.477, 0.789)
Progression-free survival based on the full ITT population	0.601 (0.475, 0.760)

Abbreviations: Abema = abemaciclib; BIRC = blinded independent review committee; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CRF = case report form; Imlun = imlunestrant; ITT = intention to treat; PFS = progression-free survival.

a Stratified by Visceral Metastases Status from IWRS, Prior CDK 4/6 Inhibitor Treatment from IWRS, Region
b Disease progression or death occurred after the start date of the new therapy were counted as events.
c No postbaseline tumor assessment available, but deaths reported after 2-scan intervals were counted as events.
d Disease progression or death documented after 2 or more missing scan intervals following the last adequate tumor assessment were counted as events.
e All disease progression or death were counted as events, unless there was no baseline tumor assessment.
f Stratified analyses by including randomization scheme (patients randomized 1:1 under the original protocol versus 1:1:1 under amendment (a)).
g Multivariate Cox regression model adjusting for prior CDK4/6i, age group, progesterone receptor status, number of metastatic sites.

In response to the GCP routine inspection critical finding on eligibility criteria, an additional sensitivity analyses was performed excluding all inadvertently enrolled patients in the concurrent ITT (n=36), HR for PFS comparing imlunestrant + abemaciclib versus imlunestrant was 0.569 (95% CI: 0.441, 0.733) in the primary analysis and 0.586 (95% CI: 0.450, 0.764) in the sensitivity analysis.

The applicant conducted additional post-hoc sensitivity analyses by testing scenarios by either removing patients from both treatment arms based on the criterion of INV PD that was not confirmed by BIRC, or by censoring or imputing the times for these patients (data not shown).

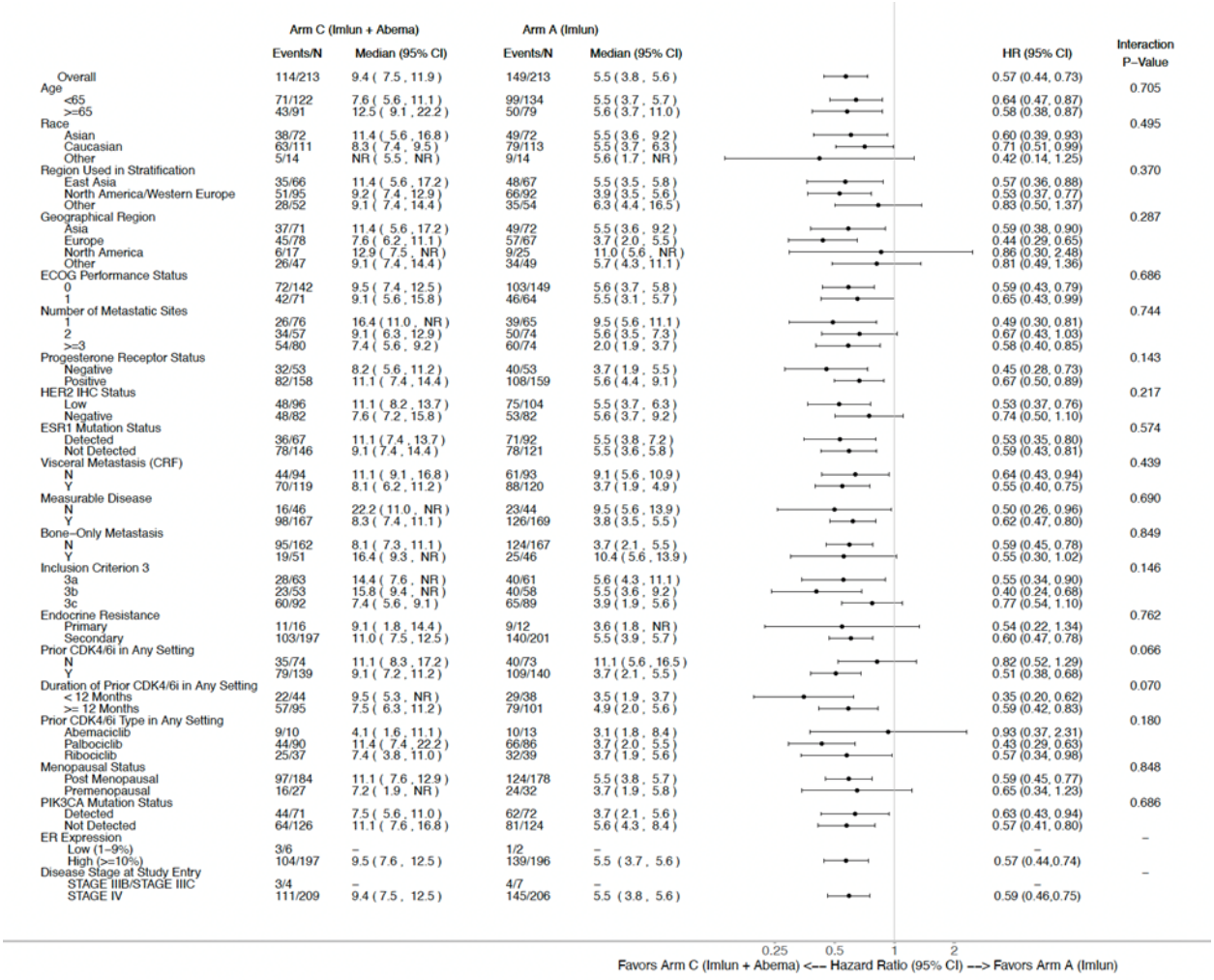
Additional sensitivity analyses INV-PFS: The Applicant performed additional sensitivity analyses looking into the robustness of the PFS results to the nature of the patients' progression (data not shown).

The applicant provided during the evaluation an updated concordance analysis between investigator and BIRC-assessed PFS in the concurrent ITT population at PO and OS IA3 with EDR and LDR proposed as measures of evaluation of discordance between local investigator and BIRC PFS (data not shown).

Subgroup analyses

Subgroup analyses are shown below.

Figure 25 Forest plot of investigator-assessed PFS for SAP pre-defined subgroups, concurrent ITT population imlunestrant + abemaciclib versus imlunestrant



Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CRF = Case Report Form; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; ET = endocrine therapy; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IHC = immunohistochemistry; imlun+abema = imlunestrant in combination with abemaciclib; INV = investigator assessment; ITT = intention-to-treat; NR = not reported; PFS = progression-free survival.
Note: Median PFS and HR (95% CI) were not calculated if the subgroup level had very small number of events. Interaction p-value was not calculated if one of subgroup levels was not analysed.
Data cutoff: 24 June 2024

Subgroup analysis by prior CDK4/6i

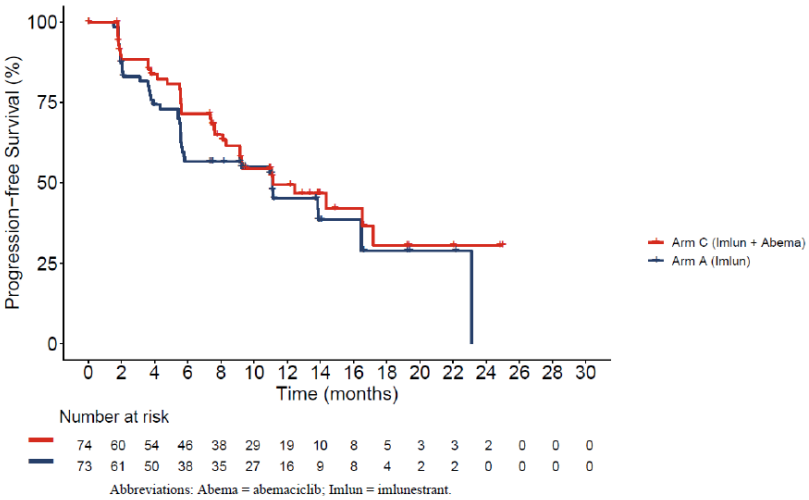
- CDK4/6i naïve subgroup

Table 55 Summary of Investigator-Assessed Progression-Free Survival for CDK4/6i Naive Subgroup Arm C (Imlun + Abema) versus Arm A (Imlun) Concurrent-Intention-to-Treat Population

	Arm C (Imlun + Abema) (N=74)	Arm A (Imlun) (N=73)	Arm C (Imlun + Abema) vs. Arm A (Imlun) Treatment Effect /Difference /p-value*c
Number of Events, n (%)	35 (47.3)	40 (54.8)	
PD, n (%)	33 (44.6)	40 (54.8)	
Death without PD, n (%)	2 (2.7)	0	
Number of Patients Censored, n (%)	39 (52.7)	33 (45.2)	
No Post-Baseline Tumor Assessment, n (%)	4 (5.4)	2 (2.7)	
Start of New Anti-Cancer Therapy, n (%)	5 (6.8)	1 (1.4)	
No documented PD with regular assessment, n (%)	30 (40.5)	29 (39.7)	
Withdrawal by Subject, n (%)	0	1 (1.4)	
Minimum *a, month	0.03+	0.03+	
25th percentile (95% CI)	5.59(3.61, 8.11)	3.91(2.04, 5.59)	
Median (95% CI)	11.14(8.31, 17.18)	11.10(5.59, 16.46)	0.03
75th percentile (95% CI)	- (16.53, -)	23.13(13.86, -)	
Maximum	25.00+	23.13	
p-value (2-sided) - Log Rank Unstratified			p = 0.3876
Hazard Ratio (95% CI) - UnStratified			0.817(0.519, 1.288)

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable; PD = progressive disease; Imlun = imlunestrant; Abema = abemaciclib; CDK 4/6i = cyclin-dependent kinase 4/6 inhibitor.
Note: Quartiles and Progression-Free Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*a - For minimum and maximum, + indicates a censored observation.
*b - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*c - Treatment Effect/Difference/p-values are computed based on comparator Arm A (Imlun).
Data cutoff date is 24-Jun-2024.

Figure 26 Kaplan-Meier plot of investigator-assessed progression-free survival for CDK4/6i naïve subgroup, concurrent intention-to-treat population imlun+abema versus imlunestrant. DCO 24 June 2024



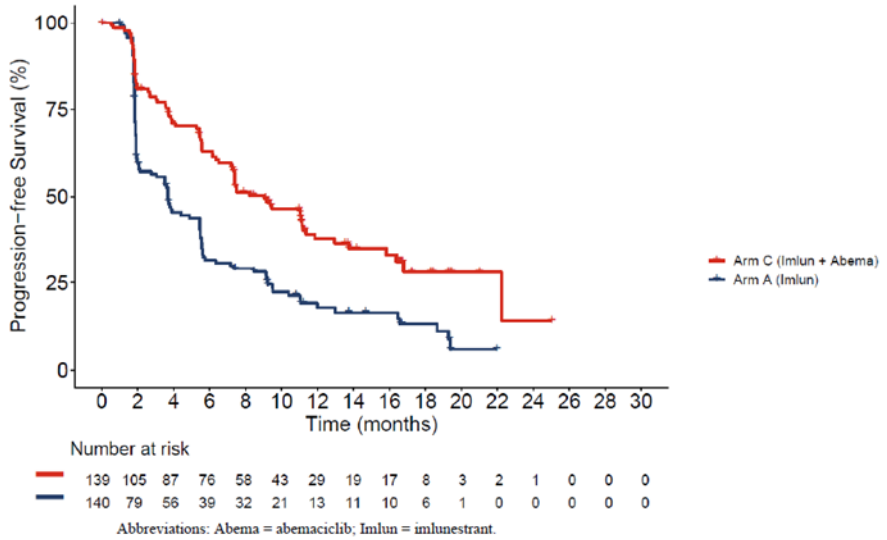
- CKD4/6i pretreated subgroup

Table 56 Summary of Investigator-Assessed Progression-Free Survival for CDK4/6i Pre-Treated Subgroup Arm C (Imlun + Abema) versus Arm A (Imlun) Concurrent-Intention-to-Treat Population DCO 24 June 2024

	Arm C (Imlun + Abema) (N=139)	Arm A (Imlun) (N=140)	Arm C (Imlun + Abema) vs. Arm A (Imlun) Treatment Effect /Difference /p-value*c
Number of Events, n (%)	79 (56.8)	109 (77.9)	
PD, n (%)	72 (51.8)	108 (77.1)	
Death without PD, n (%)	7 (5.0)	1 (0.7)	
Number of Patients Censored, n (%)	60 (43.2)	31 (22.1)	
No Post-Baseline Tumor Assessment, n (%)	5 (3.6)	4 (2.9)	
Start of New Anti-Cancer Therapy, n (%)	6 (4.3)	6 (4.3)	
No documented PD with regular assessment, n (%)	45 (32.4)	21 (15.0)	
Death or PD after two or more missed tumor Assessments, n (%)	2 (1.4)	0	
Withdrawal by Subject, n (%)	2 (1.4)	0	
Minimum *a, month	0.03+	0.03+	
25th percentile (95% CI)	3.71(1.91, 5.45)	1.84(1.81, 1.91)	
Median (95% CI)	9.07(7.20, 11.17)	3.68(2.07, 5.45)	5.39
75th percentile (95% CI)	22.24(15.84, -)	9.23(5.65, 12.98)	
Maximum	25.03+	21.98+	
p-value (2-sided) - Log Rank Unstratified			p = <.0001
Hazard Ratio (95% CI) - UnStratified			0.506(0.378, 0.679)

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable; PD = progressive disease; Imlun = imlunestrant; Abema = abemaciclib; CDK 4/6i = cyclin-dependent kinase 4/6 inhibitor.
Note: Quartiles and Progression-Free Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*a - For minimum and maximum, + indicates a censored observation.
*b - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*c - Treatment Effect/Difference/p-values are computed based on comparator Arm A (Imlun).
Data cutoff date is 24-Jun-2024.

Figure 27 Kaplan-Meier plot of investigator's-assessed progression-free survival for CDK4/6i pretreated subgroup, intention-to-treat population imlun+abema versus imlunestrant. DCO 24 June 2024



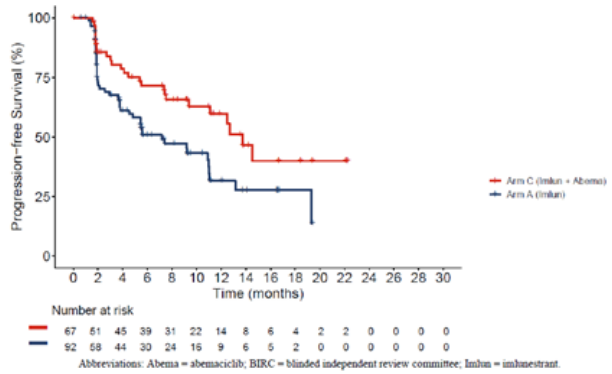
Abbreviations: Abema = abemaciclib; Imlun = imlunestrant.

Within the ORR-evaluable CDK4/6i naïve patients, ORR was 35.7% vs 14.8% in favour of combination treatment. For CDK4/6i-pretreated patients, ORR was 22.5% vs 10.2% in favour of combination treatment.

Subgroup analysis PFS by *ESR1*-mutation status

- ***Concurrent ESR1m-detected population***

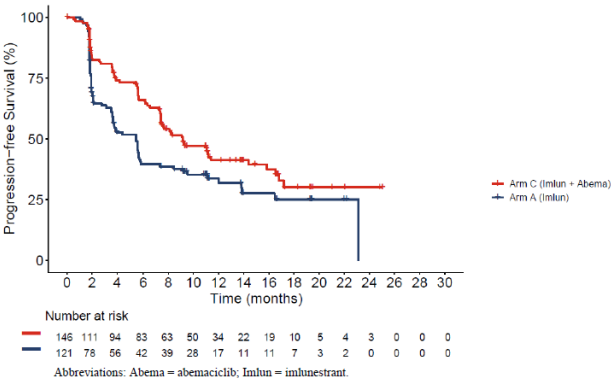
Figure 28 Kaplan-Meier plot of investigator-assessed progression-free survival imlunestrant + abemaciclib versus imlunestrant in the concurrent *ESR1*-mutation detected population



Abbreviations: Abema = abemaciclib; BIRC = blinded independent review committee; Imlun = imlunestrant.

- ***Concurrent ESR1m-not-detected (including ESR1m unknown) population***

Figure 29 Kaplan-Meier plot of investigators-assessed progression-free survival imlunestrant + abemaciclib versus imlunestrant in the concurrent *ESR1*-mutation not-detected population



Abbreviations: Abema = abemaciclib; Imlun = imlunestrant.

Subgroup analysis PFS by biomarkers:

- ***Type of ESR1-mutation***

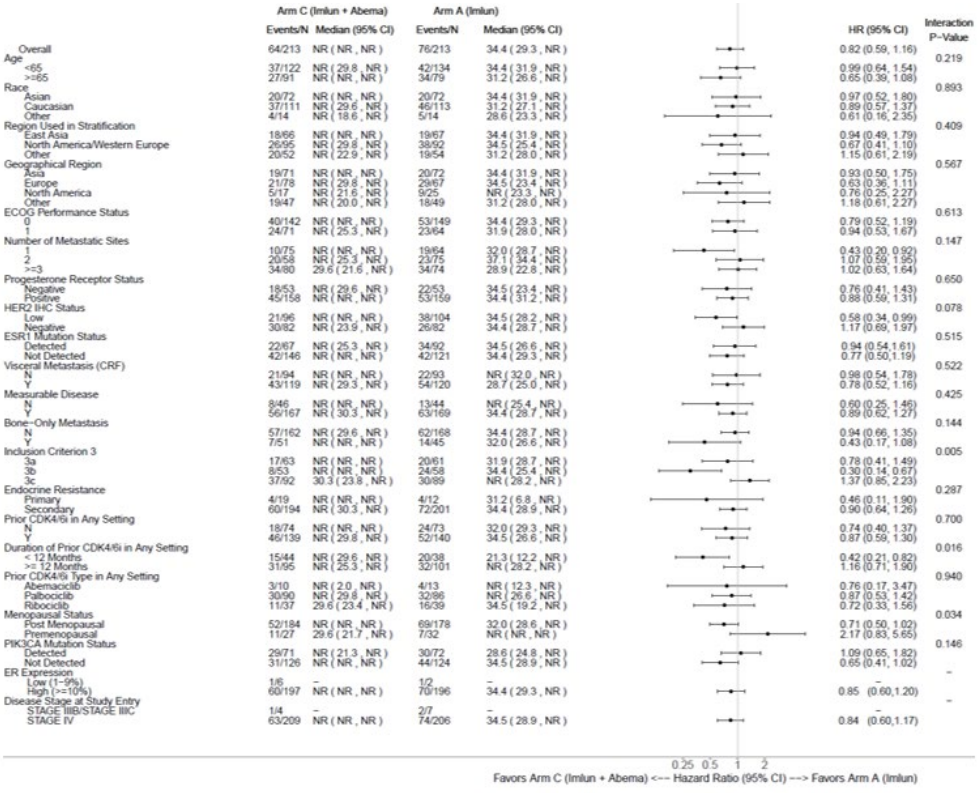
Table 57 Subgroup Analysis of investigator-assessed Progression-free Survival *ESR1*m-detected Biomarker Subpopulations Imlunestrant + Abemaciclib versus Imlunestrant

ESR1 mutation subpopulation	Arm C Imlun+Abema Events/N (%)	Arm A Imlunestrant Events/N (%)	HR (95% CI)
Single *ESR1* mutation detected	21/39 (53.9)	47/63 (74.6)	0.588 (0.350, 0.985)
Multiple *ESR1* mutations detected	15/28 (53.6)	24/29 (82.8)	0.455 (0.233, 0.887)
D538G detected (No Y537S)	10/27 (37.0)	39/49 (79.6)	0.357 (0.177, 0.719)
Y537S detected (No D538G)	9/15 (60.0)	14/17 (82.4)	0.526 (0.227, 1.221)
Y537S + D538G detected	6/8 (75.0)	8/11 (72.7)	0.586 (0.188, 1.824)
Neither Y537S or D538G detected	11/17 (64.7)	10/15 (66.7)	1.067 (0.449, 2.538)

Abbreviations: Abema = abemaciclib; CI = confidence interval; *ESR1*m = estrogen receptor 1 mutation; HR = hazard ratio; Imlun = imlunestrant; N = total number of patients in the population within the treatment group.

Subgroup analyses OS based on OS IA3 Arm C vs Arm A

Figure 30 Forest plot of overall survival at OSIA3, Arm C (Imlun + Abema) vs Arm A (Imlun) Concurrent−intention−to−treat population



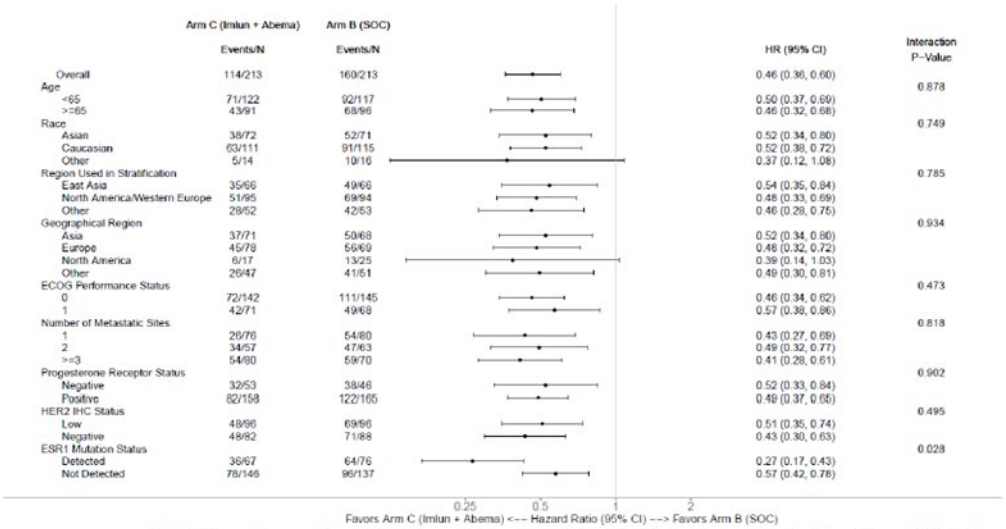
Data cutoff date is: 18−Aug−2025

Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CRF = Case Report Form; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor

receptor 2; HR = hazard ratio; IHC = immunohist; ITT = intention-to-treat; NR = not reached; OS = overall survival ; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

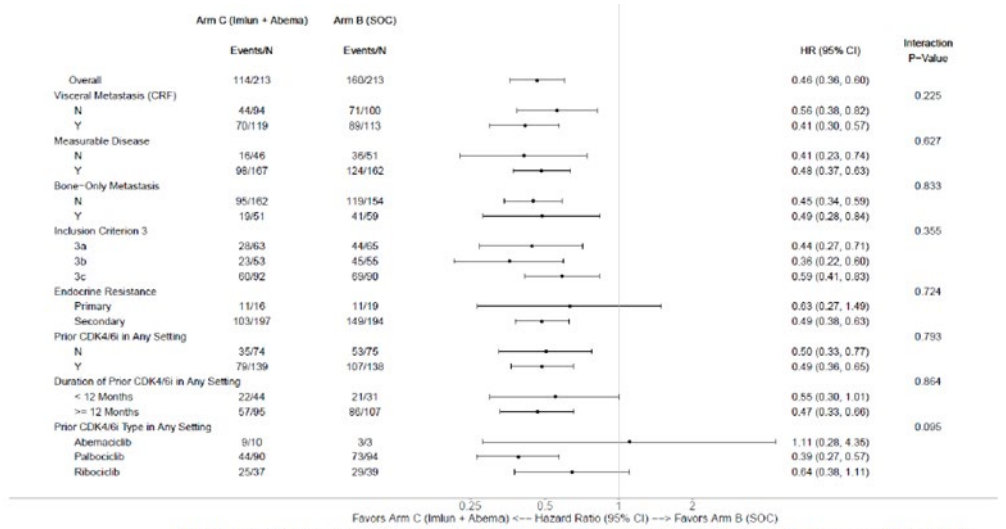
- **Subgroup analyses PFS based on the exploratory analysis Imlunestrant + abemacilib versus SOC (concurrent ITT)**

Figure 31 Forest Plot (1 of 2) of INV-Assessed PFS for SAP Pre-defined Subgroups, Concurrent ITT Population Imlun+Abema versus SOC



Abbreviations: Abema = abemaciclib; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IHC = immunohistochemistry; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
The Hazard ratio (with CI) was stratified for overall and ESR1 mutation status and unstratified for other subgroups. All interaction p-values were unstratified.
ESR1 Mutation not detected included ESR1 mutation unknown patients

Figure 32 Forest Plot (2 of 2) of INV-Assessed PFS for SAP Pre-defined Subgroups, Concurrent ITT Imlun+Abema versus SOC



Abbreviations: Abema = abemaciclib; CI = confidence interval; CDK = cyclin dependent kinase; CRF = case report form; HR = hazard ratio; Imlun = imlunestrant; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
The Hazard ratio (with CI) was stratified for overall and unstratified for other subgroups. All interaction p-values were unstratified.

Subgroup PFS results by prior CDK4/6i (y/n)

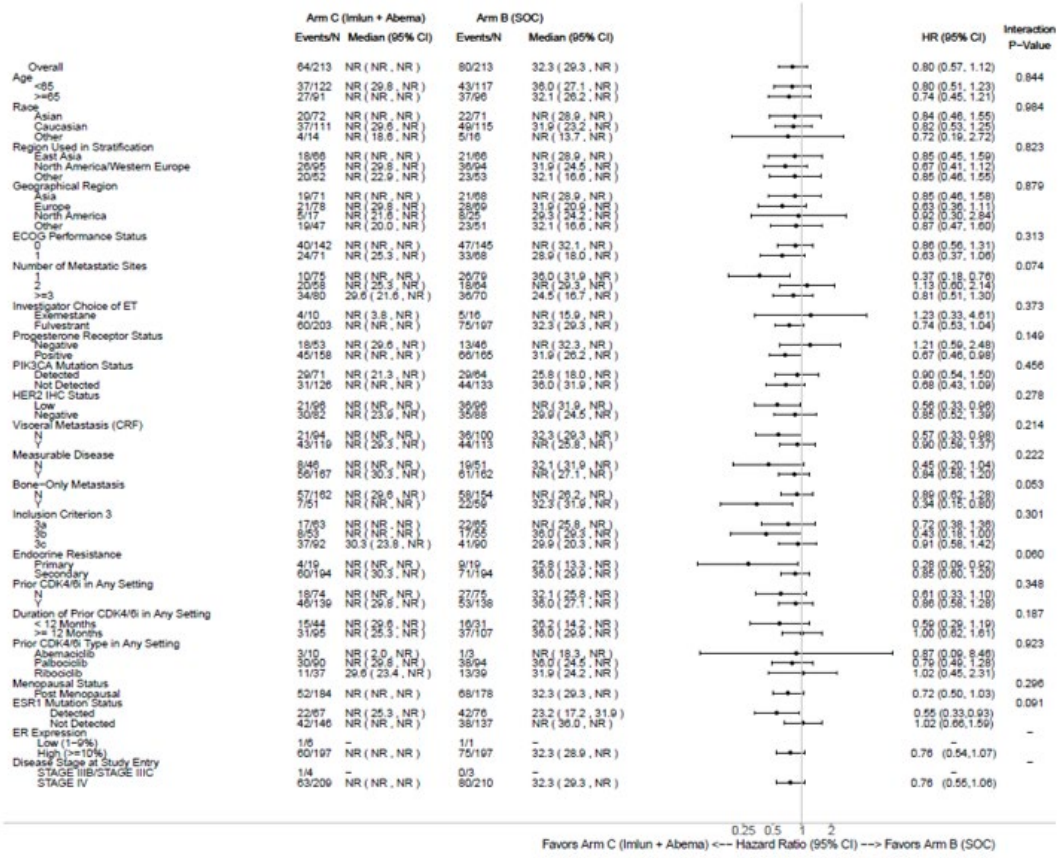
Table 58 Subgroup Analysis of Investigator-Assessed Progression-Free Survival Arm C (Imlun + Abema) vs Arm B (SOC) Concurrent-Intention-to-Treat Population J2J-OX-JZLC

Study Overall target Parameter	Arm C (Imlun + Abema) Patients with Event n/N %	Arm C (Imlun + Abema) Median*a (Month) 95% CI	Arm B (SOC) Patients with Event n/N %	Arm B (SOC) Median*a (Month) 95% CI	Arm C (Imlun + Abema) vs Arm B (SOC) Hazard Ratio HR*b 95% CI P-value *c	Inter-action P-value*d
Prior CDK4/6i in Any Setting						0.7926
N	35 /74 (47.30)	11.14 (8.31, 17.18)	53 /75 (70.67)	5.49 (3.78, 7.62)	0.505 (0.329, 0.775) 0.0014	
Y	79 /139 (56.83)	9.07 (7.20, 11.17)	107/138 (77.54)	3.75 (3.25, 5.52)	0.486 (0.362, 0.653) <.0001	

Abbreviations: N= total number of subjects in the population within the treatment group; n = number of subjects with an event in the subgroup; Imlun= imlunestrant; Abema = abemaciclib; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.
*a - estimated using the Kaplan-Meier method;
*b - Hazard ratio and 95% CI (Wald) were estimated from stratified Cox model(Overall only);
*c - two-sided p-value from stratified log-rank test(Overall only);
*d - Wald test of treatment-by-subgroup interaction from Cox model;
Stratification factors used in stratified analysis are: Visceral Metastases Status(CTS) from IWRS, JELC Prior CDK 4/6 Inhibitor Treatment from IWRS, Region
Data cutoff date is 24-Jun-2024.

Subgroup analyses OS based on OS IA3 Arm C vs Arm B

Figure 33 Forest plot overall survival at OS IA3 in the concurrent ITT population for imlun + abema versus SOC.



Abbreviations:CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; CRF = Case Report Form; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IHC = immunohistochemistry; Imlun = imlunestrant; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; NR = not reached; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS = progression-free survival; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.
Data cutoff date is: 18 August 2025.

Additional analyses performed as part of the Clinical Study Data Pilot

The primary and secondary analyses were replicated and were in line with the results presented in the Clinical Study Report (results not shown).

Given the relevance of prior treatment with a CDK 4/6 inhibitor to the assessment, prior treatment was investigated by region and country (results by country are not shown).

Table 59 Prior CDK4/6 inhibitor use by region for the ITT set of patients used for the comparison of Imlun vs SOC

	No N (% of region)	Yes N (% of region)
Asia	97 (52.4)	88 (47.6)
Europe	37 (20)	148 (80)
North America	13 (18.8)	56 (81.2)
Other	132 (59.5)	90 (40.5)

Table 60 Prior CDK4/6 inhibitor use by region for the *ESR1*-m subset of patients used for the comparison of Imlun vs SOC

	No N (% of region)	Yes N (% of region)
Asia	24 (37.5)	40 (62.5)
Europe	10 (11.9)	74 (88.1)
North America	6 (18.2)	27 (81.8)
Other	37 (49.3)	38 (50.7)

Table 61 Prior CDK4/6 inhibitor use by region for the concurrent ITT subset of patients used for the comparison of Imlun + Abema vs. Imlun

	No	Yes
	N (% by region)	N (% by region)
Asia	75 (52.4)	68 (47.6)
Europe	26 (17.9)	119 (82.1)
North America	8 (19)	34 (81)
Other	40 (41.7)	56 (58.3)

Swimlane plots (not shown in this report) were generated in order to explore the patterns of assessments in cases when an investigator-assessed progression was determined without a BIRC-assessed progression. The time to censoring (not shown) was also examined to understand whether there was a signal of informative censoring, particularly in the BIRC-assessed PFS.

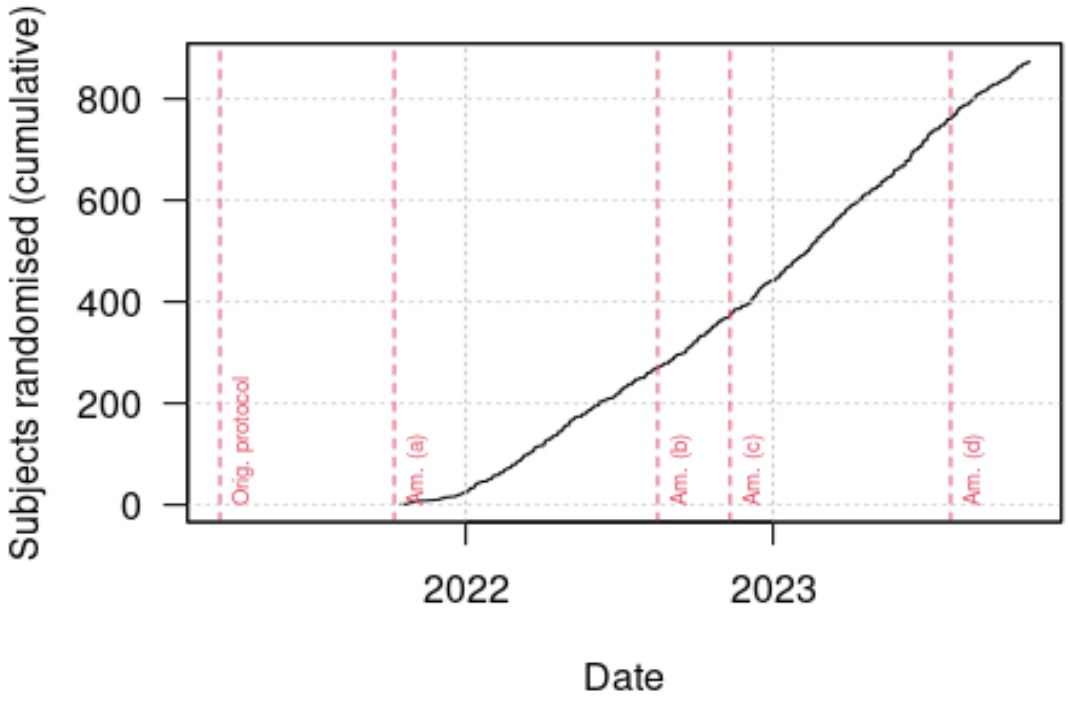
This was also explored in an alternative way by looking at the number of patients who met certain conditions (see below table). Very few patients had at least one assessment after an INV-PD without a BIRC-PD.

Table 62 Investigation of patient follow up following an investigator-determined progression

Condition	Arm.A.Imlun	Arm.B.SOC	Arm.C.ImlunAbema
Randomised	331	330	213
AND has INV-PD	233	247	107
AND has no BIRC-PD at same date	146	152	68
AND has >=1 assessment after INV-PD	16	9	7

The number of patients randomised by each protocol amendment was explored further.

Figure 34 Cumulative number of participants randomised in the study, with protocol amendment dates



Additional investigations into the agreement between the Investigator-assessed and BIRC-assessed PFS.

Arm A vs Arm B: *ESR1*-m mutated subgroup

Table 63 BIRC-assessment outcomes when an investigator concluded a PFS event, *ESR1*-m subgroup (Rapporteur's analysis)

	Arm A	Arm B
Number of investigator events (PD or death)	109/138 (79%)	102/118 (86%)
INV and BIRC event	68/109 (62%)	68/102 (67%)
Event at the same time	41/68 (60%)	49/68 (72%)
INV later than BIRC	20/68 (29%)	16/68 (24%)
INV earlier than BIRC	7/68 (10%)	3/68 (4%)
INV event, no BIRC event (BIRC censored)	41/109 (38%)	34/102 (33%)

Note: table derived from information provided in Table 44.

Arm C vs Arm A: Imlunestrant + abemaciclib versus Imlunestrant, concurrent ITT

Table 64 BIRC-assessment outcomes when an investigator concluded a PFS event, Imlunestrant + abemaciclib versus Imlunestrant, concurrent ITT (Rapporteur's analysis)

	Arm C	Arm A
Number of investigator events (PD or death)	114/213 (54%)	149/213 (70%)
INV and BIRC event	76/114 (67%)	90/149 (60%)
Event at the same time	50/76 (66%)	63/90 (70%)
INV later than BIRC	22/76 (29%)	22/90 (24%)
INV earlier than BIRC	4/76 (5%)	5/90 (6%)
INV event, no BIRC event (BIRC censored)	38/114 (33%)	59/149 (40%)

Note: table derived from information provided in Table 46

Table 65 Reasons for discordance between INV and BIRC, ITT and *ESR1*-m detected

Category	ITT		*ESR1*m-Detected	
	Arm A Imlunestrant N=331	Arm B SOC N=330	Arm A Imlunestrant N=138	Arm B SOC N=118
Events by INV but censored by BIRC, n (%)	89/331 (26.9)	104/330 (31.5)	41/138 (29.7)	34/118 (28.8)
PD by INV due to new lesion progression only	33/89 (37)	30/104 (29)	17/41 (41)	15/34 (44)
PD by INV due to non-target lesion progression only	15/89 (17)	28/104 (27)	9/41 (22)	9/34 (26)
PD by INV due to target lesion progression only	18/89 (20)	20/104 (19)	8/41 (20)	3/34 (9)
Multiple progressions[a]	23/89 (26)	26/104 (25)	7/41 (17)	7/34 (21)
Events by BIRC but censored by INV, n (%)	12/331 (3.6)	10/330 (3.0)	6/138 (4.3)	3/118 (2.5)

Note: table derived from information provided by the Applicant during the assessment

Table 66 Reasons for discordance between INV and BIRC, concurrent ITT

	Arm A monotherapy (n = 213)	Arm B SoC (n = 213)	Arm C combination (n = 213)
Events by INV by censored by BIRC	59/213 (27.7)	74/213 (34.7)	38 (17.8)
PD by INV due to new lesion progression only	17/59 (28.8)	16/74 (21.6)	20/38 (52.6)
Lesion already identified by BIRC at baseline	*7/17*	*6/16*	*7/20*
PD by INV due to NTL progression only	12/59 (20.3)	21/74 (28.4)	3/38 (7.9)
NTL at PD already identified by BIRC at baseline	*8/12*	*13/21*	*2/3*
PD by INV due to TL progression only	13/59 (22.0)	15/74 (20.3)	9/38 (23.7)
Multiple (at least two) reasons	17/59 (28.8)	22/74 (29.7)	6/38 (15.8)

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main study, EMBER-3, supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 67 Summary of efficacy for trial EMBER-3 (J2J-OX-JZLC)

Title: EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Oestrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy		
Study identifier	Protocol No.: J2J-OX-JZLC EudraCT No.: 2021-000079-35	
Design	Phase 3, randomized, open-label, 3-arm study of imlunestrant, investigator's choice of endocrine therapy of either fulvestrant or exemestane, and imlunestrant plus abemaciclib in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Ongoing (first patient randomized 15 October 2021) not applicable not applicable
Hypothesis	Superiority of investigator's assessed progression free survival of: - Imlunestrant over SOC in the intention to treat (ITT) population - Imlunestrant over SOC (Arm B) in the *ESR1*m-detected population - Imlunestrant + abemaciclib over imlunestrant monotherapy in the concurrent ITT population	
Treatments groups	Arm A: Imlunestrant	400 mg PO QD, 28-day cycles Treatment until disease progression N=331

Title: EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Oestrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy			
Study identifier	Protocol No.: J2J-OX-JZLC EudraCT No.: 2021-000079-35		
	Arm B: Investigator's standard of care (SOC); fulvestrant or exemestane		Fulvestrant: 500 mg IM on Day 1 and 15 of the first cycle and then on Day 1 of a each subsequent 28-day Exemestane: 25 mg PO QD in 28-day cycle Treatment until disease progression N=330
	Arm C: Imlunestrant + abemaciclib (imlun + abema)		Imlunestrant: 400 mg PO QD, 28-day cycle Abemaciclib: 150 mg PO BID in 28-day cycle Treatment until disease progression N=213
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	Time from randomisation until the date of objective disease progression (per RECIST 1.1 as assessed by the investigator) or death (by any cause in the absence of progression).
	Key secondary endpoint	Overall Survival (OS)	Time from the date of randomisation until death due to any cause
Database lock	Data cut-off: 24 June 2024; database lock: 02 August 2024. The data presented below are for the final analysis of PFS and third interim analysis of OS.		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat DCO: 24 June 2024 primary PFS analysis OS IA3: 18 August 2025		
Descriptive statistics and estimate variability	Treatment group	Arm A (imlunestrant)	Arm B (SOC)
	Number of subject	N=331	N=330
	Median PFS (months)	5.55	5.52
	95% CI	5.32, 7.26	4.60, 5.62
	Median OS (months)	37.13	32.33
	95% CI	32.002, NR	29.14, 43.47
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Imlunestrant versus SOC
		Hazard ratio	0.876
		95% CI	0.724, 1.039
		P-value	0.1158
	Secondary endpoint OS	Hazard ratio	0.862
		95% CI	0.675, 1.101

Title: EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Oestrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy			
Study identifier	Protocol No.: J2J-OX-JZLC EudraCT No.: 2021-000079-35		
		P-value	-
Notes	The primary analysis was based on the stratified Cox proportional hazard model with treatment as the only covariate, stratified by the randomisation strata OS not tested as PFS did not reach statistical significance NR: Not reached At randomization, patients were stratified for previous treatment with any CDK4/6 inhibitor (yes/no), presence of visceral metastases (yes/no), and region (East Asia versus North America/Western Europe versus Other).		
Analysis description	**Primary Analysis**		
Analysis population and time point description	Patients with detectable *ESR1* mutation at baseline DCO: 24 June 2024 primary PFS analysis OS IA3: 18 August 2025		
Descriptive statistics and estimate variability	Treatment group	Arm A (imlunestrant)	Arm B (SOC)
	Number of subject	N=138	N=118
	Median PFS (months)	5.49	3.84
	95% CI	3.91, 7.39	3.68, 5.52
	Median OS (months)	34.50	23.10
	95% CI	24.97, NR	18.43, 28.90
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Imlunestrant versus SOC
		Hazard ratio	0.617
		95% CI	0.464, 0.821
		P-value	0.0008
	Secondary endpoint OS	Hazard ratio	0.603
		95% CI	0.425, 0.856
		P-value	0.0043
Notes	The primary analysis was based on the stratified Cox proportional hazard model with treatment as the only covariate, stratified by the randomisation strata (region was not included to reduce the number of strata). OS immature at OS IA2; event rate 35.5% Arm A and 50.8% Arm B NR: Not reached At randomization, patients were stratified for previous treatment with any CDK4/6 inhibitor (yes/no), presence of visceral metastases (yes/no), and region (East Asia versus North America/Western Europe versus Other).		

Title: EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Oestrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy			
Study identifier	Protocol No.: J2J-OX-JZLC EudraCT No.: 2021-000079-35		
Analysis description	**Primary analysis**		
Analysis population and time point description	Concurrent ITT DCO: 24 June 2024 primary PFS analysis OS IA3: 18 August 2025		
Descriptive statistics and estimate variability	Treatment group	Arm C (imlun + abema)	Arm A (imlunestrant)
	Number of subject	N=213	N=213
	Median PFS (months)	9.36	5.49
	95% CI	7.49, 11.86	3.78, 5.62
	Median OS (months)	NR	34.43
	95% CI	NR, NR	29.31, NR
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	imlun + abema vs imlunestrant
		Hazard ratio	0.569
		95% CI	0.441, 0.733
		P-value	<0.0001
	Secondary endpoint OS	Hazard ratio	0.824
		95% CI	0.588, 1.156
		P-value	0.262
Notes	The primary analysis was based on the stratified Cox proportional hazard model with treatment as the only covariate, stratified by the randomisation strata. Enrolment to Arm C began 6 months later than for Arm A and Arm B. The concurrently enrolled population was the primary analysis population for the comparison with Arm C. The combination treatment was tested only if one of the other two primary objectives were reached. OS immature at IA3, event rate 30.0% in Arm C and 35.7% Arm A NR: Not reached At randomization, patients were stratified for previous treatment with any CDK4/6 inhibitor (yes/no), presence of visceral metastases (yes/no), and region (East Asia versus North America/Western Europe versus Other). Extrapolatory analyses of imlun+abema vs SOC in the concurrent ITT: mPFS of 9.36 (7.49, 11.86) vs 3.88 (3.71, 5.52); HR: 0.464 (95% CI: 0.361, 0.597) mOS not reached (-,-) vs 32.33 (29.34, -); HR: 801 (95% CI: 0.573, 1.119)		

2.6.5.3. Clinical studies in special populations

Child-Pugh score was not collected at baseline for studies conducted in participants with breast cancer.

Hepatic impairment was studied in study J2J-MC-JZLG in healthy volunteers which included 27 patients with Child-Pugh score B or C.

Table 68 Clinical studies in special populations ITT population

	Controlled trials (JZLC)		Non-controlled trials[b] (JZLA, JZLB, JZLF)	
	Imlun	Imlun+Abema	Imlun	Imlun+Abema
Renal impairment[c] patients (Subjects number / total number)	31/331	21/213	27/218	7/44
Hepatic impairment[d] patients (Subjects number / total number)	N/A	N/A	N/A	N/A
Paediatric patients <18 years (Subjects number / total number) [e]	N/A	N/A	N/A	N/A
Age 65-74 (Subjects number / total number)	82/331	64/213	60/218	11/44
Age 75-84 (Subjects number / total number)	32/331	23/213	27/218	2/44
Age 85+ (Subjects number / total number)	6/331	4/213	2/218	1/44
Other (Subjects number / total number)	N/A	N/A	N/A	N/A

Abbreviations: Abema = abemaciclib; CKD = chronic kidney disease; Imlun = Imlunestrant; Imlun+Abema = imlunestrant in combination with abemaciclib; ITT = intention-to-treat; N/A = not applicable.
a Complete study codes are as follows: JZLA = J2J-MC-JZLA; JZLB = J2J-MC-JZLB; JZLC = J2J-OX-JZLC; JZLF = J2J-MC-JZLF.
b Patients with early and metastatic breast cancer randomised to imlunestrant any dose
c Renal impairment is defined as having GFR <60 (CKD Stage 3a, 3b, 4 or 5 using KDIGO definition)
d Hepatic impairment is defined as having Child-Pugh score B or C. This information was not collected so is unavailable for these studies.
e Paediatric population not included in EMBER program studies reported here.
Data cutoff date: 09 March 2023 (JZLA), 19 December 2022 (JZLB), 24 June 2024 (JZLC), and 18 February 2024 (JZLF).

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Scientific rationale for *ESR1* mutation testing

Mechanism of action:

Imlunestrant is an orally bioavailable potent selective degrader and pure antagonist of wild-type and mutant ERα. In in vitro studies, imlunestrant antagonized and degraded wild-type and mutant ERα, leading to inhibition of ER-dependent gene transcription and cellular proliferation in ER+ breast cancer cells. Imlunestrant demonstrated anti-tumour activity in multiple ER+ breast cancer xenograft models, including models with *ESR1* mutations, and models with resistance to fulvestrant and CDK4/6i.

Biomarker definition:

"Any *ESR1* mutation between codons 310 and 547" was utilised to define a patient to be '*ESR1* mutation positive' ('*ESR1*-mut'). This means the definition covers any mutations in the *ESR1* ligand domain and therefore follows the rationale that any *ESR1* mutation in the ligand domain leads to resistance to endocrine therapy (Toy et al., Nat. Genetics 2013, Brett et al. Breast Cancer Res. 2021).

The following mutations including 34 specific variants (single nucleotide variant and small deletions) annotated as oncogenic or likely oncogenic by the OncoKB™ database (Chakravarty et al. 2017; Suehnholz et al. 2024) are detected by the Guarduant360 CDx:

D538G, Y537S, Y537N, E380Q, L536H, L536P, L536R, V422del, S463P, Y537D, Y537C, S463F, D538N, L536V, L536Q, Y537H, E380K, L536F, Y537G, L469V, D538H, Y537P, L536K, L536G, V422_E423del, Y537Q, M421_V422delinsI, L536I, E380D, L536N, E380D, L536N, E380A, D538V, E380V.

Justification / validation of biomarker definition:

As to the information applied, the justification for the definition of biomarker-positivity (i.e. *ESR1* mutations as specified above) is following a scientific rationale being mainly based on preclinical data. Regarding clinical validation see below.

Tests used

Guardant360 CDx is a qualitative next generation sequencing-based in vitro diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels), copy number amplifications (CNAs), and fusions. Guardant360 CDx utilizes circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs).

It was approved in the EU under the IVDR regulation (IVDR 2017/746) as a companion diagnostic for elacestrant to aid in selection of patients with breast cancer with *ESR1* missense mutations in May 2024.

As an exception for patients enrolled into study EMBER-3 from mainland China the 'Burning Rock OncoScreen Plus 520 assay' test (OncoCompass Plus) was used instead of the Guardant360 CDx test because of regulatory requirements. No local tests investigating the *ESR1*-mutation status were performed.

Analytical validation strategy

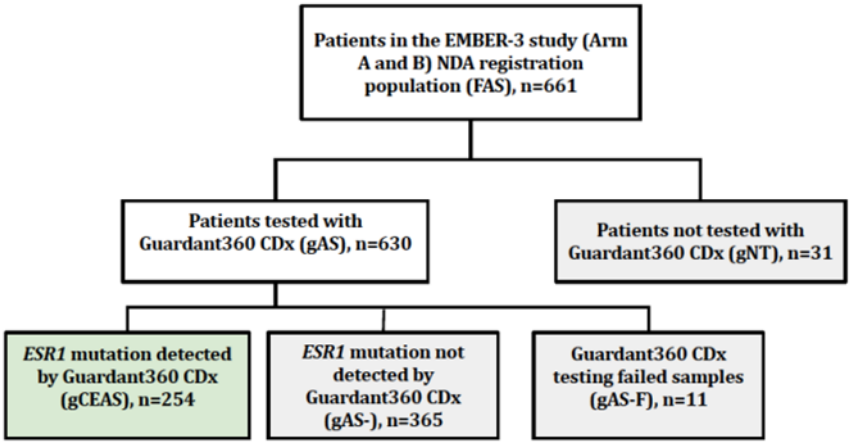
Analytical validation of Guardant360 CDx with regard to accuracy, sensitivity, specificity, precision and robustness was demonstrated previously in the context of the approval as a companion diagnostic for elacestrant.

Clinical validation strategy

The Applicant performed a diagnostic study intended to demonstrate the clinical validity of Guardant360 CDx to aid in the selection of patients with oestrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) locally advanced/metastatic breast cancer (BC) whose tumours have *ESR1* mutations for imlunestrant (LY3484356) therapy. This objective was assessed by comparing imlunestrant therapy efficacy relative to investigator's choice endocrine therapy in the EMBER-3 registration population of patients with an *ESR1* mutation detected by Guardant360 CDx (*ESR1*-mut). The primary endpoint is progression-free survival (PFS) as assessed by the investigator. OS was a secondary objective.

Samples from 630 of the primary EMBER-3 registration population subjects (Arms A and B, n=661) were tested with Guardant360 CDx, of which 254 subjects (40.3% of the Guardant360 CDx tested population) have one or more *ESR1* mutation(s) detected and 365 (57.9% of the Guardant360 CDx tested population) have none. 31 subjects did not have samples available for testing, and 11 samples failed sample QC and did not generate valid Guardant360 CDx results.

Figure 35 Diagnostic study clinical efficacy analyses patient disposition



A model-based multiple imputation (MI) was performed to impute the missing CDx test results and the primary objective analysis was repeated on the missing-value imputed complete data. The imputation of missing results was conducted by building a classifier-based logistic regression model using the valid CDx test result data and clinical baseline characteristics. Rubin's rules were used to combine log-transformed hazard ratio estimates and their variances across the imputed datasets.

The following *ESR1* mutations were detected in study EMBER-3 (regardless of number of *ESR1*-mutations detected in one patient) based on central testing:

Table 69 *ESR1* mutation variants biomarker evaluable population based on ITT population

Variant, n (%)	Arm A Imlunestrant N=318	Arm B SOC N=323	Arm C Imlun+Abema N=212	Total N=853
ESR1 mutation detected	138 (43.4)	118 (36.5)	67 (31.6)	323 (37.9)
D538G	85 (26.7)	66 (20.4)	35 (16.5)	186 (21.8)
Y537S	41 (12.9)	46 (14.2)	23 (10.8)	110 (12.9)
Y537N	32 (10.1)	31 (9.6)	18 (8.5)	81 (9.5)
E380Q	27 (8.5)	20 (6.2)	19 (9.0)	66 (7.7)
L536H	6 (1.9)	11 (3.4)	7 (3.3)	24 (2.8)
Y537C	6 (1.9)	10 (3.1)	6 (2.8)	22 (2.6)
L536P	4 (1.3)	4 (1.2)	8 (3.8)	16 (1.9)
S463P	4 (1.3)	4 (1.2)	6 (2.8)	14 (1.6)
V422del	1 (0.3)	3 (0.9)	6 (2.8)	10 (1.2)
L536R	3 (0.9)	1 (0.3)	5 (2.4)	9 (1.1)
L536K	3 (0.9)	0	0	3 (0.4)
L536Q	0	1 (0.3)	1 (0.5)	2 (0.2)
Y537D	0	2 (0.6)	0	2 (0.2)
D538E	0	1 (0.3)	0	1 (0.1)
D538N	0	1 (0.3)	0	1 (0.1)
E380K	1 (0.3)	0	0	1 (0.1)
L469V	0	1 (0.3)	0	1 (0.1)

Abbreviations: Abema = abemaciclib; *ESR1* = estrogen receptor 1; Imlun = imlunestrant; n = number of subjects in the specified category; N = number of subjects in biomarker evaluable population; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

The PFS HR observed in the *ESR1*-mut population (gCEAS) treated with imlunestrant therapy vs. investigator's choice endocrine therapy was 0.635 (95% CI 0.478 – 0.844, p=0.0017). The median

PFS in the *ESR1*-mut population treated with imlunestrant therapy was 5.49 months (95% CI 3.78 – 7.16) vs. investigator's choice endocrine therapy 3.84 months (95% CI 3.68 – 5.52). The sensitivity analysis was consistent with the primary objective, HR=0.624 (0.469-0.830).

The OS HR in the *ESR1*-mut population treated with imlunestrant therapy vs. investigator's choice endocrine therapy at the primary analysis data cut-off date was 0.553 (95% CI 0.352 – 0.868, p=0.0091).

The investigator-assessed PFS HR in *ESR1*-mutated subjects treated with imlunestrant therapy vs. investigator's choice endocrine therapy was 1.059 (95% CI 0.824 – 1.361, p=0.6605). The median PFS in the *ESR1*-mutated population treated with imlunestrant therapy was 5.52 months (95% CI 3.75 – 7.33) vs. investigator's choice endocrine therapy 5.59 months (95% CI 5.42 – 7.39). The OS HR in the *ESR1*-mutated population treated with imlunestrant therapy vs. investigator's choice endocrine therapy at the primary analysis data cut-off date was 0.915 (95% CI 0.563 – 1.489, p=0.7208).

No clinical thresholding was performed.

Use of Burning Rock OncoScreen Plus 520 assay for China samples

The *ESR1* gene results were reported for China patients and both used the same *ESR1* mutation definition. A concordance study compared results from the OncoCompass Plus (previously named OncoScreen Plus 520) and Guardant360 assays. Samples with (n=23) and without (n=65) *ESR1* mutation initially identified using the Guardant360 platform were subsequently reanalyzed with the OncoCompass Plus assay. Concordance was high; the OncoCompass Plus test had a positive predictive value (PPV) of 91.7% (90% CI 76.0, 98.5%) and NPV of 98.4% (90% CI 92.8, 99.9%). Assuming the prevalence of *ESR1*m is 0.37, the prevalence-adjusted PPV is 94.8% (90% CI 88.8, 100%) and the NPV is 97.4% (90% CI 92.9, 100%).

An ad-hoc sensitivity analysis excluding patients from China was consistent with the primary analysis in the *ESR1*m-detected population, with a stratified hazard ratio of 0.635 (95% CI: 0.478, 0.844).

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

During the evaluation, the applicant conducted and submitted post-hoc inter trial comparisons (ITCs), using patient-level data from the EMBER-3, postMONARCH, and MONARCH-2 studies as indirect comparison in the Concurrent ITT and CDK4/6i naïve subgroup. INV-assessed PFS was compared between imlun+abema (EMBER-3) versus fulvestrant+abemaciclib (MONARCH 2 and post MONARCH) (data not shown).

2.6.5.6. Supportive study

See dose responses study in section 2.6.5.1.

2.6.6. Discussion on clinical efficacy

As part of this MAA, the Applicant submitted clinical study results in support of the following claimed indications:

"Inluriyo is indicated:

- *as a monotherapy for the treatment of adult patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor 1 (ESR1)-*

mutated, advanced or metastatic breast cancer, previously treated with an endocrine based regimen, and

- *in combination with abemaciclib for the treatment of adult patients with ER-positive, HER2-negative, advanced or metastatic breast cancer, previously treated with endocrine based regimen."*

During the evaluation, the applicant withdrew the combination with abemaciclib indication.

The clinical development programme in support of the claimed indications consists of 2 clinical trials: one supportive phase 1a/1b EMBER study and the pivotal phase 3 EMBER-3 (J2J-OX-JZLC)) study.

Dose finding and dose recommendation

The recommended dose for imlunestrant of 400 mg QD is based on PK, PD, safety and efficacy data. No phase 2 dosing study was performed and the recommended dose was primarily based on efficacy and safety data from the phase 1a/1b EMBER study. PK data showed that 400 mg daily was the first dose level where steady-state plasma concentrations exceeded the in vivo TEC80 range (non-clinical data) over the entire dosing interval for 87% of the patients, thus allowing most patients to achieve biologically relevant concentrations. No dose finding studies investigating the combination with abemaciclib were performed. There was a trend for an increase in the incidence of nausea with increasing dose levels, while no increase in severity of TEAEs with increasing dose was noted. The dosing regimen is overall considered acceptable to make a benefit/risk assessment.

In terms of dose adjustment, a single dose reduction to 200 mg QD is included in section 4.2 of the SmPC to manage adverse reactions. Pop-PK data indicate that with this dose 45% of patients will exceed the TEC80 range over the entire dosing interval. Similar on-target effects with ER degradation were observed for 200 mg, 400 mg, and 800 mg QD dose in the phase 1 EMBER-2 study which was conducted in parallel with the pivotal EMBER-3 study. No clinical efficacy results are available from the EMBER-2 trial. In the EMBER-3 trial dose reduction occurred in a small number of patients (8 in the monotherapy arm and 34 in the combination arm).

Design and conduct of clinical studies

The pivotal EMBER-3 (J2J-OX-JZLC) study was initially designed as a two-arm study (randomization 1:1) with the primary objective to compare imlunestrant (imlun) monotherapy (Arm A) with SOC (Arm B) in the ITT. Arm C consisting of the combination of imlunestrant plus abemaciclib (imlun+abema), was added in amendment (a) of the protocol prior to first patient visit in any treatment arm (October 2021). Thereafter, patients were randomized 1:1:1 (A:B:C) until the target enrolment was met for arms A and B.

A proper justification for the addition of this third arm is, however, lacking. The phase 1 EMBER study included CDK4/6i-naïve patients only for the combination cohort. Lack of data from an earlier phase 1 or (preferably) a phase 2 study on efficacy/activity in a CDK4/6i pretreated population (likely) causes uncertainty on the B/R in this patient population.

Inclusion and exclusion criteria

The study population consists of adult patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. Patients were considered to have received prior CDK4/6i when available and reimbursed, however reasons were not collected.

LHRH agonists were given when clinically indicated to pre- and perimenopausal women, and men. A statement on treatment with LHRH analogues for continuous ovarian suppression has been adequately included in section 4.1 of the SmPC.

Patients were to have had only 1 line of ET therapy in the metastatic setting and no chemotherapy or other systemic treatment except CDK4/6i in the advanced/metastatic setting. Patients who relapsed with evidence of progression while on or within 12 months of completion of (neo)adjuvant AI, alone or in combination with a CDK4/6 inhibitor, with no treatment for advanced disease were also eligible. The eligibility criteria largely reflect the target population, although patients recruited into the trial are fitter than the to-be-treated population in clinical practice (e.g. patients with ECOG >1, presence of symptomatic metastatic visceral disease, or cardiac comorbidity were excluded). Key exclusion criteria are adequately reflected in section 5.1 of the SmPC. Patients also needed to have adequate organ function. Patients with known pathogenic germline mutations appropriate for treatment with a PARP inhibitor were excluded in those regions where these therapies are approved and available, which is agreed given the different prognosis of these patients.

The study population is considered to be broad and heterogeneous including pre- or postmenopausal women and men, with or without *ESR1*-mutation, PIK3CA- or AKT1-activating mutations or PTEN alterations, and prior CDK4/6i. Relevant subgroup analyses, especially based on *ESR1* mutation and prior CDK4/6i, are of importance to support a positive B/R in the broad target population. Additional subgroup analysis by ER expression status (low: 1-9% vs strong), menopausal status, locally advanced or metastatic disease, and primary/secondary endocrine resistance were also presented.

ESR1 mutational status was determined by blood circulating tumour deoxyribonucleic acid (ctDNA) using the Guardant360 CDx assay (Guardant Health, Redwood City, CA). The Guardant360 CDx assay is approved in the EU in 2024 for *ESR1* mutation with Orserdu (elecestrant). *ESR1*m positivity defined as any missense mutation between codons 310 and 547 (Orserdu EPAR). In the EMBER-3 trial, *ESR1*m positivity was based on testing for 34 pre-specified specific variants (single nucleotide variants and small deletions in *ESR1*) annotated as oncogenic or likely oncogenic by the OncoKB database, an FDA recognized somatic tumour mutation database (Chakravarty et al. 2017; Suehnholz et al. 2024). In the biomarker evaluable population, 17 specific *ESR1* mutations were identified, of which the most common were D538G (21.8%) and Y537S (12.9%). Results are discussed further below.

In patients from China, *ESR1* mutation status was determined using the 'Burning Rock OncoScreen Plus 520 assay' test (OncoCompass Plus) because of regulatory requirements. This concerned a minority of patients (n=25 ITT) and did not impact the results.

Randomisation

The stratification factors of CDK4/6i (yes vs no), presence of visceral metastases (yes vs no), and region (East Asia vs North America/Western Europe vs Others) are considered to be acceptable. However, it is unfortunate that *ESR1*-mutation was not among the used stratification factors given the known differential efficacy of oral SERDs in *ESR1*m-detected and undetected patients and the protocol amendment that included PFS in *ESR1*m-detected patients as a dual primary endpoint.

Comparator

The proposed SOC of endocrine monotherapy of fulvestrant or exemestane is an acceptable comparator after failure of CDK4/6 inhibitors in line with ESMO guidelines, although fulvestrant is considered more appropriate for patients with activating *ESR1*-mutations. Other available treatment options include a combination of ET with mTOR inhibitors or alpelisib plus fulvestrant for patients with PIK3CA-mutant tumours. Elacestrant is licensed for patients with *ESR1*-mutated tumours and CDK4/6i pre-treatment, but was not authorised at the start of the study. Overall, given that targeted therapies are currently not widely used/available as standard of care in this setting, the proposed comparator can be considered as "best available therapy" in the CDK4/6i pretreated population.

For CDK4/6i-naïve patients, combination of ET with CDK4/6i would be among the preferred treatment options. As a combination treatment arm was added to the study design, patients were considered

eligible for combination treatment with a CDK4/6i. Furthermore, it is uncertain how the combination treatment of imlunestrant + abemaciclib performs compared to the standard of care. This is further discussed later on in the results section.

Duration of treatment

Study treatment was administered until progressive disease (PD), death, unacceptable toxicity, or withdrawal of patient consent, in line with the approved treatment duration for endocrine therapy and abemaciclib. During the evaluation, the Applicant reported that 84/331 (25.4%) in Arm A (demoninator based on the ITT), 21/330 (6.4%) in Arm B and 40/213 (18.8%) in Arm C continued treatment after PD, which was allowed per protocol. The Applicant further explained that most patients continuing treatment after PD in arm A, discontinued treatment within one month of the date of PD. There are no claims in the SmPC on treatment beyond progression.

Efficacy endpoints

The open-label design can be considered acceptable in the light of the differences in administration route (IM versus oral). However, the use of investigator-assessed PFS for the primary endpoint is of concern as it is prone to bias in the context of an open-label design. Although BIRC-assessed PFS was included as a secondary endpoint, given that radiological imaging stopped at radiographic disease progression or start of new anti-cancer therapy, in cases where an investigator-determined progression was not confirmed by BIRC at the same time, a BIRC-assessment was no longer possible. If it is the case that a high percentage of patients had an investigator-determined progression without a BIRC confirmation or further assessments, then the BIRC-assessment PFS cannot be meaningfully interpreted and the question of whether investigator-assessed PFS alone is sufficient will need to be addressed. This is discussed further under 'Efficacy data and additional analyses'.

Three primary objectives were formulated. The first primary objective concerns the comparison of PFS of imlunestrant monotherapy versus SOC in the ITT (March 2021). The secondary objective on PFS by *ESR1* mutation was upgraded to a primary objective of imlunestrant monotherapy versus SOC in the *ESR1*m-detected population (August 2022, protocol amendment b) based on external data from other SERDs, which is discussed further in the section on study conduct. An additional primary objective was added with protocol amendment a, (October 2021), to compare PFS of imlunestrant plus abemaciclib (Arm C) to imlunestrant monotherapy (Arm A). The comparison with imlunestrant monotherapy provides information on the contribution of abemaciclib to the combination treatment, however, the comparison with the SOC was only added as an exploratory analysis; this would have been expected to be the primary comparison of interest. The lack of a formal alpha-controlled comparison with the SOC which has established efficacy, raises an uncertainty on the B/R of the combination treatment. The use of the concurrent ITT as the primary analysis population for the combination treatment is agreed as patients started enrolment to Arm C 6 months later than enrolment to Arm A and Arm B.

PFS is an acceptable endpoint in the proposed setting, provided sufficiently mature OS data excluding a detrimental effect are available and the effect is homogenous across important subpopulations. OS is a key secondary endpoint and powered/formal statistical analyses were planned for imlunestrant monotherapy versus SOC in the ITT and *ESR1*m-detected population and imlun+abema versus imlunestrant monotherapy. Other secondary endpoints including ORR, DoR, CBR, and a PRO parameter are overall established endpoints in the proposed setting and supported. As for PFS, all other clinical endpoints for imlun+abema vs SOC were exploratory analyses.

Sample size

Given the protocol amendments, which are discussed in the context of study conduct below, and particularly the late decision to allocate a small alpha (one-sided 0.005) to the comparison of PFS for imlunestrant monotherapy vs SoC in the ITT and a larger alpha to the same comparison in the *ESR1*-

mutated subgroup, the sample size and planned events for the ITT comparison meant that this comparison was underpowered at 76% (which could have been increased to 91% based on the graphical approach). On the other hand, the comparison for the *ESR1*-mutated subgroup had a power of 97%, based on a one-sided alpha of 0.02. The sample size for the comparison of PFS between imlun+abema versus imlunestrant was adequate. For the secondary endpoint of OS, the number of events to trigger the final analysis were given as: 390, 155, and 260 for imlun vs SOC, imlun v SOC in *ESR1*-m subgroup, and imlun+abema vs imlun, respectively. The final OS analyses for imlun vs SOC are expected within three years of the final PFS and the final OS for imlun+abema vs imlun is expected four years after the final PFS analysis. The calculations for OS were based on the assumption that all three PFS endpoints were significant and the timing of the OS analyses for the *ESR1*-m subgroup remains based on the timing of the OS analysis for the full population (ITT), which will no longer be formally tested. Updated critical boundaries for the testing of OS were provided. Given a strong treatment effect would need to be observed in order to formally conclude on superiority on OS for any of the comparisons, the fact that one of the primary objectives was not met is unlikely to impact the OS conclusions.

Statistical methods

The difference between the respective treatment groups for the primary endpoint of investigator-assessed PFS was analysed using a log-rank test stratified by the stratification factors, which is an acceptable method. In the primary PFS analysis, documented progression or death after missing $\geqslant$2 consecutive postbaseline tumour assessments and progression after the start of new anticancer therapy were not considered as PFS events. These do not follow the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1), as >1 missed visits are censored as is the start of new anti-cancer therapy. Since no further tumour assessments were required by protocol after the start of new anticancer therapy, planned analyses that intended to follow up patients regardless of new anticancer therapy were not possible. The other sensitivity analyses and concordance analysis between BIRC- and investigator-assessed PFS, which were performed as planned, are agreed.

Study conduct

There were four amendments to the initial protocol. The major change in study design concerned the addition of the arm C consisting of imlunestrant with abemaciclib (part of amendment a), which was approved in October 2021 prior to first patient entering treatment. Enrolment to Arm C began in March 2022 at which point 122 patients had been randomized across Arm A and Arm B. At end of enrolment, 426 patients had been concurrently randomized between Arm A and Arm C. As part of the *Clinical study data pilot*, a figure displaying the cumulative number of patients enrolled at the time of the various protocol amendments was created. Given the open-label nature of the study, it is possible that patients' and investigators' perceptions of the role and relative benefit of Arm A changed with the inclusion of Arm C and it is of interest to understand whether this had an impact on the results on the ITT and *ESR1*-m populations. This is considered further in in the results section. Two further amendments in August 2022 (b) and November 2022 (c) concerned an additional primary endpoint in the *ESR1*m-detected population (upgrade secondary endpoint) and an increase in sample size in Arm A and Arm B. Concerns were raised on the internal validity and the potential for data-driven decisions in the context of an open-label study. During evaluation, the Applicant provided a justification, citing emerging external data from 2 other oral SERDs, elacestrant (Bidard et al. 2022) and giredestrant (Martín et al. 2024), demonstrating increased benefit in patients with tumours harbouring an *ESR1*m. Data from oral SERDs were already available in 2022 (giredestrant acelERA Breast Cancer, ESMO 2022, abstract 211MO and amcenestrant AMEERA-3, ESMO 2022 abstract 212MO). Based on the information available, it is accepted that this amendment was based on external data, although it remains the case that the amendment was strategically in favour of the Applicant, particularly given

that the primary endpoint in the ITT population did not reach statistical significance. Without this change, the study would likely not have met its primary objective.

With the inclusion of the *ESR1*m-detected population as the third primary endpoint, the multiple testing procedure was converted from a hierarchical testing, with Arm A vs Arm B ITT as the primary endpoint, to a graphical procedure for which the PFS for Arm A vs Arm B in the ITT and *ESR1*-m analysis sets would first be tested with the condition that at least one of these needed to be significant before PFS for Arm C vs Arm A could be tested. At first, for this graphical testing procedure, the alpha allocation was higher for Arm A vs Arm B ITT (one-sided 0.02) compared with for Arm A vs Arm B *ESR1*-m (one-sided 0.005). In protocol amendment (d), which came after the futility analysis for Arm A vs Arm B ITT, these alphas were switched and the percentage of the alpha from the Arm A vs Arm B *ESR1*-m testing that could be returned to the Arm A vs Arm B ITT was reduced. Given the Arm A vs Arm B ITT null hypothesis could not be rejected, this is of particularly relevance because it means that without the switch of the alphas, most of the allocated alpha could not be recycled and the remaining tests, including Arm C vs Arm A and the tests for OS could only then be tested at the one-sided 0.005 level. The Applicant states that this amendment, approved on 31 July 2023, was also based on emerging external data showing that PFS improvement with oral SERDs was again observed to be driven by the *ESR1*m-detected population (Bidard et al. 2022, Tolaney et al. 2023, Martín et al. 2024). Analyses using the testing based on the protocol prior to the switch of the alphas were performed and the conclusion is that both PFS and (interim) OS would have been the same.

The various protocol amendments with a focus on the addition of Arm C and elevation of *ESR1*m-subgroup endpoint as primary endpoint were also discussed during the routine GCP inspection and verified in meeting minutes and other documentation. The inspectors concluded that this amendment (b) seems to not have been a data driven decision based on documentation in a decision log filed contemporaneously in the trial master file, in which reference is made to the EMERALD and Roche study (giredestrant).

A considerable percentage of the patients (30%) had at least one important deviation which were overall comparable between treatment arms. About 7-12% were related to eligibility criteria and most frequently related to prior ET +/- CDK4/6i. The per-protocol analysis, excluding patients with important deviations of eligibility criteria as predefined in the SAP, was consistent with the primary results. The routine GCP inspection revealed critical findings concerning eligibility criteria for both inspected investigator sites and the sponsor site. Even more patients than reported in the CSR for the EMBER-3 study seem to have been included in spite of violations of inclusion and exclusion criteria. The inspectors concluded that lack of appropriate training of sites/monitors on the complex inclusion criteria, inadequate quality of source documents and inadequate monitoring procedures were contributing root causes to the high number of inadvertently included patients. The possibility that additional patients not meeting eligibility have been included cannot be entirely excluded. The sensitivity analysis performed by the Applicant excluding all ineligible patients (n=88 across all arms) showed results consistent with the primary analysis, which is reassuring.

Another frequent category concerned treatment assignment/randomization (stratification errors), and most inconsistencies concerned visceral metastases. Sensitivity analyses based on the stratification factors as reported in the CRF were consistent with the primary results, which is reassuring Subgroup analyses were based on CRF stratification data.

Efficacy data and additional analyses

The clinical data cut-off (DCO) for this submission was 24 June 2024, median follow-up was 16-17 months in Arms A and B and 13 months in Arm C.

Patient disposition

A total of 1172 patients were screened and 874 were randomised, 331 to the imlunestrant arm, 330 to the SOC arm, and 213 to the imlun+abema arm at the DCO. The most common reason to not pass the screening was a failure to meet eligibility criteria (260/298 screen failures). A low percentage of patients in each treatment arm (<2%) were randomised but not treated.

At the time of DCO, most patients had discontinued treatment, mainly due to investigator-determined progressive disease. A total of 19.6% in Arm A, 13% in Arm B, and 35.2% in Arm C were on treatment at the time of DCO. Slightly more patients stopped treatment due to patient decision in the SOC arm (3.3%) vs Arm A (1.2%) and Arm C (2.3%), which may be expected due to the open-label study design, but is at an acceptable level. Patient disposition for the concurrent ITT resembled that of the ITT.

In the overall study population median age was 61 years (range: 27-89). Most patients were female (99%), and White (56%) followed by Asian (30%) and Black (3%). Patients treated with the combination were less frequently included in the geographic region "Other" compared to Arm A and arm B (24% vs 36%). This is mainly explained by fewer patients included in Mexico (2% vs 11-12%).

The proportion of men in the study program is very low, overall n=7 in ITT. However, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale. About 80% of patients were postmenopausal and ECOG performance status was 0 (65%) or 1 (35%).

Almost all patients (97%) had stage IV disease at start of the study, 78% had measurable disease, of which 55.5% had visceral metastases. About 70% of patients had one line of prior ET and 32% in the adjuvant setting only, whereas about 60% had received prior CDK4/6i mainly in the advanced/metastatic setting. Fewer than 5% received prior abemaciclib. During the evaluation, the Applicant presented data per geographic region showing that about 81% of patients within the EU had prior CDK4/6i which can be considered representative for the EU population. Overall, 37% of patients had an *ESR1*-m-detected, with the lowest percentage in the imlun+abema arm (31.5%) and highest in the imlunestrant arm (41.7%). An impact on the results of the imbalances in the distribution of *ESR1*m between treatment arms due to lack of stratification cannot be excluded. Furthermore, the sample size of the *ESR1*m subgroup is relatively small, increasing the statistical uncertainty for the primary analysis in the *ESR1*-m-detected population.

The baseline characteristics of the *ESR1*m-detected population were broadly similar to those of the ITT, except for higher percentages (>5%) of patients with PIK3CA mutations, liver metastases, and previous CDK4/6i treatment. Within the *ESR1*m-detected patient population, the known baseline characteristics were generally balanced between the monotherapy arms. The concurrent ITT population largely resembles the ITT population except for a higher percentage of prior CDK4/6i, and baseline characteristics were generally balanced among treatment arms. The frequency of *ESR1*-m-detected is about 10% lower in the combination treatment arm compared to imlunestrant monotherapy but comparable to SOC in both the ITT and the concurrent ITT. Overall, baseline demographic and disease characteristics were in general representative for the intended target population and balanced between the treatment arms.

Most patients received fulvestrant (about 90% ITT) as expected after prior AI.

Imlunestrant monotherapy vs SOC

ITT population

Primary endpoint investigator-assessed PFS and key secondary endpoint OS

At the time of DCO (24 June 2024) with a median follow-up time of approximately 17 months in both monotherapy arms, the EMBER-3 study did not meet its primary endpoint in the ITT population.

Median investigator-assessed PFS was comparable for imlunestrant and SOC (mPFS: 5.5 months; stratified HR=0.867 [95% CI: 0.724, 1.039], stratified log-rank test p=0.1158). PFS events occurred in 71.6% versus 76.7% in the imlunestrant arm versus the SOC arm, with a data maturity of ~74% (490 events of 661). OS data were immature (maturity ~23% with152/661 deaths), and mOS was not reached in the imlunestrant arm versus mOS of 26.8 months in the SOC arm (HR: 0.690; 95% CI: 0.498, 0.956, exploratory analysis). Failure to demonstrate efficacy in the ITT has been shown before for other oral SERDs like giredestrant (Apostolidou et al., 2024). Exploratory analysis in the subgroup of patients with *ESR1*m-not-detected (including *ESR1* mutation unknown), showed a similar mPFS of 5.6 months for imlunestrant monotherapy and SOC (HR=1.00 [95% CI: 0.79, 1.27]).

_ESR1_m-detected population

Primary endpoint investigator-assessed PFS

The EMBER-3 study met its primary endpoint in the *ESR1*m-detected population with a median follow-up time of 17 months in the imlunestrant arm and 14 months in the SOC. Imlunestrant demonstrated a statistically significant improvement in investigator-assessed PFS compared with SOC (stratified HR = 0.617 [95% CI: 0.464, 0.821], stratified log-rank test p=0.0008). The median investigator-assessed PFS was 5.49 months in the imlunestrant arm versus 3.84 months in the SOC arm. Although statistically significant, the improvement in mPFS of 1.64 month is considered small (anticipated/targeted difference of 2.7 months). The observed PFS benefit is in the same order of magnitude as that of Orserdu (mPFS difference 1.9 months) that was observed in a CDK4/6i pretreated population using ICR-assessed PFS (Orserdu EPAR). There are several other factors that raise uncertainty on the size of the effect.

First, investigator-assessed PFS was used, which is prone to bias in the context of the open-label design. While a blinded central review (by a BIRC) was performed as a secondary endpoint (see below), according to the protocol, patients were not followed-up in case of a radiological progression or the start of new anticancer treatment. As part of the *Clinical study data pilot*, it was confirmed that very few patients continued assessments after an investigator-determined progression and this is further reflected in the percentage of patients who had an investigator-based progression but were censored for BIRC-assessment (around 29% in both arms). This high rate of informative censoring of patients in the BIRC-assessed PFS results has also resulted in a higher median PFS in both arms, leading to the conclusion that the BIRC-assessed PFS cannot be used to support the investigator-assessed PFS results. The extent to which the investigator-assessed PFS results can be considered to be sufficiently reliable in the context of an open-label study was thoroughly evaluated. Please refer to the section "*Evaluation of potential biases in investigator-assessed PFS*" below for a more detailed assessment of this issue.

Secondly, the KM curves in both arms in the overall (ITT) and *ESR1*-mutated population show a stark drop at the time of the first tumour assessment (week 8). An early drop in PFS has been reported before for patients treated with ET monotherapy post CDK4/6i, including Orserdu. Due to the early drop, one-dimensional measures such as the HR and the restricted mean survival time (RMST) do not capture the fact that for a substantial percentage of the patients (~30%) efficacy cannot be distinguished between the arms.

It is also of relevance to note that it is not until around 5-6 months that a sustained separation of the curves is observed favouring imlunestant. At 6 months with 35% of patients still event-free, there was a difference of about 12% in the overall in the *ESR1*-m population in favour of imlunestrant.

The Applicant performed pre-specified sensitivity analyses, of which results were supportive of the primary analysis. However, as stated earlier any analyses that refer to the follow-up of patients regardless of the use of new anticancer therapy are not able to estimate the treatment effect as intended.

Key secondary endpoint: OS

At the first interim analysis (information fraction 52%), OS was not formally statistically different between the imlunestrant and SOC arms in the *ESR1*m-detected population (alpha-level interim analysis: $2.X10^{-10}$). Median OS was not reached in the imlunestrant arm and was 21.22 months in the SOC arm [HR=0.751 (95%CI: 0.542-1.038); p=0.0076]. The results from IA3 (DCO: 18 August 2025) were provided during the evaluation, with a follow-up time of about 30 months. A trend towards OS improvement at OS IA3 continues to be observed with imlunestrant in the *ESR1*m-detected population with a mOS of 34.50 in the imlunestrant arm vs 23.1 months in the SOC arm (HR: 0.603; 95% CI: 0.425, 0.856,). The OS results are somewhat unexpected in the light of the observed (small) PFS benefit. There appears to be no substantial differences in type of first subsequent post-discontinuation therapies between treatment arms (predominantly chemotherapy and endocrine therapy).

The Applicant has committed to submit the final OS analysis post-approval (REC).

Other secondary endpoints

BIRC-assessed PFS - The estimated median PFS was 7.43 months in the imlunestrant arm versus 5.49 months in the SOC arm (stratified HR: 0.657; 95% CI: 0.469, 0.920). As mentioned above, due to the study design and high discordance rates, PFS by BIRC cannot be meaningfully interpreted as a blinded assessment of progression.

Responses - ORR and clinical benefit rate (CBR) were numerically in favour of imlunestrant and thus in support of the primary endpoint.

Patient-reported outcomes - There were no noteworthy differences between the treatment groups in time to sustained worsening of "worst pain". PRO data are not included in the SmPC, which is supported given that PRO was not part of the statistical testing hierarchy and the open-label study design.

Subgroup analyses

Prespecified subgroup analyses for investigator-assessed PFS for baseline characteristics in the *ESR1*m-detected population showed HRs < 1 in support of a beneficial effect. The HR was estimated to be around 1 (HR=0.97) for the geographic region Europe, which may be partly explained by higher frequencies of prior CDK4/6i.

Subgroup analysis by prior CDK4/6i use showed a stronger effect of imlunestrant over SOC in patients without prior CDK4/6i use (HR: 0.42, mPFS 11.1 vs 5.6 months) compared to patients with prior CDK4/6i use (HR: 0.72, mPFS 3.9 vs 3.7). Based on the mechanism of action, it is not expected that efficacy of imlunestrant compared to SOC would be dependent on CDK4/6i pretreatment, and the subgroup of patients without prior CDK4/6i is limited (30% of patients), thus a chance finding might be considered. The results confirm published results that subsequent therapy is in general less effective after prior CDK4/6i when looking at mPFS of the SOC. Within the CDK4/6i pretreated subgroup (n=178, 70% patients), which is considered the main target population for ET monotherapy in the EU, mPFS was comparable between treatment arms. As seen for the total *ESR1*-mutated group, KM-curves separated at about 5-6 months following a large drop at 8 weeks, and based on RSMT, the PFS difference between imlunestrant and SOC in the CDK4/6i pretreated subgroup was estimated to be 1.75 months. Despite the uncertainty on the magnitude of PFS effect in the CDK4/6i pre-treated subgroup, it can be concluded that imlunestrant is at least as effective as the active comparator in the

proposed target population and would provide an additional oral treatment option. Furthermore, all except one PFS event was due to PD in the imlunestrant arm, and there is no sign of a detrimental effect.

Based on the OS IA3 (18 August 2025) results, subgroup results including CDK4/6i (y/n) and presence of visceral metastases (y/n), were in general consistent with the overall analysis.

Imlunestrant plus abemaciclib versus imlunestrant monotherapy (concurrent ITT)

Primary endpoint investigator-assessed PFS

The EMBER-3 study met its primary endpoint in the concurrent ITT population with a median follow-up time of around 14 months in both treatment arms. Imlunestrant + abemaciclib demonstrated a statistically significant improvement in investigator-assessed PFS compared with imlunestrant monotherapy (stratified HR = 0.569 [95% CI: 0.441, 0.733], stratified log-rank test p<0.0001). The estimated median investigator-assessed PFS was 9.36 months versus 5.49 months. The improvement in mPFS of 3.9 months can be considered clinically relevant. However, the primary analysis based on the comparison between Arm C (combination therapy) and Arm A (imlunestrant monotherapy) lacks a sound rationale, given that imlunestrant monotherapy was not demonstrated to be effective against SOC in the ITT arm. A formal comparison with the SOC, which has an established and proven benefit in the target population, is lacking. Exploratory analyses showed a mPFS 9.4 months in the combination arm vs 3.9 months in the SOC arm. It is noted that the mPFS for the SOC in the concurrent ITT is lower than for the SOC ITT (mPFS of 5.5 months), which may be explained by differences in patient characteristics (e.g. higher frequency of CDK4/6i pretreated patients (65% vs 57% ITT). Superiority of imlunestrant monotherapy over SOC was only shown in the *ESR1*m-detected population and thus an added beneficial effect in terms of PFS has not been demonstrated for the ITT/*ESR1*m-not-detected population. Non-inferiority for the ITT/*ESR1*m-not-detected subgroup cannot be established post-hoc. Therefore, the study design does not allow to formally isolate the impact of imlunestrant as add-on to abemaciclib in the ITT. The applicant also submitted additional post-hoc inter trial comparisons using patient-level data from the EMBER-3, postMONARCH, and MONARCH-2 studies with the goal to support this conclusion. In addition to their post-hoc nature, both MONARCH studies were double-blind and therefore the comparability of the investigator-based assessments was questioned, leading to the conclusion that these results were not sufficient to resolve this issue.

The Applicant performed pre-specified sensitivity analyses, of which results were supportive of the primary analysis. However, as for the previous set of results any analyses that refer to the follow-up of patients regardless of use of new anticancer therapy are not able to estimate the treatment effect as intended.

Key secondary endpoint OS

At the first interim analysis at DCO 24 June 2024 (information fraction 25%), OS data was not statistically different between the combination and imlunestrant monotherapy arms in the concurrent ITT. With 13-16% OS events, median OS was not reached in either of the treatment arms. With the updated OS results from OS IA3 (DCO 18 August 2025) with 27 months of follow-up, the HR improved further to 0.824 (95% CI: 0.588, 1.156) and mOS was 34.43 months in the imlunestrant arm and not reached in the combination arm. It is observed that with each updated interim analysis, the point estimate continues to move further below 1. The KM-plot of OS shows that the curves begin to separate in favour of the combination arm from 26 months onwards, the administrative censoring rate remains high, and consequently the number of patients still in follow up markedly reduces from this point. It is observed that with each updated interim analysis, the point estimate continues to move further below 1. OS results do not allow to conclude on these data being supportive for a positive benefit-risk in the very heterogenous study population (see also subgroups below). This is especially of importance given the uncertainties associated with the investigator-assessed PFS.

Most patients received chemotherapy or endocrine therapy as their first subsequent post-discontinuation therapy in both treatment arms. CDK4/6 inhibitors were more frequently prescribed in the imlunestrant monotherapy arm as can be expected.

In the exploratory analysis comparing imlun+abema to SOC, the updated OS IA3 results continue to show a positive trend for OS for imlun+abema (HR: 0.801; 95% CI: 0.573, 1.119).

Other secondary endpoints

BIRC-assessed PFS - Based on BIRC assessment, the median PFS was 14.52 months in the combination arm versus 9.23 months in the imlunestrant monotherapy arm (stratified HR: 0.617, 95% CI: 0.453, 0.0.841). As previously stated, BIRC PFS cannot be meaningfully interpreted.

*Response*s - ORR and clinical benefit rate (CBR) were numerically in favour of the combination treatment over imlunestrant monotherapy and thus in support of the primary endpoint.

Patient-reported outcomes - There were no noteworthy differences between the treatment groups in time to sustained worsening of "worst pain".

Subgroup analyses

Prespecified subgroup analyses for investigator-assessed PFS for baseline characteristics in the concurrent ITT population showed HRs<1, consistent with the overall analysis. A majority of patients had prior CDK4/6i in both treatment arms (65%). Based on the current data, subgroup analyses in the CDK4/6i-pretreated group showed a median PFS of 9.1 months in the combination arm vs 3.7 months in the monotherapy arm. The Applicant did not submit phase 1 or phase 2 study data on re-challenge with CDK4/6i in support of this treatment strategy which raises uncertainty on the results in the context of a single pivotal trial as per the CHMP's 'Points to consider on application with one pivotal trial' (CPMP/EWP/2330/99). Recently, some data have become available in support of efficacy of a combination of ET plus CDK4/6i post-progression on CDK4/6i, especially when a different CDK4/6i is used (Ashai and Swain 2023, Kalinsky et al. 2024). However, contradictory results have been published (Ashai and Swain 2023).

Few patients received prior abemaciclib and no conclusions can be drawn on re-treatment with abemaciclib.

In the CDK4/6i-naïve group KM-curves overlap with comparable mPFS of 11.1 months in both arms. Of note, a comparison with the appropriate comparator of abemaciclib + fulvestrant is lacking in the study.

Subgroup analysis by *ESR1*-mutation status support a beneficial effect independent of *ESR1*-mutation status (*ESR1*m-detected in about 43% in the monotherapy arm). The effect appears somewhat more pronounced in the *ESR1*m-detected population which may be expected.

Based on the OS IA3 (18 August 2025) results, subgroup analyses are in general consistent with the overall analyses with HR <1 in most subgroups, including CDK4/6i. However, heterogeneity is noted for the ESRm1-subgroups and dependent on the comparator arm (imlunestrant or SOC) HR could be around 1 for eitherESRm1-subgroup. The Applicant agreed to submit the final OS data including subgroup analyses post-marketing (**REC**).

Evaluation of potential biases in investigator-assessed PFS

Given BIRC cannot be used as supportive evidence for the investigator-assessed PFS, the critical question is whether investigator-assessed PFS can be trusted in an open-label trial. As clearly stated in the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1) "[the] evaluation of disease progression by investigators can be subject to systematic bias in favour of one of the treatment arms, leading to incorrect treatment comparisons. [….] Clinical trials that are not adequately blinded are particularly at risk of ascertainment bias when a change in the clinical status of the patient prompts an unscheduled assessment of disease status."

An overview of the concordance between investigator-assessed PFS and BIRC was provided. To understand these data better, an overview of the BIRC-determined progression events with respect to the number of investigator-determined PFS events was prepared. For the comparison of Arm A and Arm B in the *ESR1*-m population, in both arms the percentage of investigator-assessed events that were not confirmed by the BIRC assessment was high (38% in Arm A and 33% in Arm B). As a percentage of the patients included in the arms this was 29.7% and 28.8%. A concordance table that was separated by whether patients were recruited before and after the inclusion of Arm C confirms that the direction of any systematic bias in favour of or against arm Arm A did not differ based on whether Arm C was also available as a study treatment. It can therefore be concluded that in this regard, there are no strong signals of systematic bias that would favour Arm A compared with Arm B.

For the comparison of Arm C vs Arm A in the concurrent ITT population, 33% of the investigator-determined progressions were not confirmed by BIRC in Arm C and 40% were not confirmed in Arm A. Based on the number of patients in these arms, this was 17.8% and 27.7% respectively, thus potentially favouring Arm C.

While not formally compared, the relatively high percentage of progression events that were called by the investigator but were censored by the BIRC in the SOC arm B for the concurrent ITT is notable. Based on the number of patients allocated to the SOC arm in the concurrent ITT, this was 34.7%. For the comparisons between the monotherapy arm and the SOC in the *ESR1*-m subpopulation ITT analysis set, there were no concerning signals of differential bias detected, but these were not being compared with Arm C.

The extent to which the *baseline* assessments were in agreement between the investigator and BIRC, in terms of the target lesion(s) and non-target lesions was investigated. Given the focus on imlunestrant + abemaciclib, these were only requested for the concurrent ITT analysis set. The level of full agreement between the investigator and BIRC at baseline, defined as agreement on both the number and locations of the target and non-target lesions was low: Arm A: 25/213 (11.7%); Arm B 37/213 (17.4%); Arm C: 26/213 (12.2%). The highest percentage of agreement was for the total number of target lesions at baseline: Arm A: 107/213 (50.2%); Arm B 121/213 (56.8%); Arm C: 106/213 (49.8%). These baseline levels of agreement were similar for patients who were identified as informatively censored in the BIRC analysis (i.e. had an investigator-determined progression and were censored for BIRC). The mean number of target tumours at baseline was around 1.9 and was similar between the groups and the investigator and BIRC. The mean number of non-target tumours at baseline was higher for investigators, with the respective values of 2.1 (arm A), 2.3 (arm B) and 2.4 (Arm C). By BIRC, the mean number of target tumours was around 1.7.

The overall level of agreement between investigators and BIRC is perhaps unexpected, but somewhat understood given the RECIST 1.1 criteria, and the non-target tumour identification. The level of agreement on the target lesions is higher, although it is noted that a comparison of baseline measurements (i.e., the size) of these was not requested and therefore not investigated.

The Applicant has provided an overview of the reasons for discordance between investigator and BIRC with a break-down of baseline agreement category within these reasons. The reasons for discordance were categorised by: PD by INV due to new lesion progression only; PD by INV due to non-target lesions (NTL) progression only; PD by INV due to TL progression only; and multiple progressions.

Looking at the reasons for discordance, the pattern is different for Arm C compared with Arms A and B, with more PDs being declared on the basis of the appearance of a new lesion. Numerically and as a percentage of the concurrent ITT, the difference is not large (20 vs 17 and 16), however this represents about 50% of the patients in Arm C who were informatively censored. The number (and percentage) of PDs based on the non-target tumour progression (i.e. determination of unequivocal progression) is much lower in Arm C compared with Arms A and B. The category of multiple

progressions is also higher for Arms A and B, although the breakdown of actual reasons is unfortunately not available. For the new lesions and progression of non-target lesions, the number of lesions that had already been identified by the BIRC at baseline are provided, meaning they would have been considered present and unequivocal by the BIRC.

In addition to the extent of informative censoring in the SOC arm, the difference between Arm C and the two comparator arms in the number of non-target tumour progressions is concerning. In the RECIST 1.1 guideline (New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), it is stated that the determination of progressive disease on the basis of non-target tumours with the target tumour being at least stable is expected to be "very rare", which is indeed the case in Arm C, but not in Arms A and B. This could be seen as a signal of investigator bias, although it is acknowledged that non-target tumours for which there are doubts at baseline (leading to an equivocal status at baseline) could also respond to treatment. Although a series of sensitivity analyses were performed to address the concerns related to investigator bias, these were unable to provide sufficient insight into the robustness of the treatment effect and in particular, the robustness under more extreme worst-case scenarios was not tested.

It is also stated in Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man that "Investigators may also examine more frequently patients on the control arm (or delay evaluations for patients on experimental arm) in view of an inherent bias in favour of the experimental arm. Clinical trials that are not adequately blinded are particularly at risk of ascertainment bias when a change in the clinical status of the patient prompts an unscheduled assessment of disease status." In the Kaplan-Meier curves for PFS, the SOC arm appears to have more events in-between the scheduled visits. This suggests that there is some detection bias present.

Across all arms and analysis sets, around 20% of post-baseline scans were performed outside of the scheduled assessment window (i.e. 8 weeks ± 4 days). In terms of the percentage of out-of-window assessments, there is no clear difference between the treatment arms that would suggest a bias against the comparator arm for the comparison of interest. In terms of timing of the out of window scans, the median difference between actual and planned dates suggests that the SOC arm (Arm B) for the ITT and *ESR1*m analysis sets tended to be assessed earlier compared with the monotherapy arm (Arm A). For the Arm A v Arm C comparison in the concurrent ITT, although the percentage of out-of-window assessments are comparable, the median times in both directions (early and late) tend to suggest a systematic bias in favour of Arm C. Sensitivity analyses were also performed for which the Applicant moved the timing of the scan for which a PD was determined to the nearest planned scan date. The results from these are consistent with the results from the primary analysis, in terms of both median PFS and the estimated hazard ratios. Based on the sensitivity analyses, it can be concluded that while there may be a weak signal of ascertainment bias given the timing of the scans, the conclusions would have remained largely the same had the scans been performed within the planned window.

The Applicant was also asked to provide information on any training or other initiatives that were in place in order to minimise investigator bias. The Applicant highlighted a range of initiatives that were put in place. The Applicant noted that "All primary investigators were required to document their understanding and commitment to compliance with RECIST1.1. Training was provided by Clinical Research Associates upon request and when recurrent errors were identified."

Based on the low level of agreement between the investigator and BIRC at baseline, it is clear that for the majority of patients, the investigator and BIRC were following their own assessment trajectories. It is even clearer that the stopping of assessments from the time of an investigator-determined PD has introduced informative censoring in the BIRC-based results, and that these cannot be meaningfully interpreted.

Conclusion regarding the monotherapy arm in the *ESR1*-m population: While the investigator-assessed PFS in an open label study is concerning, based on the available information, it can be concluded that there are no strong signals of differential systematic bias for the investigator-assessed PFS that favoured Arm A compared with Arm B in the *ESR1*-m population.

Conclusions regarding combination arm: Given the low level of agreement between the investigator and BICR assessments that was already present at baseline, and the complexity related to the determinations of progressive disease, it cannot be unequivocally concluded that the pattern of discordance that appears to favour the combination arm is entirely due to systematic bias. However, given most of the discordances arose through the identification of new lesions or the progression of a non-target lesion, the essentially subjective nature of these progression events still raises concerns regarding the influence that knowledge of the treatment that was allocated to the patient would have had on the judgement calls that the investigators needed to make, potentially leading to systematic bias. Therefore, the evaluation of OS results would also have been necessary in a comprehensive assessment of benefit.

During the evaluation, the applicant withdrew the combination with abemaciclib indication.

In vitro biomarker test *ESR1*-mutation status

ESR1-mutation status was tested with the Guardant360 CDx (Guardant Health, Redwood City, CA) which is approved in the EU with elacestrant. All 34 mutations used to determine *ESR1* mutation positivity for imlunestrant were annotated as oncogenic or likely oncogenic by the US-FDA-recognized OncoKB database, all known or expected to activate ERα resistance. Mutation results are provided as 'biomarker positive' or 'biomarker negative', i.e. Guardant360 CDx is a purely qualitative binary test. No clinical thresholding was performed. Therefore, it remains unclear whether the threshold applied in the EMBER-3 study was optimal or whether a lower or higher threshold defining patients as '*ESR1*-mutant' would lead to a better benefit-risk ratio. The Applicant stated that analytical performance of the Guardant 360 assay is currently under evaluation, as the Guardant assay has been submitted to the Notified Body TUV SUD in December 2024.

The results of the study support the clinical validity of the test for imlunestrant to aid selection of patients with *ESR1* mutations that benefit from imlunestrant monotherapy. The explorative analysis by mutation, though hampered by small numbers for certain mutations, do not contradict the assumption of a homogeneous effect across mutations. No definite conclusion on consistency of effects across mutations is possible based on the clinical data. The Applicant has no further plans for studies that could further optimise patient selection for imlunestrant. The details of the biomarker test used (test name, detectable alterations) are adequately presented in the SmPC section 5.1 as well as the type of alterations found in study EMBER-3. The Applicant included the cross-reference to the information on biomarker-based patient selection from section 4.2 of the SmPC in section 4.1 of the SmPC.

2.6.7. Conclusions on the clinical efficacy

The EMBER-3 trial showed superiority of imlunestrant monotherapy over SOC in terms of investigator-assessed PFS in the *ESR1*m-detected population. The absolute PFS benefit is considered limited (estimated gain in mPFS of 1.7 months). This result is supported by a trend for an OS benefit.

2.6.8. Clinical safety

Data from the pivotal phase-3 study EMBER-3 safety population are the primary basis for the identification of ADRs and overall assessment of safety.

In total, data from 408 patients treated with imlunestrant 400 mg (327 patients in EMBER-3, 51 patients in EMBER and 30 patients with EBC in EMBER-2) and 246 patients treated with imlunestrant 400 mg plus abemaciclib (150 mg twice daily) (208 patients in EMBER-3 and 38 patients in EMBER) in patients with ABC contribute to the safety analysis in the clinical program. The safety data from EMBER-2 were not included in the pooled dataset due to short duration of treatment and EBC patient population.

Table 70 Safety Analysis Sets

Analysis Set[a]	Population	Treatment Groups Comparisons	Number of Patients Enrolled
Monotherapy			
Primary monotherapy analysis set	ABC (ER+, HER2-)	EMBER-3 Arm A (Imlunestrant) versus Arm B (SOC)	Arm A: 331 Arm B: 330
Supportive monotherapy analysis set (side-by-side presentation of EMBER-3 and EMBER)	ABC (ER+, HER2-)	EMBER-3 Arm A (Imlunestrant) EMBER-3 Arm B (SOC) EMBER Imlunestrant 400 mgb	EMBER-3 Arm A: 331 EMBER-3 Arm B: 330 EMBER Imlunestrant 400 mg: 51b
Pooled monotherapy analysis set (pooled analysis of EMBER-3 and EMBER)	ABC (ER+, HER2-)	EMBER-3 Arm A (Imlunestrant) EMBER Imlunestrant 400 mgb All Imlunestrant Monotherapyc	EMBER-3 Arm A: 331 EMBER Imlunestrant 400 mg: 51b All Imlunestrant Monotherapy: 382c
Additional monotherapy EBC analysis set	EBC	EMBER-2 imlunestrant 400 mg	30
Combination therapy with abemaciclib			
Primary combination therapy abemaciclib analysis set	ABC (ER+, HER2-)	EMBER-3 Arm C (Imlun+Abema) versus Arm A (Imlunestrant)	Arm C: 213 Arm A: 331
Supportive combination therapy abemaciclib analysis set (side-by-side presentation of EMBER-3 and EMBER)	ABC (ER+, HER2-)	EMBER-3 Arm C (Imlun+Abema) versus Arm A (Imlunestrant) EMBER Imlunestrant 400 mg plus Abemaciclibd	EMBER-3 Arm C: 213 EMBER-3 Arm A: 331 EMBER Imlunestrant + Abemaciclib: 38d
Pooled combination therapy abemaciclib analysis set (pooled analysis of EMBER-3 and EMBER)	ABC (ER+, HER2-)	EMBER-3 Arm C (Imlun+Abema) EMBER[d] Imlunestrant 400 mg plus Abemaciclib All Imlunestrant plus Abemaciclib[e] All Imlunestrant Monotherapy[c]	EMBER-3 Arm C: 213 EMBER Imlunestrant + Abemaciclib: 38[d] All Imlunestrant + Abemaciclib: 251[e] All Imlunestrant Monotherapy: 382c

Abbreviations: ABC = locally advanced breast cancer; EBC = early breast cancer; ER+ = oestrogen receptor-positive; HER2- = human epidermal growth factor receptor 2 negative; SOC = standard of care: investigator's choice of endocrine therapy of fulvestrant or exemestane.

[a] Analysis population used for each analysis.
[b] Imlunestrant 400 mg (Phase 1a, Phase 1b Cohort E3).
[c] All imlunestrant monotherapy (EMBER-3 Arm A and EMBER imlunestrant 400 mg).
[d] Imlunestrant 400 mg plus abemaciclib (Phase 1b Cohort E1).
[e] All imlunestrant plus abemaciclib (EMBER-3 Arm C and EMBER imlunestrant 400 mg plus abemaciclib [Cohort E1]).

2.6.8.1. Patient exposure

Data on patient exposure is shown in the table below.

Table 71 Patient Exposure

	ITT	Imlunestrant monotherapy or imlunestrant in combination with abemaciclib for ER+/HER2- breast cancer			
	Patients enrolled (all indications and arms)	Patients exposed[a]	Patients exposed to the proposed dose (400 mg)	Patients with long term safety data (more than 6 months) 400 mg	Patients with long term safety data (more than 12 months) 400 mg
Blinded studies (placebo-controlled)	N/A	N/A	N/A	N/A	N/A
Blinded studies (active-controlled)	N/A	N/A	N/A	N/A	N/A
Open label studies	1363	794	663	329	158
EMBER	385	156	89	52	31
EMBER-2	87	86	30	0	0
EMBER-3[b]	874	535	535	274	127
JZLF	17	17	9	3	0
Post marketing	N/A	N/A	N/A	N/A	N/A
Compassionate use	N/A	N/A	N/A	N/A	N/A

Abbreviations: ER = oestrogen receptor; ER+ = oestrogen receptor-positive; HER2- = human epidermal growth factor receptor 2-negative; ITT = intention-to-treat; N/A = not applicable.

a Received at least 1 dose of imlunestrant (at any dose level).

b Sponsor blinded, but open label at sites.

A summary of the subject disposition is provided in the clinical efficacy section (see section 2.6.5.2.), as well as a description of the patient demographics and disease characteristics.

Exposure, dose intensities and dose adjustments are provided in the table below.

Table 72 Summary of Exposure, Dose Intensities, and Dose Adjustments

Category	Arm A Imlunestrant N = 327	Arm B SOC N = 324		Arm C Imlunestrant + Abemaciclib N = 208	
	Imlunestrant N = 327	Fulvestrant N = 292	Exemestane N = 32	Imlunestrant N = 208	Abemaciclib N = 208
Cycles received per patient					
Median (min–max)	6 (1-32)	5 (1-32)	7 (1-25)	9 (1-28)	9 (1-28)
Relative dose intensity[a]					
Median (Q1- Q3)	99.67 (97.34-100)	100 (100-100)	100 (98.86-101.14)	97.74 (88.82-99.81)	88.85 (64.99-97.89)
Dose withheld, n (%)	57 (17.4)	**NA[b]**	3 (9.4)	104 (50.0)[d]	121 (58.2)[d]
1 episode of dose withheld	46 (14.1)	**NA[b]**	3 (9.4)	60 (28.8)	57 (27.4)
2 episodes of dose withheld	6 (1.8)	**NA[b]**	0	23 (11.1)	36 (17.3)
≥3 episodes of dose withheld	5 (1.5)	**NA[b]**	0	21 (10.1)	28 (13.5)
Reason for dose withheld, n (%)					

Category	Arm A Imlunestrant N = 327	Arm B SOC N = 324		Arm C Imlunestrant + Abemaciclib N = 208	
	Imlunestrant N = 327	Fulvestrant N = 292	Exemestane N = 32	Imlunestrant N = 208	Abemaciclib N = 208
AE	36 (11.0)	**NA[b]**	2 (6.3)	96 (46.2)	115 (55.3)
Scheduling conflict	3 (0.9)	**NA[b]**	0	3 (1.4)	3 (1.4)
Treatment availability	5 (1.5)	**NA[b]**	0	2 (1.0)	3 (1.4)
Other	16 (4.9)	**NA[b]**	1 (3.1)	8 (3.8)	8 (3.8)
Other epidemic/pandemic reasons/ mitigations	1 (0.3)	**NA[b]**	0	0	0
Dose reductions, n (%)	8 (2.4)	0	**NA[c]**	34 (16.3)[d]	81 (38.9)[d]
1 dose reduction	8 (2.4)	0	**NA[c]**	34 (16.3)	59 (28.4)
2 dose reductions	**NA[c]**	**NA[c]**	**NA[c]**	**NA[c]**	22 (10.6)
Reason for dose reductions, n (%)					
AE	8 (2.4)	0	**NA[c]**	34 (16.3)	81 (38.9)
Injection delay fulvestrant[b], n (%)	**NA**	48 (16.4)	**NA**	**NA**	**NA**
1 dose delay	**NA**	41 (14.0)	**NA**	**NA**	**NA**
2 dose delays	**NA**	5 (1.7)	**NA**	**NA**	**NA**
3 and more dose delays	**NA**	2 (0.7)	**NA**	**NA**	**NA**
Reason for dose delays, n (%)					
AE	**NA**	21 (7.2)	**NA**	**NA**	**NA**
Scheduling conflict	**NA**	30 (10.3)	**NA**	**NA**	**NA**
Dose re-escalation after reduction, n (%)	0	**NA**	**NA[c]**	1 (0.5)	1 (0.5)

At the latest data cut-off date (DCO: 30 January 2025), the safety profile of imlunestrant remained consistent with the primary outcome (PO).

2.6.8.2. Adverse events

Imlunestrant monotherapy

Table 73. Overview of Adverse Events, Safety Population Imlunestrant versus SOC

Category, n (%)	PO Data Cutoff: 24 Jun2024		OS IA2 Data Cutoff: 30 Jan 2025	
	Arm A Imlunestrant N=327	Arm B SOC N=324	Arm A Imlunestrant N=327	Arm B SOC N=324

Patients with ≥1 TEAE	270 (82.6)	273 (84.3)	272 (83.2)	273 (84.3)
Patients with Grade 1 TEAE[a]	89 (27.2)	92 (28.4)	85 (26.0)	89 (27.5)
Patients with Grade 2 TEAE[a]	125 (38.2)	114 (35.2)	126 (38.5)	114 (35.2)
Patients with Grade ≥3 TEAE	56 (17.1)	67 (20.7)	61 (18.7)	70 (21.6)
Patients with Grade 3 TEAE[a]	46 (14.1)	54 (16.7)	48 (14.7)	56 (17.3)
Patients with Grade 4 TEAE[a]	4 (1.2)	7 (2.2)	7 (2.1)	7 (2.2)
Patients with ≥1 SAE[b]	34 (10.4)	38 (11.7)	37 (11.3)	41 (12.7)
Patients with TEAE leading to dose adjustment	34 (10.4)	23 (7.1)	36 (11.0)	24 (7.4)
Patients who discontinued study treatment due to AE	14 (4.3)	4 (1.2)	14 (4.3)	4 (1.2)
Patients who discontinued study treatment due to SAE	9 (2.8)	4 (1.2)	9 (2.8)	4 (1.2)
Patients who died due to AE on study treatment or within 30 days of discontinuation of study treatment[c]	5 (1.5)[d]	6 (1.9)	5 (1.5)	7 (2.2)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients in the specific category; N = number of patients; OS IA2 = overall survival interim analysis 2; PO = primary outcome; SAE = serious adverse event; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.
a Includes patients with maximum CTCAE grade.
b Includes serious events that occurred during the study treatment and short-term follow-up.
c Deaths are also included as SAEs and discontinuations due to AEs.
d One additional patient was reported to have died due to study disease but also experienced an SAE considered fatal by the investigator.

TEAEs (any Grade and Grade ≥3): Imlunestrant monotherapy

The table below summarizes treatment-emergent adverse events (TEAEs) reported in at least 5% of the patients in either arm (imlunestrant arm or SOC arm) for the safety population.

The most common any-grade TEAEs in the imlunestrant arm were fatigue, diarrhoea, and nausea, with fatigue and diarrhoea with incidences at least 5% higher in the imlunestrant arm compared with the SOC arm. These events were predominantly Grade 1, occurring early in treatment. The incidence of Grade ≥3 TEAEs was comparable in the SOC arm and the imlunestrant arm. These events were predominantly Grade 3 (14.1% versus 16.7%), with low but similar incidences for Grade 4 (1.2% versus 2.2%) and Grade 5 (1.8% versus 1.9%) TEAEs for the imlunestrant and SOC arms, respectively.

Table 74 Summary of TEAEs by Maximum CTCAE Grade Occurring in at least 5% of Patients in Either Treatment Arm, Preferred Term by Decreasing Frequency in the Imlunestrant Arm EMBER-3 Safety Population

Preferred or Consolidated Terms	**Arm A Imlunestrant N = 327 n (%)**		**Arm B SOC N = 324 n (%)**	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with at least 1 TEAE	270 (82.6)	56 (17.1)	273 (84.3)	67 (20.7)
Fatigue	74 (22.6)	1 (0.3)	43 (13.3)	2 (0.6)
Diarrhoea	70 (21.4)	1 (0.3)	38 (11.7)	0

Preferred or Consolidated Terms	Arm A Imlunestrant N = 327 n (%)		Arm B SOC N = 324 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	56 (17.1)	1 (0.3)	42 (13.0)	0
Arthralgia	46 (14.1)	2 (0.6)	46 (14.2)	1 (0.3)
Aspartate aminotransferase increased	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)
Back pain	35 (10.7)	2 (0.6)	23 (7.1)	1 (0.3)
Alanine aminotransferase increased	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)
Anemia	33 (10.1)	7 (2.1)	41 (12.7)	9 (2.8)
Constipation	32 (9.8)	0	18 (5.6)	1 (0.3)
Abdominal pain	29 (8.9)	1 (0.3)	18 (5.6)	2 (0.6)
Vomiting	29 (8.9)	2 (0.6)	16 (4.9)	1 (0.3)
Cough	28 (8.6)	0	15 (4.6)	0
Headache	28 (8.6)	0	29 (9.0)	0
Decreased appetite	26 (8.0)	1 (0.3)	12 (3.7)	1 (0.3)
Dyspnoea	25 (7.6)	2 (0.6)	18 (5.6)	3 (0.9)
Hot flush	22 (6.7)	0	22 (6.8)	0
COVID-19	21 (6.4)	0	25 (7.7)	1 (0.3)
Blood alkaline phosphatase increased	18 (5.5)	3 (0.9)	23 (7.1)	2 (0.6)
Thrombocytopenia	18 (5.5)	3 (0.9)	16 (4.9)	4 (1.2)
Leukopenia	17 (5.2)	2 (0.6)	15 (4.6)	0
Neutropenia	17 (5.2)	7 (2.1)	15 (4.6)	6 (1.9)
Pyrexia	17 (5.2)	1 (0.3)	11 (3.4)	0
Pain in extremity	15 (4.6)	2 (0.6)	24 (7.4)	0
Gamma-glutamyltransferase increased	14 (4.3)	5 (1.5)	17 (5.2)	6 (1.9)
Hyperglycaemia	13 (4.0)	0	19 (5.9)	1 (0.3)
Injection site reaction	0	0	26 (8.0)	0

Abbreviations: COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria of Adverse Events; n = number of patients in the specific category; N = number of patients; SOC = standard of care: investigator's choice of endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.
Note: Consolidated terms are italicised.

The table below summarizes Grade ≥3 TEAEs by PT or consolidated term, where appropriate, reported in at least 1% of the patients in either arm (imlunestrant or SOC arm) for the safety population.

Table 75 Summary of Grade ≥3 Treatment-Emergent Adverse Events Occurring in at least 1% of Patients in Either Treatment Arm by Decreasing Frequency in the Imlunestrant Arm EMBER-3 Safety Population

Category	Arm A Imlunestrant (N = 327) n (%)	Arm B SOC (N = 324) n (%)
Patients with at least 1 Grade ≥3 TEAE	56 (17.1)	67 (20.7)
Anaemia	7 (2.1)	9 (2.8)
Neutropenia	7 (2.1)	6 (1.9)
Gamma-glutamyltransferase increased	5 (1.5)	6 (1.9)
Cancer pain	4 (1.2)	1 (0.3)
Thrombocytopenia	3 (0.9)	4 (1.2)
Pneumonia	2 (0.6)	4 (1.2)
Fracture	1 (0.3)	5 (1.5)

Imlunestrant plus abemaciclib

Table 76. Overview of Adverse Events, Safety Population Imlun+Abema versus Imlunestrant

Category, n (%)	PO Data Cutoff: 24 Jun2024		OS IA2 Data Cutoff: 30 Jan 2025	
	Arm C Imlun+Abema N=208	**Arm A Imlunestrant N=324**	**Arm C Imlun+Abema N=208**	**Arm A Imlunestrant N=324**
Patients with ≥1 TEAE	204 (98.1)	270 (82.6)	204 (98.1)	272 (83.2)
Patients with Grade 1 TEAE[a]	21 (10.1)	89 (27.2)	15 (7.2)	85 (26.0)
Patients with Grade 2 TEAE[a]	82 (39.4)	125 (38.2)	80 (38.5)	126 (38.5)
Patients with Grade ≥3 TEAE	101 (48.6)	56 (17.1)	109 (52.4)	61 (18.7)
Patients with Grade 3 TEAE[a]	93 (44.7)	46 (14.1)	97 (46.6)	48 (14.7)
Patients with Grade 4 TEAE[a]	5 (2.4)	4 (1.2)	5 (2.4)	7 (2.1)
Patients with ≥1 SAE[b]	35 (16.8)	34 (10.4)	40 (19.2)	37 (11.3)
Patients with TEAE leading to dose adjustment	126 (60.6)	34 (10.4)	131 (63.0)	36 (11.0)
Patients who discontinued study treatment due to AE	13 (6.3)	14 (4.3)	17 (8.2)	14 (4.3)
Patients who discontinued study treatment due to SAE	5 (2.4)	9 (2.8)	9 (4.3)	9 (2.8)
Patients who died due to AE on study treatment or within 30 days of discontinuation of study treatment[c]	3 (1.4)	5 (1.5)[d]	7 (3.4)	5 (1.5)

Abbreviations: Abema = abemaciclib AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; Imlun = imlunestrant; n = number of patients in the specific category; N = number of patients; OS IA2 = overall survival interim analysis 2; PO = primary outcome; SAE = serious adverse event; TEAE = treatment emergent adverse event.
a Includes patients with maximum CTCAE grade.
b Includes serious events that occurred during the study treatment and short-term follow-up.
c Deaths are also included as SAEs and discontinuations due to AEs.
d One additional patient was reported to have died due to study disease, but also experienced an SAE considered fatal by the investigator.

TEAEs (any Grade and Grade ≥3): imlunestrant plus abemaciclib

The table below summarizes TEAEs by PT or consolidated term, where appropriate, reported in at least 10% of the patients in either arm (imlun+abema arm compared with the imlunestrant arm) for the safety population. Consolidated terms are italicised.

Table 77 Summary of TEAEs by Maximum CTCAE Grade Occurring in at least 10% of Patients in Either Treatment Arm, Preferred Term by Decreasing Frequency in the Imlun+Abema Arm EMBER-3 Safety Population

Preferred or Consolidated Terms	Arm C Imlunestrant + Abemaciclib N = 208		Arm A Imlunestrant N = 327	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with at least 1 TEAE, n (%)	204 (98.1)	101 (48.6)	270 (82.6)	56 (17.1)
Diarrhoea	179 (86.1)	17 (8.2)	70 (21.4)	1 (0.3)
Nausea	101 (48.6)	4 (1.9)	56 (17.1)	1 (0.3)
Neutropenia	100 (48.1)	41 (19.7)	17 (5.2)	7 (2.1)
Anaemia	91 (43.8)	16 (7.7)	33 (10.1)	7 (2.1)
Fatigue	80 (38.5)	10 (4.8)	74 (22.6)	1 (0.3)
Vomiting	65 (31.3)	1 (0.5)	29 (8.9)	2 (0.6)
Leukopenia	54 (26.0)	9 (4.3)	17 (5.2)	2 (0.6)
Hypercreatininaemia	45 (21.6)	2 (1.0)	9 (2.8)	1 (0.3)
Abdominal pain	41 (19.7)	4 (1.9)	29 (8.9)	1 (0.3)
Decreased appetite	41 (19.7)	2 (1.0)	26 (8.0)	1 (0.3)
Thrombocytopenia	38 (18.3)	3 (1.4)	18 (5.5)	3 (0.9)
Aspartate aminotransferase increased	34 (16.3)	5 (2.4)	41 (12.5)	3 (0.9)
Alanine aminotransferase increased	28 (13.5)	10 (4.8)	34 (10.4)	1 (0.3)
Rash	21 (10.1)	3 (1.4)	9 (2.8)	0
Arthralgia	19 (9.1)	1 (0.5)	46 (14.1)	2 (0.6)
Back pain	10 (4.8)	1 (0.5)	35 (10.7)	2 (0.6)

Abbreviations: CTCAE = Common Terminology Criteria of Adverse Events; n = number of patients in the specific category; N = number of patients; TEAE = treatment-emergent adverse event.

Note: Consolidated terms are *italicised*.

Table 78 Overview of TEAEs by System Organ Class for EMBER-3 Study

System Organ Class	Arm A (Imlunestrant) N = 327		Arm B (SOC) N = 324		Arm C (Imlunestrant + Abemaciclib) N = 208	
	Any Grade n (%)	Grade 3/4/5 n (%)	Any Grade n (%)	Grade 3/4/5 n (%)	Any Grade n (%)	Grade 3/4/5 n (%)
Gastrointestinal disorders	149 (45.6)	5 (1.5)	112 (34.6)	5 (1.5)	193 (92.8)	24 (11.5)
Musculoskeletal and connective tissue disorders	107 (32.7)	11 (3.4)	104 (32.1)	7 (2.2)	52 (25.0)	5 (2.4)
General disorders and administration site conditions	107 (32.7)	4 (1.2)	97 (29.9)	6 (1.9)	105 (50.5)	13 (6.3)
Investigations	100 (30.6)	14 (4.3)	106 (32.7)	18 (5.6)	116 (55.8)	38 (18.3)
Infections and infestations	72 (22)	9 (2.8)	81 (25)	10 (3.1)	64 (30.8)	9 (4.3)
Respiratory, thoracic and mediastinal disorders	69 (21.1)	4 (1.2)	45 (13.9)	5 (1.5)	43 (20.7)	2 (1.0)
Metabolism and nutrition disorders	64 (19.6)	5 (1.5)	50 (15.4)	7 (2.2)	78 (37.5)	7 (3.4)
Nervous system disorders	59 (18)	2 (0.6)	60 (18.5)	3 (0.9)	51 (24.5)	4 (1.9)
Blood and lymphatic system disorders	46 (14.1)	10 (3.1)	49 (15.1)	12 (3.7)	110 (52.9)	37 (17.8)
Skin and subcutaneous tissue disorders	46 (14.1)	0	44 (13.6)	0	50 (24.0)	3 (1.4)
Vascular disorders	36 (11.0)	3 (0.9)	37 (11.4)	3 (0.9)	35 (16.8)	4 (1.9)
Cardiac disorders	23 (7.0)	4 (1.2)	12 (3.7)	3 (0.9)	19 (9.1)	4 (1.9)
Psychiatric disorders	22 (6.7)	0	27 (8.3)	0	20 (9.6)	0
Injury, poisoning and procedural complications	17 (5.2)	2 (0.6)	18 (5.6)	7 (2.2)	19 (9.1)	2 (1.0)
Eye disorders	17 (5.2)	1 (0.3)	14 (4.3)	0	18 (8.7)	0
Reproductive system and breast disorders	10 (3.1)	0	16 (4.9)	0	5 (2.4)	0
Ear and labyrinth disorders	9 (2.8)	0	6 (1.9)	1 (0.3)	4 (1.9)	0
Renal and urinary disorders	8 (2.4)	1 (0.3)	12 (3.7)	2 (0.6)	21 (10.1)	6 (2.9)
Hepatobiliary disorders	8 (2.4)	1 (0.3)	9 (2.8)	0 (0)	9 (4.3)	2 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.4)	4 (1.2)	7 (2.2)	2 (0.6)	3 (1.4)	1 (0.5)
Immune system disorders	6 (1.8)	0	1 (0.3)	0	1 (0.5)	0
Surgical and medical procedures	3 (0.9)	0	8 (2.5)	2 (0.6)	5 (2.4)	1 (0.5)
Endocrine disorders	1 (0.3)	0	3 (0.9)	1 (0.3)	2 (1.0)	0
Social circumstances	0	0	1 (0.3)	0	0	0

Abbreviations: N = number of subjects in safety population; n = number of subjects in the specified category; SOC = standard of care; TEAE = treatment-emergent adverse event.
Data cutoff: 24 June 2024.

Adverse drug reactions

ADR determination was based on the review of all the planned summaries, analyses, or both plus any additional ad hoc displays and case reviews needed to assist physicians and clinical research scientists involved in the clinical development program in such determination. Using medical judgment, all AEs and categorical numerical safety data were evaluated for a possible causal relationship with the study drug.

Key factors considered included statistical evidence of imbalance (p-values, hazard ratios), dose-response relationships, biological plausibility, clinical relevance, severity and seriousness, consistency across studies, epidemiological and nonclinical data, background incidence, and at-risk subgroups.

Inferential and descriptive statistics were seen solely as an aid to an initial triage of a large amount of safety data, but medical judgment always prevailed in the determination of ADRs.

The Applicant used analytical criteria to conduct an initial screen of the AE and laboratory data in EMBER-3. Events and laboratory findings meeting these criteria were evaluated as potential ADRs for imlunestrant. In addition, events considered ADRs for fulvestrant or elacestrant were reviewed and evaluated as potential ADRs for imlunestrant. The Applicant then applied scientific and medical judgment to the candidate list of potential ADRs that were identified to:

- assess the likelihood of a causal relationship between an AE and imlunestrant, and
- determine whether an AE was medically informative and clinically significant.

The below table presents the frequencies (percentages) of adverse reactions for imlunestrant monotherapy for ABC.

The frequencies presented are based on pooled data from patients with ABC from EMBER and EMBER-3 receiving 400 mg imlunestrant.

Table 79 Frequencies of Adverse Reactions for Imlunestrant Monotherapy in ER+ / HER- Advanced or Metastatic Breast Cancer Pooled Frequencies from EMBER-3 and EMBER

System Organ Class ***Preferred Term and/or Narrow FMQ and/or Lilly-Consolidated Term***	**Imlunestrant N = 378**	
	Any Grade (%)	**Grade ≥3 (%)**
Gastrointestinal Disorders		
Diarrhoea	22.5	0.5
Nausea	20.1	0.5
Vomiting	9.0	0.5
Constipation[a]	9.5	0
Abdominal pain[a]	9.5	0.3
General Disorders and Administration Site Conditions		
Fatigue[a]	25.7	0.8
Metabolism and Nutrition Disorders		
Decreased appetite[a]	8.7	0.3
Musculoskeletal Disorders		
Joint and musculoskeletal pain[b]	23.8	1.6
Back pain	10.3	0.5
Nervous System Disorders		
Headache	9.0	0
Respiratory Thoracic and Mediastinal Disorders		
Cough[a]	9.3	0
Vascular Disorders		
Hot flush[b]	7.4	0
Laboratory Parameters[c]		
ALT increased	34.3	1.1
AST increased	33.2	1.6
Triglycerides increased	21.0	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ER+ = oestrogen receptor-positive; FMQ = FDA Medical Query; HER2- = human epidermal growth factor receptor 2 negative; N = number of participants in the analysis population; PT = preferred term.

Consolidated terms are *italicised*.

a As defined by Narrow FMQ, the PTs included in each FMQ term are as follows:
Constipation (FMQ): *Constipation*; *Abdominal pain (FMQ): Abdominal pain, Abdominal pain upper, Abdominal pain lower, Abdominal discomfort, Abdominal rigidity, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain*; Fatigue (FMQ): *Fatigue, Asthenia, Lethargy, Malaise*; Decreased appetite (FMQ): *Decreased appetite, Early satiety*; and Cough (FMQ): *Cough, Productive cough*.

b Lilly consolidated term: The PTs included in each consolidated term are as follows:
Joint and musculoskeletal pain (consolidated term): *Arthralgia, Myalgia, Musculoskeletal discomfort, Musculoskeletal chest pain, Musculoskeletal pain, Pain in extremity, Neck pain;* and Hot flush (consolidated term): *Flushing*, *Hot flush*.

c n = all treated patients with at least 1 assessment at baseline and during treatment or the short-term follow-up period for the specified laboratory parameter; n = 364 for ALT increased; n = 371 for AST increased, and n = 252 for *Triglycerides increased.*

The below table provides an overview of the ADRs and their rationale.

Table 80 ADRs in Patients Receiving Imlunestrant with or without Abemaciclib (SmPC)

ADR	Rationale
Diarrhoea (PT)	• In EMBER-3 study, the frequency of diarrhoea for imlunestrant monotherapy was higher compared to standard of care. • The frequency of diarrhoea is higher when imlunestrant is administered in combination with abemaciclib compared to imlunestrant monotherapy. The frequency of diarrhoea observed for the combination is comparable to the frequency observed in studies with abemaciclib combined with endocrine therapies, where diarrhoea is causally related to abemaciclib and therefore is an ADR for abemaciclib. • Diarrhoea is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Nausea (PT)	• In EMBER-3 study, the frequency of nausea for imlunestrant monotherapy was similar compared with the standard of care. • The frequency is higher when imlunestrant is administered in combination with abemaciclib compared to imlunestrant monotherapy. The frequency of nausea observed for **imlun+abema** is comparable to the frequency of nausea observed in other studies with abemaciclib combined with endocrine therapies, where nausea is causally related to abemaciclib and therefore is an ADR for abemaciclib. • Nausea is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Vomiting (PT)	• In EMBER-3 study, the frequency of vomiting for imlunestrant monotherapy was similar compared to standard of care. • The frequency of vomiting is higher when imlunestrant is administered in combination with abemaciclib compared to imlunestrant monotherapy. The frequency of vomiting observed for imlunestrant + abemaciclib is comparable to the frequency of vomiting observed in other abemaciclib studies. Vomiting is causally related to abemaciclib and as such is established as an ADR for abemaciclib. • Vomiting is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Constipation (PT)	• In EMBER-3 study, the frequency of constipation for imlunestrant monotherapy was similar compared with the standard of care. • The frequency of constipation is similar when imlunestrant is administered in combination with abemaciclib compared with imlunestrant monotherapy. • The frequency of constipation observed for imlunestrant + abemaciclib is comparable to the frequency of constipation observed in other studies with abemaciclib combined with endocrine therapies, where constipation is causally related to abemaciclib and therefore is an ADR for abemaciclib. • Constipation is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Abdominal pain (consolidated term)	• In the EMBER-3 study, the frequency of abdominal pain for imlunestrant monotherapy was similar compared with the standard of care. • The frequency of abdominal pain is higher when imlunestrant is administered in combination with abemaciclib compared with imlunestrant monotherapy. The frequency of abdominal pain observed for imlunestrant + abemaciclib is comparable to the frequency of abdominal pain observed in other studies with abemaciclib combined with endocrine therapies. • Abdominal pain is a recognised ADR for elacestrant, which shares a mechanism of action.
Fatigue (consolidated term)	• In the EMBER-3 study, the frequency of fatigue for imlunestrant monotherapy was higher compared with the standard of care.

ADR	Rationale
	• The frequency of fatigue is higher when imlunestrant is administered in combination with abemaciclib compared with imlunestrant monotherapy. The frequency of fatigue observed for imlunestrant + abemaciclib is comparable to the frequency of fatigue observed in other studies with abemaciclib combined with endocrine therapies, where a causal relationship with fatigue was established and is an ADR. • Fatigue is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Decreased appetite (consolidated term)	• In EMBER-3, the frequency of decreased appetite was higher for imlunestrant monotherapy compared with the standard of care. • The frequency of decreased appetite is higher when imlunestrant is administered in combination with abemaciclib compared with imlunestrant monotherapy. The frequency of decreased appetite observed for imlunestrant + abemaciclib is comparable to the frequency of decreased appetite observed in other studies with abemaciclib combined with endocrine therapies, where a causal relationship with decreased appetite was established and is an ADR. • Decreased appetite is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action
Joint and musculoskeletal pain (consolidated term)	• In EMBER-3, the frequency of joint and musculoskeletal pain for imlunestrant monotherapy was similar to the standard of care. • There is a biological plausibility as joint aches and pains are commonly seen in menopausal women and may be associated with oestrogen deficiency. • Joint and musculoskeletal pain, including myalgia, are recognised ADRs for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Back pain (PT)	• There is a biological plausibility that imlunestrant may lead to back pain as oestrogen receptors have been found within intervertebral disc (IVD) tissue and nearby joints highlighting the potential roles of oestrogen at these sites. Changes in oestrogen levels may be an important contributor to pain (Pang et al. 2023). • Back pain was reported at a similar frequency to the standard of care. • Back pain was very commonly reported in EMBER-3 study and in pooled monotherapy data for EMBER-3 and EMBER studies. • Back pain is a recognised ADR for the oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Headache (PT)	• Headache was commonly reported in EMBER-3 study and in pooled monotherapy data for EMBER-3 and EMBER studies. • The frequency of headache for imlunestrant monotherapy was similar to the standard of care. • The frequency of headache was similar for imlunestrant monotherapy and in combination with abemaciclib (uncommon). • The frequency of headache observed for imlunestrant + abemaciclib is comparable to the frequency of headache observed in other studies with abemaciclib combined with endocrine therapies. • Headache is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action
Cough (consolidated term)	• Cough was commonly reported for imlunestrant monotherapy in the EMBER-3 study and pooled monotherapy data for EMBER-3 and EMBER studies. • Chronic cough (≥ 8 weeks) is associated with post-menopausal women. A potential mechanism is that hormonal changes might affect lung function and the mucous membrane of the airways, causing hypersensitivity of the cough reflex. • Of the 26 monotherapy patients, 11 patients had cough lasting ≥ 8 weeks.

ADR	Rationale
	• Cough is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
Hot flush (consolidated term)	• There is strong biological plausibility that explains vasomotor symptoms, such as hot flushes, which are common with SERDs. These symptoms are mainly due to decreasing estradiol concentrations in the serum and in the hypothalamic temperature regulating centre, which in turn alters neurotransmitter activity in the serotonergic and noradrenergic pathways (Rossmanith and Ruebberdt 2009). • Hot flush was commonly reported in EMBER-3 and in pooled monotherapy data for EMBER-3 and EMBER. • The frequency of hot flush was similar for imlunestrant monotherapy and in combination with abemaciclib (uncommon). • The frequency of hot flush observed for imlunestrant + abemaciclib in EMBER-3 is comparable to the frequency of hot flush observed in other studies with abemaciclib combined with endocrine therapies. • Hot flush is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action.
ALT increased	• In EMBER-3, the frequency of ALT increased as a TEAE and an abnormal laboratory parameter was similar for imlunestrant monotherapy compared with the standard of care. • The frequency of ALT increased (TEAE) for the monotherapy was similar to that of the combination of imlunestrant + abemaciclib. The frequency of ALT increased observed for imlunestrant + abemaciclib is comparable to the frequency of ALT increased observed in other studies with abemaciclib combined with endocrine therapies, where a causal relationship with ALT increased was established and is an ADR. • ALT increased is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action. • In rats and monkeys, transient, low-grade increases in ALT and AST activity with or without increased alkaline phosphatase were occasionally observed. There was no concurrent increase in bilirubin in animals. These effects occurred in the absence of degenerative or inflammatory hepatobiliary changes
AST increased	• AST increased was very commonly reported for imlunestrant monotherapy as a laboratory parameter in EMBER-3. • The frequency of AST increased (all grades) was similar when imlunestrant was administered in combination with abemaciclib compared with imlunestrant monotherapy. The frequency of AST increased observed for imlunestrant + abemaciclib is comparable to the frequency of AST increased observed in other studies with abemaciclib combined with endocrine therapies, where a causal relationship with AST increased was established and is an ADR. • AST increased is a recognised ADR for the other oestrogen receptor degraders, fulvestrant, and elacestrant, which share a mechanism of action. • In rats and monkeys, transient, low-grade increases in ALT and AST activity with or without increased alkaline phosphatase were occasionally observed. There was no concurrent increase in bilirubin in animals. These effects occurred in the absence of degenerative or inflammatory hepatobiliary changes.
Triglycerides increased	• Serum triglycerides increased were very commonly reported as a laboratory parameter in EMBER-3 and in pooled monotherapy data for EMBER-3 and EMBER. • There is a known mechanism of action of aromatase inhibitors and selective oestrogen receptor modulators affecting lipid levels. • The frequency of serum triglycerides increased (all grades) was higher when imlunestrant was administered in combination with abemaciclib.

ADR	Rationale
	• Hypertriglyceridaemia is a recognised ADR for the other oral oestrogen receptor degrader and elacestrant, which shares a mechanism of action.

Abbreviations: ADR = adverse drug reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FMQ = FDA Medical Queries; PT = preferred term; TEAE = treatment-emergent adverse event.

The below table presents the proposed frequencies (percentages) of adverse reactions for imlunestrant plus abemaciclib combination therapy.

Table 81 Frequencies of Adverse Reactions for Imlunestrant Administered in Combination with Abemaciclib for ER+ / HER- Advanced Metastatic Breast Cancer Pooled Frequencies from EMBER-3 and EMBER

System Organ Class ***Preferred Term and/or Narrow FMQ and Lilly-Consolidated Term***	**Imlunestrant + Abemaciclib N = 246**	
	Any Grade (%)	**Grade ≥3 (%)**
Gastrointestinal Disorders		
Diarrhea	87.4	8.5
Nausea	50.0	1.6
Vomiting	31.7	0.4
Constipation[a]	8.5	0
Abdominal pain[a]	22.8	2.0
General Disorders and Administration Site Conditions		
Fatigue[a]	41.5	4.9
Infections and Infestations		
Infections	34.1	4.1
Nervous System Disorders		
Dizziness	7.7	0
Headache	12.6	0
Metabolism and Nutrition Disorders		
Decreased appetite[a]	20.3	0.8
Musculoskeletal Disorders		
Joint and musculoskeletal pain[b]	19.1	0.4
Back pain	6.5	0.4
Respiratory Thoracic and Mediastinal Disorders		
Cough[a]	10.2	0.0
Skin and Subcutaneous Tissues Disorders		
Rash[b]	11.8	1.2
Alopecia	9.8	0
Vascular Disorders		
Hot flush[b]	6.5	0
Laboratory Parameters		
ALT increased[c]	33.3	4.2
AST increased[c]	34.2	2.1
Triglycerides increased[C]	36.4	2.3
Creatinine increased[c]	34.3	1.3
White blood cell decreased[c]	85.6	10.3
Neutrophil count decreased[c]	86.8	16.5
Lymphocyte count decreased[c]	56.0	6.2
Platelet count decreased[c]	47.7	1.2
Haemoglobin decreased[c]	78.6	7.0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ER+ = oestrogen receptor-positive; FMQ = FDA Medical Query; HER2- = human epidermal growth factor receptor 2 negative; N = number of participants in analysis population; PT = preferred term.

Consolidated terms are *italicised*.

a As defined by Narrow FMQ, the PTs included in each FMQ term are as follows: *Constipation (FMQ):* Constipation; *Abdominal pain (FMQ):* Abdominal pain, Abdominal pain upper, Abdominal pain lower, Abdominal discomfort, Abdominal rigidity, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain; *Fatigue (FMQ):* Fatigue, Asthenia, Lethargy, Malaise; *Decreased appetite (FMQ)*: Decreased appetite, Early satiety; and *Cough (FMQ)*: Cough, Productive cough.

[b] Lilly consolidated term: The PTs included in each Consolidated term are as follows: *Joint and musculoskeletal pain* (consolidated term): Arthralgia, Myalgia, Musculoskeletal discomfort, Musculoskeletal chest pain, Musculoskeletal pain, Pain in extremity, Neck pain; *Hot flush* (consolidated term): Flushing, Hot flush; and *Rash* (consolidated term): Dermatitis acneiform, Drug eruption, Erythema multiforme, Rash, Rash erythematous, Rash maculo-papular, Rash popular, Rash pruritic, Rash pustular, Rash vesicular.

[c] n = all treated patients with at least 1 assessment at baseline and during treatment or the short-term follow-up period for the specified laboratory parameter; n = 240 for *ALT increased and AST increased; n = 176 for triglycerides increased; n = 239 for creatinine increased;* and *n = 243 for White blood cell decreased, Neutrophil count decreased, Lymphocyte count decreased, Platelet count decreased, and Hemoglobin decreased.*

The adverse reaction frequencies from clinical trials are based on all-causality AE frequencies, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility as recommended in the SmPC guideline (https://health.ec.europa.eu/document/download/6a043dea-7d0f-4252-947b-cef58f53d37e_en).

The frequency categories below are based on pooled data from patients with ABC from studies EMBER and EMBER-3 receiving 400 mg imlunestrant (N= 378).

Table 82 Adverse drug reactions in patients receiving Inluriyo

System organ class	Very common	Common
Metabolism and Nutrition Disorders		Decreased appetite [a]
Nervous System Disorders		Headache
Vascular Disorders		Venous thromboembolism [a] Hot flush [a]
Respiratory, Thoracic and Mediastinal Disorders		Cough [a]
Gastrointestinal Disorders	Diarrhoea Nausea	Vomiting Constipation Abdominal pain [a]
Musculoskeletal Disorders	Joint and muscular skeletal pain [b] Back pain	
General Disorders and Administration Site Conditions	Fatigue [a]	
Investigations [c]	ALT increased AST increased Triglycerides increased	

[a] Consolidated term consisting of analogous preferred terms.
[b] Consolidated term consisting of preferred terms: arthralgia, myalgia, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, pain in extremity, neck pain.
[c] Consolidated term consisting of preferred terms: dermatitis acneiform, drug eruption, erythema multiforme, rash, rash erythematous, rash maculo-papular, rash popular, rash pruritic, rash pustular, rash vesicular.
[b] Based on laboratory assessments

2.6.8.3. Serious adverse event/deaths/other significant events

2.6.8.3.1. Imlunestrant monotherapy

Adverse events of special interest

Based upon considerations of preclinical toxicology and safety data observed during healthy volunteer early phase studies and ongoing clinical trials, transaminase increases are deemed an AESI for imlunestrant.

Per protocol, imlunestrant was required to be withheld, dose reduced or discontinued in case of specified ALT/AST elevations and for grade 3 and above other non-hematologic toxicities. No dose adjustments were allowed for exemestane and dose reductions for fulvestrant were at investigator discretion based on the fulvestrant label but recommended for patients with moderate hepatic impairment.

Table 83 Summary of Treatment-Emergent Elevated Transaminases by Decreasing Frequency in the Imlunestrant and SOC Arm EMBER-3 Safety Population

Preferred Term	Arm A Imlunestrant N = 327 n (%)		Arm B SOC N = 324 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with at least 1 TEAE of *elevated transaminases*	51 (15.6)	4 (1.2)	48 (14.8)	4 (1.2)
Alanine aminotransferase increased	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)
Aspartate aminotransferase increased	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)
Hepatic enzyme increased	0	0	2 (0.6)	0
Hepatotoxicity	2 (0.6)	1 (0.3)	0	0
Hypertransaminasaemia	1 (0.3)	0	0	0
Transaminases increased	0	0	1 (0.3)	0

Abbreviations: n = number of patients in the specific category; N = number of patients; SOC = standard of care: investigator's choice of endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.

The table below shows characteristics of these elevated transaminases events.

Table 84 Summary of Characteristics of Treatment-Emergent Elevated Transaminase Adverse Events in the Imlunestrant and SOC Arm EMBER-3 Safety Population

Category	Arm A Imlunestrant N = 327	Arm B SOC N = 324
Patients with at least 1 *Elevated Transaminases*, n (%)	**51 (15.6)**	**48 (14.8)**
Incidences per patient, n (%)	**51 (15.6)**	**48 (14.8)**
1	24 (7.3)	19 (5.9)
2	20 (6.1)	16 (4.9)
≥3	7 (2.1)	13 (4.0)
Incidences of Grade ≥3 AEs per patient, n (%)	**4 (1.2)**	**4 (1.2)**
1	3 (0.9)	3 (0.9)
2	1 (0.3)	1 (0.3)
≥3	0	0
TE-SAEs, n (%)	**1 (0.3)**	**0**
Dose adjustments, n (%)		
None	46 (14.1)	46 (14.2)
Dose reduction of study drug	2 (0.6)	0
Dose withheld/delay of study drug	5 (1.5)	0
Treatment discontinuation, n (%)	**4 (1.2)**	**0**
Time to onset of first AE (Any Grade), n (%)		
Median (range), days	58.0 (1-521)	42.5 (1-476)
Time to onset of first Grade ≥3 AE, n (%)		
Median (range), days	186.5 (11-283)	239.0 (55-253)
Duration of AE, days median (range)		
Grade 1	29.5 (14-281)	30.0 (14-281)
Grade 2	27.0 (11-97)	29.0 (5-86)
Grade 3	5.0 (4-27)	2.0 (2-2)

Abbreviations: AE = adverse event; n = number of patients in the specific category; N = number of patients; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

Table 85 Summary of Treatment-Emergent Maximum Postbaseline CTCAE Laboratory Toxicities for ALT and AST in the Imlunestrant and SOC Arms EMBER-3 Safety Population

Laboratory Parameter	Arm A Imlunestrant N = 327	Arm B SOC N = 324
Serum alanine aminotransferase (U/L)		
Total, n[a]	314	303
Any Grade, n (%)	103 (32.8)	94 (31.0)
Grade 3 or 4, n (%)	4 (1.3)	3 (1.0)
Serum aspartate aminotransferase (U/L)		
Total, n[a]	321	309
Any Grade, n (%)	102 (31.8)	98 (31.7)
Grade 3 or 4, n (%)	6 (1.9)	7 (2.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria of Adverse Events; n = number of subjects in the specified category; N = number of subjects in analysis population; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane.

[a] Refers to all treated patients with at least 1 assessment at baseline and during treatment or the short-term follow-up period for the specified laboratory parameter.

Note: Postbaseline grades were derived based on baseline status per CTCAE Version 5.

Elevated ALT or AST >3 × ULN and T.bil >2 × ULN

More than 96% of patients with ALT or AST increases in the imlunestrant arm did not experience concurrent increases in total bilirubin (T.bil).

Three patients in the imlunestrant arm and no patients in the SOC arm had postbaseline ALT/AST >3 × ULN and T.bil >2 × ULN. All 3 had liver metastasis at baseline, and in all 3 cases, alkaline phosphatase was >3× ULN.

No cases of Hy's law for liver injury were identified in the imlunestrant arm.

The incidence of TEAEs of ALT and AST increased observed in EMBER-3 were similar to those observed in EMBER for patients with ABC receiving 400 mg.

Other Significant Adverse Events

Diarrhoea and nausea are included as they are among the most common TEAEs in patients receiving imlunestrant. Both AEs were reported with a higher incidence in the imlunestrant arm than in the SOC arm, however the majority of these events were low grade, did not trigger treatment discontinuation, and only one patient had the imlunestrant dose reduced due to nausea.

The table below provides a summary of the characteristics of diarrhoea TEAEs in the imlunestrant arm and the SOC arm. Diarrhoea was the second most frequently reported TEAE for the imlunestrant arm (21.4%) and was reported at a higher incidence than in the SOC arm (11.7%). The majority of events were Grade 1 (18.3%), occurred early in treatment (any grade median time to first onset 30 days), and patients could continue treatment without any discontinuations or dose reductions in either arm. The majority of patients experienced only 1 episode of diarrhoea.

Among the patients with at least 1 diarrhoea event in the imlunestrant arm, 35.7% received antidiarrheal medication. Loperamide was the most common treatment used to manage diarrhoea.

Table 86 Summary of Treatment-Emergent Adverse Events of Diarrhoea, Safety Population Imlunestrant versus SOC

	Arm A Imlunestrant N = 327 n (%)	Arm B SOC N = 324 n (%)
TEAE Diarrhoea		
Any Grade	70 (21.4)	38 (11.7)
Grade 2	9 (2.8)	8 (2.5)
Grade 3	1 (0.3)	0
Grade 4	0	0
TE-SAE Diarrhoea	0	0
TEAE Diarrhoea Leading to		
All Treatment Discontinuation	0	0
Treatment Dose Withheld	2 (0.6)	0
Treatment Dose Reductions	0	0
Patients with TEAE Diarrhoea Using Antidiarrheal Therapy	25 (35.7)	10 (26.3)

Abbreviations: n = number of patients in the specific category; N = number of patients; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

Table 87 Summary of Characteristics of Treatment-Emergent Adverse Events of Diarrhoea in the Imlunestrant and SOC Arms EMBER-3 Safety Population

	Arm A Imlunestrant N = 327	Arm B SOC N = 324
Number of events, n (%)	70 (21.4)	38 (11.7)
Incidences per patient, n (%)		
1	54 (16.5)	34 (10.5)
2	10 (3.1)	4 (1.2)
≥3	6 (1.8)	0
Incidences of Grade ≥3 events per patient, n (%)	1 (0.3)	0
1	1 (0.3)	0
2	0	0
≥3	0	0
Time to onset of first diarrhoea AE, n (%)		
Median (range), days	30 (1-652)	52 (1-311)
Time to onset of first Grade ≥3 diarrhoea, AE, n (%)		
Median (range), days	22	NA
Duration of diarrhoea, days median (range)		
Grade 1	9.5 (1-354)	8.5 (1-602)
Grade 2	3.0 (1-28)	5.0 (1-55)
Grade 3	8 (8-8)	NA

Abbreviations: AE = adverse event; n = number of patients in the specified category; N = number of patients in the population; NA = not applicable; SOC = investigator's choice: endocrine therapy of fulvestrant or exemestane.

Table 88 Summary of Treatment-Emergent Adverse Events of Nausea in the Imlunestrant and SOC Arms EMBER-3 Safety Populations

	Arm A Imlunestrant N = 327 n (%)	**Arm B SOC N = 324 n (%)**
TEAE Nausea		
Any Grade	56 (17.1)	42 (13.0)
Grade 2	11 (3.4)	15 (4.6)
Grade 3	1 (0.3)	0
TE-SAE Nausea	**1 (0.3)**	**0**
TEAE Nausea Leading to		
All Treatment Discontinuation	0	0
Treatment Dose Withheld	0	0
Treatment Dose Reductions	1 (0.3)	0

Abbreviations: n = number of patients in the specific category; N = number of patients; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

Table 89 Summary of Characteristics of Treatment-Emergent Nausea Events in the Imlunestrant and SOC Arms EMBER-3 Safety Population

	Arm A Imlunestrant N = 327	**Arm B SOC N = 324**
Number of events, n (%)	**56 (17.1)**	**42 (13.0)**
Incidences per patient, n (%)		
1	48 (14.7)	38 (11.7)
2	6 (1.8)	3 (0.9)
≥3	2 (0.6)	1 (0.3)
Incidences of Grade ≥3 events per patient, n (%)		
1	1 (0.3)	0
2	0	0
≥3	0	0
Time to onset of first all grades nausea TEAE, n (%)		
Median (range), days	19.5 (1-591)	57 (1-474)
Time to onset of first Grade ≥3 nausea, AE, n (%)		
Median (range), days	26 (26-26)	NA
Duration of nausea, days median (range)		
Grade 1	37 (1-867)	34 (1-381)
Grade 2	16 (4-89)	10 (1-90)
Grade 3	24 (24-24)	NA

Abbreviations: AE = adverse event; n = number of patients in the specified category; N = number of patients in the population; NA = not applicable; SOC = investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.

Treatment-Emergent Serious Adverse Events (TE-SAEs)

The table below summarizes TE-SAEs by PT or consolidated term reported in patients in the imlunestrant arm and the SOC arm on study or during short-term follow-up for the Safety Population. The pleural effusions occurred in patients with either a history of pleural effusion, disease progression or concurrent sepsis. Six patients (1.8%) in each arm had fatal TE-SAEs.

Table 90 Summary of TE-SAEs Occurring in at Least 2 Patients in Either Treatment Arm by Decreasing Frequency in the Imlunestrant Arm, EMBER-3 Safety Population

Preferred Term	Arm A Imlunestrant N = 327 n (%)	Arm B SOC N = 324 n (%)
Patients with at least 1 TE-SAE[a]	34 (10.4)	37 (11.4)
Pleural effusion	4 (1.2)	0
Atrial fibrillation	2 (0.6)	0
Pneumonia	2 (0.6)	3 (0.9)
Pulmonary embolism	2 (0.6)[b]	0
Pyrexia	2 (0.6)	0
Septic shock	2 (0.6)	0
Fracture	1 (0.3)	5 (1.5)
Abdominal pain	1 (0.3)	2 (0.6)
Cardiac arrest	1 (0.3)	2 (0.6)
Small intestinal obstruction	0	2 (0.6)

Abbreviations: AE = adverse event; n = number of patients in the specific category; N = number of patients; SOC = standard of care: investigator's choice of endocrine therapy of fulvestrant or exemestane; TE-SAE = treatment-emergent serious adverse event.

[a] Includes TE-SAEs that occurred while on treatment or in short-term follow-up.

[b] Considered related to imlunestrant by the investigator.

Note: Consolidated terms are *italicised*.

Deaths

The table below summarizes patient deaths that occurred in the imlunestrant arm and the SOC arm. At the time of data cutoff, 62 deaths due to any cause were reported in the imlunestrant arm and 90 deaths were reported in the SOC arm. The most common cause of death was disease progression in both the imlunestrant arm and SOC arm.

The frequency of death due to AEs on treatment, or up to 30 days after discontinuation from study treatment, was low and comparable in both the treatment arms. According to the Applicant, no pattern was identified, indicating a common pathophysiology associated with imlunestrant.

The frequency of death due to AEs on treatment or up to 30 days after discontinuation from study treatment was low in the imlunestrant arm (1.5%) and the SOC arm (1.9%).

Of the 5 patients in the imlunestrant arm, 3 patients died due to cardiac related events (acute myocardial infarction, right ventricular failure and cardiac arrest). Two of these events occurred in patients with risk factors (e.g., elderly, cardiac medical history hypertension, hypercholesterolaemia). The event of right ventricular failure occurred in a patient with confirmed bone marrow progression that may have contributed to the events that led to the patient's death.

Of the 2 patients who died due to gastrointestinal haemorrhage, one patient died due to hypovolemic shock as a consequence of gastrointestinal bleeding 20 days after last dose. Both patients had risk factors that may have contributed to the fatal events.

Four out of the 5 patients had significant relevant medical history, or important risk factors including prior therapies.

One additional patient was reported as having died due to study disease but also to have suffered a fatal septic shock related to a dengue infection.

Of the 6 patients in the SOC arm, all deaths occurred in patients receiving fulvestrant. Two patients died due to cardiac arrest, one patient each died due to chronic kidney disease, blood calcium increased, abdominal infection and one due to unknown cause.

According to the Applicant, no clear pattern was identified indicating a common pathophysiology associated with imlunestrant.

At the latest data cut-off date, 1 additional patient died due to AE on study treatment or within 30 days of discontinuation of study treatment in arm B.

Table 91 Summary of Deaths in the Imlunestrant Arm and SOC Arm EMBER-3 Safety Populations

Category	Arm A Imlunestrant N = 327 n (%)	Arm B SOC N = 324 n (%)
All deaths	62 (19)	90 (27.8)
Total deaths on therapy or within 30 days of treatment discontinuation	12 (3.7)	16 (4.9)
Adverse events	5 (1.5)	6 (1.9)
Cardiac arrest	1 (0.3)	2 (0.6)
Acute myocardial infarction	1 (0.3)	0
Right ventricular failure	1 (0.3)[a]	0
Hypovolaemic shock	1 (0.3)	0
Upper gastrointestinal haemorrhage	1 (0.3)	0
Abdominal infection	0	1 (0.3)
Blood calcium increased	0	1 (0.3)
Chronic kidney disease	0	1 (0.3)
Death	0	1 (0.3)
Study disease	7 (2.1)[b]	10 (3.1)
Total deaths after 30 days of treatment discontinuation	50 (15.3)	74 (22.8)
Adverse event	3 (0.9)[c]	4 (1.2)[d]
Study disease	47 (14.4)	70 (21.6)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; LTFU = long-term follow-up; n = number of patients in the specified category; N = number of patients; SOC = standard of care: investigator's choice of endocrine therapy of fulvestrant or exemestane.

a AE was considered related to imlunestrant by the investigator.

b One patient was reported to have died due to study disease but also suffered a septic shock due to a dengue infection considered fatal by the investigator.

c Adverse events in LTFU were gastrointestinal haemorrhage, pleural effusion, and pneumonitis.

d Adverse events in LTFU were cardiac arrest, death, COVID-19, and sepsis.

2.6.8.3.2. Imlunestrant plus abemaciclib

Adverse events of special interest

Based upon considerations of preclinical toxicology and ongoing clinical trials, transaminase increases are deemed an AESI for imlunestrant. ALT and AST increased are also recognised ADRs for abemaciclib, and relevant data from the imlun+abema arm are presented in this section. Management of these events is important to minimize the potential for the development of more severe liver injury.

The table below provides a summary of elevated transaminase TEAEs in the imlun+abema arm and the imlunestrant arm.

Table 92 Treatment-Emergent Elevated Transaminases by Decreasing Frequency in the Imlun+Abema Arm EMBER-3 Safety Population

	Arm C Imlunestrant + Abemaciclib N = 208 n (%)		Arm A Imlunestrant N = 327 n (%)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with at least 1 *elevated transaminases*[a]	42 (20.2)	11 (5.3)	51 (15.6)	4 (1.2)
Alanine aminotransferase increased	28 (13.5)	10 (4.8)	34 (10.4)	1 (0.3)
Aspartate aminotransferase increased	34 (16.3)	5 (2.4)	41 (12.5)	3 (0.9)
Drug-induced liver injury	1 (0.5)	0	0	0
Hepatic enzyme increased	1 (0.5)	0	0	0
Hepatotoxicity	0	0	2 (0.6)	1 (0.3)
Hypertransaminasemia	3 (1.4)	1 (0.5)	1 (0.3)	0
Transaminases increased	1 (0.5)	0	0	0

Abbreviations: n = number of patients in the specific category; N = number of patients.

[a] Some patients may have experienced several events.

Shifts from baseline showed similar shifts for patients with normal and abnormal baselines.

The majority of patients with transaminase increases in the imlun+abema arm did not experience concurrent increases in T.bil. Three patients in the imlun+abema arm had elevated ALT/AST >3 × ULN and T.bil >2 × ULN. In all 3 cases, alkaline phosphatase was >2 × ULN. One patient's increases were due to a bile duct stone, another occurred more than 30 days after discontinuation in a patient with liver metastases, and the third was confounded by comorbid conditions of obesity with hepatic steatosis noted on ultrasound.

No cases meeting Hy's liver law were identified in either treatment arm.

Adverse Events of Interest for abemaciclib

This section details selective AESIs for abemaciclib that are not discussed elsewhere but considered clinically relevant in the context of use in combination with abemaciclib. These include neutropenia, infections, VTE, and ILD. These were chosen based upon medical assessment of relevance in the target population, potential overlapping toxicities, or both. A review of these topics showed that the incidences and severities were comparable to abemaciclib product labeling, and no additive increase in incidence was noted in combination with imlunestrant.

The data observed for these topics in study EMBER-3 are consistent with those observed in EMBER for patients receiving imlunestrant 400 mg and abemaciclib, given the small number of patients in this EMBER cohort.

Neutropenia is associated with abemaciclib.

The below table provides a summary of neutropenia TEAEs in the imlun+abema arm and the imlunestrant arm.

Table 93 Summary of Treatment-Emergent Neutropenia Events and Laboratory Neutrophil Counts in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

	Arm C Imlunestrant + Abemaciclib N = 208 n (%)	**Arm A Imlunestrant N = 327 n (%)**
TEAE *Neutropenia*		
Any Grade	100 (48.1)	17 (5.2)
Grade 3	40 (19.2)	6 (1.8)
Grade 4	1 (0.5)	1 (0.3)
TEAE Febrile Neutropenia		
Grade ≥3	1 (0.5)	1 (0.3)
TE-SAE *Neutropenia*	0	0
TE-SAE Febrile Neutropenia	0	1 (0.3)
Laboratory Neutrophil Count Decreased		
Any Grade	175 (85.4)	86 (26.5)
Grade 3 or 4	34 (16.6)	13 (4.0)
TEAE *Neutropenia* Leading to		
Study treatment discontinuation	0	0
Dose reduction of any study drug	14 (6.7)[a]	1 (0.3)
Abemaciclib (Arm C)	13 (6.3)[b]	NA
Imlunestrant (Arm C)	6 (2.9)[b]	NA
Dose withheld of any study drug	31 (14.9)[c]	3 (0.9)
Abemaciclib (Arm C)	31 (14.9)[b]	NA
Imlunestrant (Arm C)	26 (12.5)[b]	NA

Abbreviations: n = number of patients in the specified category; N = number of patients in the population; NA = not applicable; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

a Eight patients had only abemaciclib dose reduced, 1 patient had only imlunestrant dose reduced, and 5 patients had doses of both study drugs reduced.

b Includes patients with a dose adjustment of only 1 of the 2 study drugs and patients with a dose adjustment of both study drugs.

c Twenty-six patients had both abemaciclib and imlunestrant doses withheld, and 5 patients had only abemaciclib dose withheld.

Note: Consolidated terms are *italicised*.

The table below provides a summary of treatment-emergent infection events in the imlun+abema arm and the imlunestrant arm.

Table 94 Summary of Treatment-Emergent Infection Events in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

	Arm C Imlunestrant + Abemaciclib N = 208 n (%)	Arm A Imlunestrant N = 327 n (%)
TEAE Infection (System Organ Class)[a]		
Any Grade	64 (30.8)	72 (22.0)
Grade 3	8 (3.8)	7 (2.1)
Grade 4	0	1 (0.3)
Grade 5	1 (0.5)	1 (0.3)
TEAE preferred terms within infection (system organ class)[a], with >3% any-grade incidence in either arm		
COVID-19	11 (5.3)	20 (6.1)
Urinary tract infection	9 (4.3)	6 (1.8)
Upper respiratory tract infection	8 (3.8)	12 (3.7)
Nasopharyngitis	8 (3.8)	6 (1.8)
TE-SAE infection (system organ class)[a]	12 (5.8)	8 (2.4)
TEAE infection (system organ class)[a] leading to		
Study treatment discontinuation	1 (0.5)	0
Dose reduction of any study drug	3 (1.4)	0
Dose withheld of any study drug	13 (6.3)	7 (2.1)

Abbreviations: n = number of subjects in the specified category; N = number of subjects in the safety population; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

a Includes all reported and preferred terms that are part of the Infections and infestations system organ class.

One patient in each arm died due to an infection. In the imlun+abema arm, a female patient who was an ex-smoker developed community-acquired pneumonia and died secondary to unspecified complications of pneumonia. The patient in the imlunestrant arm died as a result of septic shock due to dengue fever.

The patient that died due to pneumonia was the same patient that discontinued treatment due to an infection TEAE.

No additive increase in incidence of infections was noted when imlunestrant was administered with abemaciclib compared to abemaciclib alone.

The table below provides a summary of treatment-emergent VTEs in the imlun+abema arm and the imlunestrant arm.

Table 95 Treatment-Emergent VTEs by Decreasing Frequency in the Imlun+Abema Arm in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

	Arm C Imlunestrant +Abemaciclib N = 208 n (%)	Arm A Imlunestrant N = 327 n (%)
SMQ embolic and thrombotic events, venous	6 (2.9)	4 (1.2)
Pulmonary embolism	4 (1.9)	3 (0.9)
Deep vein thrombosis	0	1 (0.3)
Pelvic venous thrombosis	1 (0.5)	0
Peripheral vein thrombosis	1 (0.5)	0
Superficial vein thrombosis	1 (0.5)	0
Venous thrombosis limb	1 (0.5)	0
TE-SAE SMQ VTE	0	2 (0.6)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in safety population; SMQ = standardized MedDRA query; TE-SAE = treatment-emergent serious adverse event; VTE = venous thrombotic event.

In the imlun+abema arm, no patients discontinued the treatment due to VTE and only 1 patient had the abemaciclib dose withheld and subsequently reduced.

No additive increase in the incidence of VTE was noted when imlunestrant was administered with abemaciclib compared to abemaciclib monotherapy.

The incidence of patients experiencing ILD or pneumonitis was low in both arms, with 5 patients (2.4%) in the imlun+abema arm and 2 patients (0.6%) in the imlunestrant arm. All events were Grade 1 or 2, and none resulted in discontinuation of any study drug.

One TEAE of pneumonitis in the imlun+abema arm was considered a TE-SAE. The patient fully recovered a week later, and no action was taken with imlunestrant. Abemaciclib treatment was interrupted briefly and restarted after the patient recovered.

No additive increase in the incidence of ILD/pneumonitis was noted when imlunestrant was administered with abemaciclib compared to abemaciclib monotherapy.

Other Significant Adverse Events

The below table provides a summary of the characteristics of diarrhoea TEAEs.

Table 96 Summary of Treatment-Emergent Adverse Events of Diarrhoea in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

Category	Arm C Imlunestrant +Abemaciclib N = 208 n (%)	Arm A Imlunestrant N = 327 n (%)
TEAE Diarrhoea		
Any Grade	179 (86.1)	70 (21.4)
Grade 2	59 (28.4)	9 (2.8)
Grade 3	17 (8.2)	1 (0.3)
Grade 4	0	0
TE-SAE Diarrhoea	2 (1.0)	0
TEAE Diarrhoea Leading to		
Treatment Discontinuation	1 (0.5)	0
Treatment Dose Withheld	40 (19.2)	2 (0.6)
Treatment Dose Reductions	38 (18.3)	0
Patients with TEAE Diarrhoea Using Antidiarrheal Therapy	132 (73.7)	25 (35.7)

Abbreviations: n = number of patients in the specific category; N = number of patients; TEAE = treatment-emergent adverse event.

Among patients with at least 1 diarrhoea event in the imlun+abema arm, 73.7% received antidiarrheal medication. Loperamide was the most common treatment used to manage diarrhoea. The table below provides a summary of the characteristics of nausea TEAEs in the imlun+abema arm and the imlunestrant arm.

Table 97 Summary of Treatment-Emergent Adverse Events of Nausea in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

	Arm C Imlunestrant + Abemaciclib N = 208 n (%)	Arm A Imlunestrant N = 327 n (%)
TEAE Nausea		
Any Grade	101 (48.6)	56 (17.1)
Grade 2	32 (15.4)	11 (3.4)
Grade 3	4 (1.9)	1 (0.3)
TE-SAE Nausea	0	1 (0.3)
TEAE Nausea Leading to		
Treatment Discontinuation	0	0
Treatment Dose Withheld	12 (5.8)	0
Treatment Dose Reductions	10 (4.8)	1 (0.3)

Abbreviations: n = number of patients in the specific category; N = number of patients; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

Treatment-Emergent Serious Adverse Events (TE-SAEs)

The table below summarizes TE-SAEs by consolidated terms or PTs reported in patients in the imlun+abema arm and the imlunestrant arm on study or during short-term follow-up for the safety population.

Of the reported TE-SAEs, 3 in the imlun+abema arm were fatal.

Table 98 Summary of TE-SAEs Occurring in at Least 2 Patients in Either Treatment Arm by Decreasing Frequency in the Imlun+Abema Arm, EMBER-3 Safety Population

Preferred Term	Arm C Imlunestrant + Abemaciclib N = 208 n (%)	Arm A Imlunestrant N = 327 n (%)
Patients with at least 1 TE-SAE[a]	35 (16.8)	34 (10.4)
Pneumonia	3 (1.4)[b]	2 (0.6)
Abdominal pain	3 (1.4)	1 (0.3)
Anaemia	2 (1.0)	0
Diarrhoea	2 (1.0)	0
Hypokalaemia	2 (1.0)	0
Osteonecrosis of jaw	2 (1.0)	1 (0.3)
Renal failure	2 (1.0)	0
Atrial fibrillation	0	2 (0.6)
Pleural effusion	0	4 (1.2)
Pulmonary embolism	0	2 (0.6)
Pyrexia	0	2 (0.6)
Septic shock	0	2 (0.6)

Abbreviations: n = number of patients in the specific category; N = number of patients; TE-SAE = treatment-emergent serious adverse event.
Consolidated terms are *italicised*

a Includes TE-SAEs that occurred while on treatment or in short-term follow-up.

b One pneumonia event was fatal and not related.

The incidence of TE-SAEs with the imlun+abema combination in EMBER was similar to the incidence in EMBER-3. No additional safety findings were identified following review of EMBER TE-SAEs.

During the long-term follow-up (LTFU) period, the incidence of any-grade SAEs reported for the imlun+abema arm was low (3.8%). These events occurred at least approximately 30 days after the discontinuation of the study drugs.

Deaths

Most deaths in the EMBER-3 study were related to the study disease. The table below summarises patient deaths that occurred in the imlun+abema arm and the imlunestrant arm.

Importantly, the safety analyses include all 327 patients treated with imlunestrant monotherapy in the imlunestrant arm and 208 in imlun+abema arm, whereas the efficacy analyses include only concurrently enrolled patients (213 in each arm).

Table 99 Summary of Deaths in the Imlun+Abema Arm and Imlunestrant Arm EMBER-3 Safety Populations

	Arm C Imlunestrant + Abemaciclib N = 208 n (%)	Arm A Imlunestrant N = 327 n (%)
All deaths	36 (17.3)	62 (19.0)
Total deaths on therapy or within 30 days of treatment discontinuation	8 (3.8)	12 (3.7)
Adverse events	3 (1.4)	5 (1.5)
Acute myocardial infarction	0	1 (0.3)
Cardiac arrest	0	1 (0.3)
Hypovolaemic shock	0	1 (0.3)
Myocardial infarction	1 (0.5)	0
Pneumonia	1 (0.5)	0
Right ventricular failure	0	1 (0.3)[a]
Upper gastrointestinal haemorrhage	0	1 (0.3)
Death	1 (0.5)[a]	0
Study disease	5 (2.4)	7 (2.1)
Total deaths after 30 days of treatment discontinuation	28 (13.5)	50 (15.3)
Adverse event[b]	1 (0.5)	3 (0.9)
Study disease	27 (13.0)	47 (14.4)

Abbreviations: AE = adverse event; n = number of patients in the specified category; N = number of patients.

[a] Considered related to study treatment.

[b] No AEs were considered related to the study treatment or study disease.

Of the 3 patients that died due to AEs in the imlun+abema arm, 1 patient each had a fatal AE due to MI, pneumonia, and due to an unknown cause. All 3 patients had relevant medical history and important risk factors, for example, both MI and pneumonia occurred in elderly patients, and the patient with MI had a medical history of hypertension. In addition, the death due to an unknown cause occurred over 45 days after the last dose of imlunestrant and 64 days after the last dose of abemaciclib. This patient's underlying renal failure, diabetes, hyperlipidemia, and extensive bone metastases likely contributed to the events leading up to the patient's death. No temporal pattern was noted between starting imlunestrant and the event leading to a fatal outcome.

Overall, the 3 deaths due to AEs in the imlun+abema arm were consistent with those expected in the patient population with the risk factors observed in those patients.

At the latest data cut-off date (30 January 2025), the frequency of deaths due to AEs while on treatment or up to 30 days after discontinuation from study was 3.4% in the **imlun+abema** arm (n=7) and 1.5% in the **imlunestrant** arm (n=5). In the imlun+abema arm, 1 patient who died due to an AE considered unrelated to study treatment, disease or protocol proceedures. Of the additional deaths due to AE within 30 days of discontinuation, 2 were due to pneumonia and 1 due to sepsis. Of note, 1 of the deaths due to pneumonia was not a recent death, but a change in coding from study disease which was reported in the PO data cut-off.

2.6.8.4. Laboratory findings

Haematology

The incidence of serum haematology findings was similar between imlunestrant and the standard of care arm. In the combination arm of imlunestrant and abemaciclib the incidence of hematology findings was higher. Anaemia (78.9%), lymphocyte count decreased (55.1%), neutrophil count decreased (85.4%) and platelet count decreased (45.9%) were common in the imlunestrant and abemaciclib treatment arm.

Shifts from NCI CTCAE Grade 0, 1, or 2 at baseline to any incidence of Grade 3 or 4 on treatment were low for anaemia (5.7%), lymphocyte count decreased (2.9%) and platelet count decreased (1.5%).

Neutropenia was considered an adverse event of special interest for abemaciclib. Neutrophil count decreased was common and 30 patients (14.4%) shifted from NCI CTCAE Grade 0 to a worst post-baseline CTCAE grade of 3. In total 16.6% had a Grade 3 or 4 event of neutrophil count decreased in the imlunestrant and abemaciclib combination arm, compared to 4.0% in the imlunestrant monotherapy arm. Neutropenia did not result in study treatment discontinuation. In the imlunestrant/abemaciclib combination arm, neutropenia resulted in a dose reduction of abemaclib in 6.3% of patients, and the dose of imlunestrant was reduced in 2.9% of patients. In 14.9% there was a dose withheld of any study drug (abemaciclib 14.9%; imlunestrant 12.5%).

Clinical chemistry

Transaminase increases were considered an adverse event of special interest and are described in the below table. There were 3 cases of hepatotoxicity, of which 1 case was Grade ≥3 in a patient with liver metastases at baseline. There was no increase in the percentage of patients reporting ALT/AST increased by cycle as the study progressed for the imlunestrant arm.

No TE-SAEs were reported. One TEAE of drug induced liver injury was reported. There was no increase in the percentage of patients reporting ALT/AST increased by cycle as the study progressed for the imlunestrant and abemaciclib arm.

Table 100 Summary of Characteristics of Treatment-Emergent Elevated Transaminase Adverse Events Safety Population.

	Imlunestrant Arm A N=327	SOC Arm B N=324	Imlunestrant + abemaciclib Arm C N=208
Patients with ⩾1 Elevated Transaminases, n (%)	51 (15.6)	48 (14.8)	42 (20.2)
Grade ⩾3	4 (1.2)	4 (1.2)	11 (5.3)
Alanine aminotransferase increased	34 (10.4)	33 (10.2)	28 (13.5)
Grade ⩾3	1 (0.3)	2 (0.6)	10 (4.8)
Aspartate aminotransferase increased	41 (12.5)	41 (12.7)	34 (16.3)
Grade ⩾3	3 (0.9)	3 (0.9)	5 (2.4)
Incidences per patient, n (%)			
1	24 (7.3)	19 (5.9)	18 (8.7)
2	20 (6.1)	16 (4.9)	14 (6.7)
≥3	7 (2.1)	13 (4.0)	10 (4.8)
Dose adjustments, n (%)			
None	46 (14.1)	46 (14.2)	36 (17.3)
Dose reduction of study drug	2 (0.6)	0	5 (2.4)
Dose withheld/delay of study drug	5 (1.5)	0	6 (2.9)
Treatment discontinuation, n (%)	4 (1.2)	0	4 (1.9)
Time to onset of first AE (any grade)			
Median (range), days	58.0 (1-521)	42.5 (1-476)	66.0 (1-603)
Time to onset of first Grade ⩾3 AE			
Median (range), days	186.5 (11-283)	239.0 (55-253)	57.0 (28-418)
Duration of AE, days median (range)			
Grade 1	29.5 (14-281)	30.0 (14-281)	29.0 (8-246)
Grade 2	27.0 (11-97)	29.0 (5-86)	19.0 (3-82)
Grade 3	5.0 (4-27)	2.0 (2-2)	9.0 (2-58)
Grade 4	NA	NA	4.0 (4-4)

Abbreviations: AE = adverse event; n = number of patients in the specific category; N = number of patients; TESAE
= treatment-emergent serious adverse event; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane.

The reported incidence of Grade ≥3 TEAEs of ALT and AST increased was similar to the incidence of Grade ≥3 laboratory evaluations of ALT and AST increased.

In the imlunestrant monotherapy arm, 1 patient developed ALT>10 x ULN. This was a patient with liver lesions at baseline. The patient did not experience any associated symptoms or increase in total bilirubin during the study. In the imlunestrant monotherapy arm, the majority of patients with transaminase increases did not experience concurrent increases in total bilirubin. Three patients receiving imlunestrant monotherapy and no patients in the SOC arm had postbaseline ALT/AST >3 × ULN and total bilirubin >2 × ULN. All 3 patients had liver metastasis and in all 3 cases alkaline phosphatase was >3 × ULN. Per sponsor assessment, no cases of Hy's law for liver injury were identified in the imlunestrant arm.

In the imlunestrant with abemaciclib combination arm, one patient developed ALT >10 × ULN and a concurrent increase in total bilirubin. Three patients in the combination arm had elevated ALT/AST >3 × ULN and total bilirubin >2 × ULN. In all 3 cases alkaline phosphatase was >2 × ULN. One patient's increases were due to a bile duct stone, another occurred more than 30 days after discontinuation in a patient with liver metastasis and the third was confounded by comorbid conditions of obesity with hepatic steatosis. Per sponsor assessment, no cases meeting Hy's law for liver injury were identified. One case was considered as drug-induced liver injury by investigator assessment. This patient had normal ALT, AST and total bilirubin values at baseline. Elevated transaminases with a normal total bilirubin were observed on day 29, and resolved without intervention by the next visit. On day 148, both ALT and AST were elevated with a normal total bilirubin after which both imlunestrant and abemaciclib were withheld and ALT and AST decreased. Both study drugs were restarted (day 162) after which ALT and AST increased in combination with an increase in total bilirubin (2.5xULN). The patient discontinued from the study. Serology for hepatitis A was positive. Abdominal ultrasound performed on day 180 showed hepatic steatosis and no signs of tumuor metastasis. Other investigations, including viral studies and autoantibodies, did not suggest any potential cause for the enzyme elevations. ALT and ALT decreased and total bilirubin returned to normal. The Applicant assessed this as a DILI case for which a causal relationship with imlunestrant + abemaciclib could not be ruled out, but not a Hy's law case because most of the time the total bilirubin was <2.

Table 101 Summary of Abnormal Hepatic Laboratory Results Safety Population.

	Imlunestrant Arm A N=327	**SOC Arm B N=324**	**Imlunestrant + abemaciclib Arm C N=208**
Serum alanine aminotransferase (U/L)		**N (%)**	
⩾ULN	95 (29.1)	80 (24.7)	59 (28.4)
⩾3 × ULN	11 (3.4)	5 (1.5)	12 (5.8)
⩾5 × ULN	5 (1.5)	1 (0.3)	8 (3.8)
⩾10 × ULN	1 (0.3)	0	2 (1.0)
Serum aspartate aminotransferase (U/L)			
⩾ULN	115 (35.2)	104 (32.1)	74 (35.6)
⩾3 × ULN	15 (4.6)	13 (4.0)	10 (4.8)
⩾5 × ULN	7 (2.1)	6 (1.9)	5 (2.4)
⩾10 × ULN	0	1 (0.3)	0
Serum alkaline phosphatase (U/L)			
⩾2 × ULN	45 (13.8)	45 (13.9)	30 (14.4)
⩾3 × ULN	23 (7.0)	26 (8.0)	13 (6.2)
Serum bilirubin (µmol/L)			
⩾2 × ULN	3 (0.9)	1 (0.3)	3 (1.4)
⩾5 × ULN	0	0	1 (0.5)
⩾8 × ULN	0	0	0

Abbreviations: n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane; ULN = upper limit of normal.

The incidence of serum chemistry findings was similar between imlunestrant and the standard of care arm. In the combination arm of imlunestrant and abemaciclib the incidence of serum chemistry findings was higher. Increased creatinine (33.3%), hyperglycaemia (26.7%), hypertriglyceridemia (36.4%), hypercholesterolemia (15.7%), hypocalcaemia (36.6%) and hypokalaemia (17.5%) were common in the imlunestrant and abemaciclib treatment arm. The incidence of Grade ≥3 serum chemistry findings was low.

Vital signs

There were relevant changes in vital signs observed during the study for both the imlunestrant monotherapy arm and imlunestrant and abemaciclib combination arm.

ECG

Single local ECGs were performed at baseline for all patients and on study only in patients receiving imlunestrant 2-4 hr post-dose C1D1, then pre-dose C2D1, C4D1, and at short-term follow-up.

Three patients experienced TEAEs of electrocardiogram QT prolonged in the imlunestrant arm (maximum QTcF 521 ms) and none in the SOC arm. All TEAEs were Grade 1 or 2. Two of the patients had QTc prolongation at baseline (QTcF 466 ms and 470 ms) and one had a medical history of QTc prolongation. The other event (QTcF 472 ms) occurred during the short-term follow-up visit 32 days after imlunestrant discontinuation. Grade 1 TEAE of syncope was reported in a patient who had discontinued study drug 29 days prior to the event. None of the TEAEs of QTc prolonged or syncope were deemed related to study drug by the investigator. No dose reduction, dose hold, or dose discontinuation was reported because of these events. Four patients experienced TEAEs of QTc prolongation in the imlunestrant and abemaciclib combination arm (maximum QTcF 545 ms). Three patients had either baseline QTc prolongation, concurrent concomitant medications (loperamide or famotidine), or concurrent TEAEs (hypokalaemia in a patient with decreased glomerular filtration rate) contributing to the events. The remaining patient who was receiving loperamide had ECG QTc prolongation continuing for more than 1 month after stopping the treatment. In one patient who experienced 2 Grade 3 TEAEs of QTc prolonged (both nonserious) both imlunestrant plus abemaciclib were held, then dosages were reduced, followed by discontinuation of both study drugs. The second event occurred 10 days after resuming study drug and QTc interval remained high greater than 1 month after stopping study treatment. No dose reduction, dose hold, or dose discontinuation was reported for ECG QTc prolonged in the remaining patients. No TEAEs of Torsade de Pointes, ventricular tachycardia, or ventricular fibrillation/flutter were reported.

Safety in special populations

The number of patients in the safety population per age category and per treatment arm is shown in the below table.

Table 102 Number of patients in the safety population per age category and per treatment arm

Age category	Imlunestrant monotherapy	SOC	Imlunestrant + Abemaciclib
18 – 64 years	209[a]	193	118[a]
65 – 74 years	81[a] +13[b]	81	63[a] + 10[b]
75 years and older	37[a] + 8[b]	50	27[a] + 2[b]

a EMBER-3 (Arm C and Arm A) Safety population

b EMBER (Phase 1b Cohort E1 at 400 mg Imlunestrant) Safety population

For imlunestrant monotherapy, the number of patients with at least 1 TEAE was similar between age categories (81.5 – 86.5%). The incidence of Grade ≥3 TEAEs was higher in the age category 18 – 64 years (19.1%) compared to 65 – 74 years (14.8%) and ≥75 years (10.8%). TEAEs with a ≥10% difference in incidence between age categories 18 -64 years, 65 -74 years and ≥75 years were

diarrhoea (21.5%, 25.9% and 10.8% respectively), fatigue (12.0%, 9.9% and 24.3% respectively), asthenia (9.1%, 6.2% and 21.6%) and dyspnoea (4.8%, 8.6% and 16.2% respectively).

For imlunestrant in combination with abemaciclib, the number of patients with at least 1 TEAE was similar between age categories (96.3 – 100%). The incidence of Grade ≥3 TEAEs was lower in the age category 18 – 64 years (45.8%) compared to 65 – 74 years (50.8%) and ≥75 years (55.6%). TEAEs with a ≥10% difference in incidence between age categories were nausea (42.4%, 55.6% and 59.3% respectively), anaemia (40.7%, 44.4% and 51.9% respectively), vomiting (28.0%, 39.7% and 25.9% respectively), neutropenia (28.8%, 27.0% and 11.1% respectively), decreased appetite (19.5%, 14.3% and 33.3% respectively), ALAT increased (11.9%, 19.0% and 7.4% respectively), abdominal pain (13.6%, 15.9% and 3.7% respectively) and leukopenia (11.0%, 11.1% and 3.7%).

Table 103 EMBER-3 Study Summary of TEAEs by Age Range – Imlun+Abema Versus Imlunestrant

MedDRA Terms, n (%)	Imlun+Abema N = 208				Imlunestrant N = 327			
	Age <65 (n = 118)	Age 65-74 (n = 63)	Age 75-84 (n = 23)	Age 85+ (n = 4)	Age <65 (n = 209)	Age 65-74 (n = 81)	Age 75-84 (n = 31)	Age 85+ (n = 6)
Patients with ⩾1 TEAE	115 (97.5)	63 (100)	22 (95.7)	4 (100)	172 (82.3)	66 (81.5)	28 (90.3)	4 (66.7)
Patients with ⩾1 TE-SAEs	19 (16.1)	12 (19.0)	4 (17.4)	0	24 (11.5)	7 (8.6)	2 (6.5)	1 (16.7)
- Fatal	1 (0.8)	0	2 (8.7)	0	4 (1.9)	2 (2.5)	0	0
- Life-threatening	1 (0.8)	2 (3.2)	0	0	2 (1.0)	0	1 (3.2)	0
- Hospitalization/prolong existing hospitalization	17 (14.4)	10 (15.9)	2 (8.7)	0	18 (8.6)	4 (4.9)	1 (3.2)	1 (16.7)
- Disability/incapacity	0	0	0	0	0	0	0	0
- Other (medically significant)	0	0	0	0	0	1 (1.2)	0	0
Patients with ⩾1 TEAE leading to treatment discontinuation	5 (4.2)	3 (4.8)	4 (17.4)	1 (25.0)	9 (4.3)	3 (3.7)	1 (3.2)	1 (16.7)
Psychiatric disorders	6 (5.1)	9 (14.3)	4 (17.4)	1 (25.0)	12 (5.7)	8 (9.9)	2 (6.5)	0
Nervous system disorders	28 (23.7)	17 (27.0)	5 (21.7)	1 (25.0)	35 (16.7)	16 (19.8)	8 (25.8)	0
Accidents and injuries[a]	5 (4.2)	10 (15.9)	4 (17.4)	0	9 (4.3)	4 (4.9)	4 (12.9)	0
Cardiac disorders	10 (8.5)	6 (9.5)	3 (13.0)	0	13 (6.2)	7 (8.6)	3 (9.7)	0
Vascular disorders	17 (14.4)	11 (17.5)	5 (21.7)	2 (50.0)	19 (9.1)	13 (16.0)	4 (12.9)	0

MedDRA Terms, n (%)	Imlun+Abema N = 208				Imlunestrant N = 327			
	Age <65 (n = 118)	Age 65-74 (n = 63)	Age 75-84 (n = 23)	Age 85+ (n = 4)	Age <65 (n = 209)	Age 65-74 (n = 81)	Age 75-84 (n = 31)	Age 85+ (n = 6)
Cerebrovascular disorders[b]	1 (0.8)	1 (1.6)	0	0	1 (0.5)	1 (1.2)	0	0
Infections and infestations	35 (29.7)	21 (33.3)	6 (26.1)	2 (50.0)	45 (21.5)	19 (23.5)	8 (25.8)	0
Anticholinergic syndrome[c]	0	0	0	0	0	0	0	0
Quality of life decreased[d]	0	0	0	0	0	0	0	0
Sum of below TEAEs:	8 (6.8)	9 (14.3)	2 (8.7)	0	9 (4.3)	6 (7.4)	3 (9.7)	0
- Orthostatic hypotension	0	0	0	0	0	0	0	0
- Falls	1 (0.8)	1 (1.6)	1 (4.3)	0	1 (0.5)	2 (2.5)	1 (3.2)	0
- Loss of consciousness (black outs)	0	0	0	0	0	0	0	0
- Syncope	2 (1.7)	0	0	0	1 (0.5)	0	0	0
- Dizziness	5 (4.2)	7 (11.1)	0	0	6 (2.9)	3 (3.7)	2 (6.5)	0
- Ataxia	0	0	0	0	0	0	0	0
- Fractures	0	1 (1.6)	2 (8.7)	0	1 (0.5)	2 (2.5)	0	0

Abbreviations: Imlun+Abema = imlunestrant in combination with abemaciclib; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients per category; N = number of patients in the population; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

Data cutoff: 24 June 2024

a Defined as Injury, poisoning and procedural complications SOC.

b Defined as Central nervous system vascular disorders (SMQ) using broad terms.

c Defined as Anticholinergic syndrome (SMQ) using narrow terms.

d Defined as Quality of life decreased preferred term.

Sex

For imlunestrant monotherapy, 323 females and 4 males were treated. For imlunestrant in combination with abemaliciclib 206 females and 2 males were treated.

Hepatic impairment

There were no patients with moderate or severe hepatic impairment in the pivotal study and there was one patient with moderate hepatic impairment in the phase 1 EMBER-study.

Renal impairment

TEAEs in patients with renal impairment (defined as GFR<60) are shown in the below table.

Table 104 TEAEs in patients with renal impairment (GFR <60 mL/min)

	Imlunestrant + Abemaciclib	Imlunestrant Monotherapy
MedDRA Terms, n (%)	**Renally Impaired (n = 21)**	**Renally Impaired (n = 28)**
Patients with ⩾1 TEAE	21 (100)	23 (82.1)
Patients with ⩾1 TE-SAEs	11 (52.4)	3 (10.7)
- Fatal	2 (9.5)	2 (7.1)
- Life-threatening	2 (9.5)	0
- Hospitalization/prolong existing hospitalization	7 (33.3)	1 (3.6)
- Disability/incapacity	0	0
- Other (medically significant)	0	0
Patients with ⩾1 TEAE leading to discontinuation	3 (14.3)	3 (10.7)

Race

Approximately 349 patients (39.9%) enrolled in the study were from North America/Western Europe and 233 patients (26.7%) were from East Asia. No clinically relevant differences in safety profile were observed in the analysis by race

***ESR1*-mutation**

The overall safety profile for imlunestrant was comparable for *ESR1*-mut-detected and *ESR1*-mut-not detected subject groups.

2.6.8.5. Immunological events

Not applicable.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Please refer to the assessment of clinical pharmacology.

2.6.8.7. Discontinuation due to adverse events

2.6.8.7.1. Imlunestrant monotherapy

Withheld/delay

The below table summarises the TEAEs leading to dose withheld or dose delay for patients in the imlunestrant arm and the SOC arm.

One patient each withheld exemestane dose due to rash and femoral neck fracture.

Table 105 Summary of TEAEs Leading to Dose Withheld/Dose Delay Occurring in ≥2 Patients in Either Treatment Arm Safety Population Imlunestrant versus SOC

Category, n(%)	Arm A Imlunestrant N = 327 n (%)	Arm B SOC N = 324 n (%)
Patients reporting TEAEs leading to dose withheld/delays, n (%)	**34 (10.4)**	**23 (7.1)**
Patients reporting TEAEs leading to dose withheld, n (%)	34 (10.4)	2 (0.6)
Vomiting	5 (1.5)	0
Aspartate aminotransferase increased	3 (0.9)	0
COVID-19	3 (0.9)	0
Alanine aminotransferase increased	2 (0.6)	0
Anaemia	2 (0.6)	0
Diarrhoea	2 (0.6)	0
Neutrophil count decreased	2 (0.6)	0
Pyrexia	2 (0.6)	0
Patients reporting TEAEs leading to dose delay, n (%)	0	21 (6.5)
COVID-19	0	5 (1.5)
Upper respiratory tract infection	0	3 (0.9)
Aspartate aminotransferase increased	0	2 (0.6)

Abbreviations: COVID-19 = coronavirus disease 2019; n = number of patients in the specific category; N = number of patients; PT = preferred term;

SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane;

TEAE = treatment-emergent adverse event.

Note: TEAEs listed are unconsolidated PTs.

Dose reduction

Table 106 Summary of TEAEs Leading to Dose Reduction Safety Population Imlunestrant versus SOC

Category, n(%)	Arm A Imlunestrant N = 327 n (%)	Arm B SOC N = 324 n (%)
Patients reporting TEAEs leading to dose reduction, n (%)	8 (2.4)	**0**
TEAEs leading to dose reduction, n (%)		
Aspartate aminotransferase increased	2 (0.6)	0
Alanine aminotransferase increased	1 (0.3)	0
Anaemia	1 (0.3)	0
Fatigue	1 (0.3)	0
Interstitial lung disease	1 (0.3)	0
Nausea	1 (0.3)	0
Neutropenia	1 (0.3)	0
Vomiting	1 (0.3)	0

Abbreviations: n = number of patients in the specific category; N = number of patients; SOC = standard of care investigator's choice endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.

Note: TEAEs listed are unconsolidated PTs.

Discontinuation

The table below summarizes the TEAEs leading to treatment discontinuation for patients in the imlunestrant arm and the SOC arm. All treatment discontinuations due to TEAEs in the SOC arm were in patients who received fulvestrant.

The majority of discontinuations were due to serious adverse events (9, 2.8% in imlunestrant arm and 4, 1.2% in SOC arm) including fatal events (5, 1.5% and 4, 1.2% respectively).

Table 107 Summary of TEAEs Leading to Treatment Discontinuation in the Imlunestrant Arm and the SOC Arm EMBER-3 Safety Populations

Preferred Term	Arm A Imlunestrant N = 327 n (%)	Arm B SOC N = 324 n (%)
Patients with at least 1 TEAE leading to treatment discontinuation[a]	14 (4.3)	4 (1.2)
Alanine aminotransferase increased	3 (0.9)	0
Abdominal pain	1 (0.3)	0
Acute myocardial infarction	1 (0.3)[a]	0
Asthenia	1 (0.3)	0
Cardiac arrest	1 (0.3)[a]	2 (0.6)[a]
Fractured sacrum	1 (0.3)	0
Hepatotoxicity	1 (0.3)	0
Hypovolemic shock	1 (0.3)[a]	0
Neuropathy peripheral	1 (0.3)	0
Pyrexia	1 (0.3)	0
Right ventricular failure	1 (0.3)[a]	0
Upper gastrointestinal haemorrhage	1 (0.3)[a]	0
Abdominal infection	0	1 (0.3)[a]
Blood calcium increased	0	1 (0.3)[a]

Abbreviations: AE = adverse event; n = number of patients in the specific category; N = number of patients; SOC = standard of care: investigator's choice of endocrine therapy of fulvestrant or exemestane; TEAE = treatment-emergent adverse event.

[a] Including patients who died due to a TEAE during the study treatment

Note: TEAEs listed are unconsolidated PTs.

2.6.8.7.2. Imlunestrant plus abemaciclib

Withheld/delay

The table below summarizes the TEAEs leading to dose withheld/delay for patients in the imlun+abema arm (any or both study drugs) and the imlunestrant arm.

Table 108 Summary of TEAEs Leading to Dose Withheld Occurring in at least 2% of Patients in Either Arm in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

Category	Arm C Imlunestrant + Abemaciclib N = 208 n (%)			Arm A Imlunestrant N = 327 n (%)
	Any Drug	Imlunestrant[a]	Abemaciclib[a]	
Patients reporting at least 1 TEAEs leading to dose withheld	115 (55.3)	95 (45.7)	112 (53.8)	34 (10.4)
Diarrhoea	40 (19.2)	26 (12.5)	37 (17.8)	2 (0.6)
Neutropenia	17 (8.2)	15 (7.2)	16 (7.7)	1 (0.3)
Neutrophil count decreased	15 (7.2)	12 (5.8)	15 (7.2)	2 (0.6)
Nausea	12 (5.8)	11 (5.3)	11 (5.3)	0
Anaemia	9 (4.3)	9 (4.3)	8 (3.8)	2 (0.6)
Fatigue	5 (2.4)	2 (1.0)	5 (2.4)	1 (0.3)
Vomiting	5 (2.4)	5 (2.4)	5 (2.4)	5 (1.5)

Abbreviations: n = number of patients in the specific category; N = number of patients; TEAE = treatment-emergent adverse event.
[a] Dose withheld for each drug.
Note: TEAEs listed are unconsolidated PTs.

The incidence of dose withheld due to TEAEs in the EMBER-3 study was similar to that observed in patients with ABC receiving imlunestrant 400 mg and abemaciclib in the EMBER study (abemaciclib: 52.6%; imlunestrant: 42.1%). The TEAEs leading to dose omission are also generally consistent between studies.

Dose reduction

Table 109 Summary of TEAEs Leading to Dose Reduction in 3 or More Patients in the Imlun+Abema Arm and the Imlunestrant Arm EMBER-3 Safety Population

Category	Arm C Imlunestrant + Abemaciclib N = 208 n (%)			Arm A Imlunestrant N = 327 n (%)
	Any Drug	Imlunestrant[a]	Abemaciclib[a]	
Patients reporting TEAEs leading to dose reduction	82 (39.4)	34 (16.3)	78 (37.5)	8 (2.4)
TEAEs leading to dose reduction				
Diarrhoea	38 (18.3)	9 (4.3)	38 (18.3)	0
Nausea	10 (4.8)	5 (2.4)	8 (3.8)	1 (0.3)
Neutropenia	7 (3.4)	3 (1.4)	7 (3.4)	1 (0.3)
Neutrophil count decreased	7 (3.4)	3 (1.4)	6 (2.9)	0
Fatigue	6 (2.9)	1 (0.5)	5 (2.4)	1 (0.3)
Alanine aminotransferase increased	3 (1.4)	3 (1.4)	2 (1.0)	1 (0.3)
Aspartate aminotransferase increased	3 (1.4)	1 (0.5)	3 (1.4)	2 (0.6)

Abbreviations: n = number of patients in the specific category; N = number of patients; TEAE = treatment-emergent adverse event.
[a] Dose reduction for each drug.
Note: TEAEs listed are unconsolidated PTs.

The incidence of dose reductions due to TEAEs observed in the EMBER-3 study was consistent with that observed in patients with ABC receiving imlunestrant 400 mg plus abemaciclib in the EMBER study (abemaciclib: 31.6%; imlunestrant 7.9%), considering the small number of patients. The types of TEAEs leading to dose reductions in the EMBER study are also consistent with those observed in the EMBER-3 study, with diarrhoea being the most common TEAE leading to dose reductions in both trials.

Discontinuation

The table below summarizes the TEAEs leading to treatment discontinuation for patients in the imlun+abema arm and the imlunestrant arm.

Discontinuations of either imlunestrant or abemaciclib and continuation of the other study drug were allowed, in which case patients were considered to have continued the study treatment.

The incidence of treatment discontinuations due to TEAEs (including deaths on therapy due to TEAEs) was low and similar between the imlun+abema arm and the imlunestrant arm.

Table 110 TEAEs leading to treatment discontinuation for patients in the imlun+abema arm and the imlunestrant arm

Category	Arm C Imlunestrant + Abemaciclib N = 208 n (%)			Arm A Imlunestrant N = 327 n (%)
	Imlunestrant + Abemaciclib	Imlunestrant Only	Abemaciclib Only	
Patients with at least 1 TEAE leading to treatment discontinuation[a]	13 (6.3)	1 (0.5)	6 (2.9)	14 (4.3)
Alanine aminotransferase increased	3 (1.4)[b]	1 (0.5)	1 (0.5)	3 (0.9)
Bile duct stone	1 (0.5)[b]	0	0	0
Diarrhoea	1 (0.5)[b]	0	1 (0.5)	0
Drug-induced liver injury	1 (0.5)	0	0	0
Electrocardiogram QT prolonged	1 (0.5)[b]	0	0	0
Fatigue	1 (0.5)[b]	0	1 (0.5)	0
Myocardial infarction	1 (0.5)[b]	0	0	0
Pneumonia	1 (0.5)[b]	0	0	0
Rash maculo-papular	1 (0.5)[b]	0	0	0
Renal failure	1 (0.5)[b]	0	0	0
Vomiting	1 (0.5)	0	0	0
Abdominal pain	0	0	0	1 (0.3)
Acute myocardial infarction	0	0	0	1 (0.3)
Asthenia	0	0	0	1 (0.3)
Cardiac arrest	0	0	0	1 (0.3)
Fractured sacrum	0	0	0	1 (0.3)
Hepatotoxicity	0	0	0	1 (0.3)
Hypovolaemic shock	0	0	0	1 (0.3)
Neuropathy peripheral	0	0	0	1 (0.3)
Pyrexia	0	0	0	1 (0.3)
Right ventricular failure	0	0	0	1 (0.3)
Upper gastrointestinal haemorrhage	0	0	0	1 (0.3)
Blood creatinine increased	0	0	1 (0.5)	0
Embolism	0	0	1 (0.5)	0
Nausea	0	0	1 (0.5)	0

Abbreviations: n = number of patients in the specific category; N = number of patients; TEAE = treatment-emergent adverse event.

[a] Including patients who died due to a TEAE during the study treatment. [b] One TEAE Grade ≥3.

In the imlun+abema arm, the majority of discontinuations were due to Grade ≥3 events (4.3% in the imlun+abema arm and 2.4% in the imlunestrant arm), indicating that most discontinuations are not due to the most common observed TEAEs but rather due to less frequent events.

2.6.8.8. Post marketing experience

Imlunestrant was approved in the USA on 25 September 2025; however, no post-marketing data are available.

2.6.9. Discussion on clinical safety

During the evaluation, the applicant withdrew the indication of imlunestrant in combination with abemaciclib.

EMBER-3 safety population is used as the primary basis for the overall assessment of safety and the identification of ADRs, which includes patients with ER+, HER2-, advanced breast cancer previously treated with endocrine therapy (ET) with or without a CDK4/6 inhibitor, receiving at least 1 dose of study treatment (n = 859). The phase 1 EMBER study and the randomised controlled study EMBER-2 provide data on additional patients (n>100) receiving the proposed 400 mg dose of imlunestrant ± abemaciclib. In general, data should be pooled across studies where possible. However, for this procedure, it is considered acceptable to focus mainly on data from the EMBER-3 study. Namely, it is not expected that the addition of data from the EMBER-1 and EMBER-2 studies will add considerably to the safety analyses. The study population in EMBER-1 was small and the duration of treatment in EMBER-2 was short. For the ADR frequency calculation, the safety data pooled of imlunestrant 400 mg monotherapy from studies EMBER-3 and EMBER N= 378 was used which is considered acceptable.

The adverse event definition in the clinical study protocol of the EMBER-3 study is not in line with the anti-cancer guideline as adverse events associated with the underlying disease or expected progression were not considered as adverse event unless more severe than expected. Therefore, there is potential underreporting of (S)AEs.

The total safety database is limited with a total of 378 subjects with advanced/metastatic breast cancer receiving monotherapy and 246 subjects receiving combination treatment. Long-term safety information is limited in the target population. The safety database is however considered of sufficient size when taking into account the regulatory precedents for the sought indication. It should however be remarked that the database is too small to detect rare adverse reactions.

For readability, the safety will be discussed for imlunestrant monotherapy and imlunestrant plus abemaciclib separately. The applicant has withdrawn the indication of imlunestrant in combination with abemaciclib during the procedure.

At the latest cut-off date (30 January 2025), updated safety data was provided by the Applicant. The safety profile of imlunestrant monotherapy and imlunestrant plus abemaciclib remained consistent with the primary outcome (PO).

Imlunestrant monotherapy (Arm A vs Arm B)

The number of cycles received was similar between imlunestrant monotherapy and standard of care. There were no differences in relative dose intensity between the two arms, as treatment compliance was high in both arms. The frequency of dose withheld or dose reduction was low in the imlunestrant monotherapy and the SOC arms, indicating that most patients tolerated the proposed starting dose.

In the EMBER-3 study, imlunestrant monotherapy was compared with standard of care. The latter consisted of fulvestrant (n=292; 90%), or exemestane (n=32; 10%). Hence, safety of the SOC is mostly reflecting the safety profile of fulvestrant. Fulvestrant and imlunestrant are both SERDs, and overlap in safety is therefore expected. However, imlunestrant is administered orally and fulvestrant intramuscularly. Hence, potential differences between products cannot entirely be excluded. In addition, a recent review showed that there are also differences in mechanisms of action, PK and PD profiles between oral SERDs, which can lead to differences in adverse events within this class of products (Scafetta et al. Breast Cancer Res Treat. 2025). This is relevant to take into consideration when discussing potential class-effects.

The overall burden of toxicity of imlunestrant is higher than for the SOC comparator. Although the overall incidence of patients with at least one TEAE of any grade is similar between imlunestrant monotherapy and SOC, the cumulative proportion of TEAEs in patients were higher with monotherapy vs SOC, especially regarding gastrointestinal toxicity (see below).. Most frequently reported treatment emergent adverse events in the imlunestrant monotherapy arm were fatigue (22.6%), diarrhoea (21.4%) and nausea (17.1%). Fatigue (22.6% vs 13.3%, respectively) and diarrhoea (21.4% vs 11.7%) were also more frequently reported in the imlunestrant monotherapy arm compared to the standard of care arm (difference of ≥5%). On SOC level, the largest differences between study arms were within "GI disorders". This may be attributed to the oral route of administration. In general, GI adverse events such as nausea, diarrhoea, and vomiting can be quite bothersome for patients. It is therefore reassuring that diarrhoea and nausea were mostly of low grade and that the majority of patients experienced the event only once. Diarrhoea was generally tolerated in participants and managed with antidiarrheal therapy, if needed. Nausea was also tolerated and dose adjustments were rare.

The frequencies of the other relevant TEAEs, such as transaminases increased, hot flushes and arthralgia, were comparable between treatment arms and in line with what is known for these types of products. Injection site reactions were only reported in the SOC arm, as expected. The overall incidence of Grade ≥3 TEAEs was also comparable between study arms, which is reassuring.

Transaminases increased is the only **adverse event of special interest**. The percentages of "elevated transaminases" were similar between imlunestrant monotherapy and SOC and mostly of low grade (i.e. grade 1 or 2). One of the TEAEs of hepatotoxicity in the imlunestrant monotherapy arm was serious, but this patient had liver metastasis as confounding factor.

The percentage of **serious adverse events** was similar between imlunestrant monotherapy and SOC (10.4% vs 11.4%). Four patients in the imlunestrant monotherapy arm had a pleural effusion, which were not considered treatment-related by the investigator. These events occurred in patients with either a history of pleural effusion, disease progression or concurrent sepsis. Hence, it can be agreed that a causal relationship between these events and study treatment is unlikely. Pulmonary embolism was reported in two patients in the imlunestrant monotherapy arm. In both cases considered treatment-related by the investigator, patients were at increased risk due to cancer and had additional risk factors.. Pulmonary embolisms can be life-threatening. During the evaluation, a causal relationship between thromboembolism and imlunestrant could not entirely be excluded. Besides, thromboembolic events are included as a warning in the SmPC of Faslodex and Orserdu (Faslodex SmPC; SmPC Orserdu), making it likely a class effect. Venous thromboembolism has therefore been included as an ADR for imlunestrant monotherapy (frequency common) but no warning was included in SmPC section 4.4.

Deaths due to an AE (on treatment or up to 30 days after discontinuation from study treatment) were reported at a low incidence in both the imlunestrant monotherapy arm and the SOC arm (1.5% vs 1.9%). Right ventricular failure was considered related to imlunestrant by the investigator. There is insufficient evidence to suggest a causal association between imlunestrant and right ventricular failure in this case. Furthermore, it is noted that 3 patients died of gastrointestinal bleeding in the monotherapy arm, which is considered to be a novel safety signal. During the evaluation, the Applicant provided additional narrative information and elaborated further on the clinical circumstances regarding these deaths. For one of these deaths, it is indeed unlikely that imlunestrant contributed to gastrointestinal bleeding, considering the time between the last dose of study drug and death (241 days). However, the remaining two deaths (due to GI bleeding) raise a suspicion of an association with imlunestrant, and gastrointestinal bleeding has therefore been included as a potential important risk in the RMP and also as a safety concern in the PSUR.

Most patients could continue therapy without any **dose adjustments**. Dose modifications were mainly delays and only a few patients had a dose reduction. Moreover, the incidence of **discontinuations** was low in both arms. Hence, treatment was generally tolerated in both treatment arms. There was no clear pattern/trend with regard to reasons for discontinuation, except for liver-related events.

The safety analyses to investigate **safety in special population,** which included age, race and *ESR1* status, did not reveal any signals of relevant differences between subgroups. Yet, compared to older patients receiving fulvestrant monotherapy, older patients receiving imlunestrant monotherapy had slightly higher increased rates of diarrhoea and nausea than younger patients (~4-8% increased rates). With the small therapeutic index of digoxin and the increase in diarrhoea (even of low grade) with imlunestrant, one could foresee the possibility of digoxin poisoning through dehydration with the use of imlunestrant vs. fulvestrant, especially in the frail and elderly patients. During the evaluation, the Applicant discussed this potential risk. It is agreed that the risk of digoxin poisoning is low and is adequately addressed in the section 4.5 of the SmPC. The subgroups of males and patients with hepatic impairment were considered too limited to draw any conclusions about the safety profile in these subgroups. Imlunestrant is metabolised by the liver. No clinical data is available in patients with severe hepatic impairment. The recommended dose of 200 mg QD daily in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is based on a PK hepatic impairment study.

Laboratory findings did not show an increased incidence of abnormal haematology findings in the imlunestrant monotherapy arm. Elevated transaminases and serum chemistry were also comparable between the imlunestrant monotherapy arm and the SOC arm.

In general, no clinically meaningful differences in **vital signs** were observed for imlunestrant (alone and in combination with abemaciclib). This is in line with the vital sign results as described for Orserdu (EPAR Orserdu). Although for camizestrant, another oral SERD, bradycardia was observed as a side effect with an unclear mechanism, this was uncommon for imlunestrant (Scafetta et al, 2024). Few cases of electrocardiogram QT prolongation were reported in the imlunestrant arm. The current totality of evidence does not suggest a proarrhythmic potential for imlunestrant.

Considering the TEAEs reported – and the incidence thereof, the potential toxicities based on non-clinical data, and the mechanism of action, the selection of **adverse drug reactions** (ADRs) to be included in the SmPC seems adequate. As to be expected, there is much overlap with the ADRs listed for Orserdu (Orserdu SmPC) and Faslodex (Faslodex SmPC). Dyspnoea is included as an ADR for Orserdu and has also been reported for imlunestrant. However, currently available evidence is too limited to conclude on a (possible) causal relationship between imlunestrant and dyspnoea.

Imlunestrant exhibits a safety profile generally comparable to other oral SERD agents.

Imlunestrant plus abemaciclib (Arm C vs Arm A)

The number of cycles received was slightly higher in Arm C compared to Arm A, reflecting the PFS results. Dose adjustments were frequent in the imlunestrant plus abemaciclib combination arm. This was mainly due to adverse events. However, the number of discontinuations due to adverse events was low in all treatment arms, and therefore the treatment was tolerable with dose adjustments and supportive management. Similar as for imlunestrant monotherapy, the information on long-term exposure is relatively limited, considering the duration of therapy.

The incidence of **treatment emergent adverse events** – any Grade (98.1% vs 82.6%) and Grade ≥3 (48.6% vs 17.1%)– was higher in the imlunestrant plus abemaciclib arm compared to the imlunestrant monotherapy arm, which is to be expected with the addition of a CDK4/6 inhibitor to a SERD (with overlap in safety profiles; Verzenios SmPC). For example, diarrhoea (86.1% vs 21.4%), vomiting (31.3% vs 8.9%) and nausea (48.6% vs 17.1%) were more frequently reported in the

combination arm compared to the imlunestrant monotherapy arm. The noted increase in toxicity is comparable to the known side effects profile of abemaciclib (observed in the MONARCH studies). No detrimental synergistic or additive effect on side effects (for instance in gastrointestinal toxicity) seems present for the combination (Arm C) compared to the monotherapy (Arm A) other than what is expected with the addition of a CDK4/6 inhibitor. With regard to diarrhoea and nausea, some patients had multiple episodes and the median duration of the events were longer compared to the imlunestrant monotherapy arm. Nevertheless, the few discontinuations due to these events indicate that GI disorders can overall be tolerated if adequately managed, also for the combination therapy. GI disorders are adequately reflected for the monotherapy in section 4.8 of the SmPC.

The incidence of anaemia (43.8% vs 10.1%), neutropenia (48.1% vs 5.2%) and thrombocytopenia (18.3% vs 5.5%) was also higher in the imlunestrant plus abemaciclib arm compared to the imlunestrant monotherapy arm, which could lead to potential bleedings or infections. These TEAEs are consistent with the safety profiles of the products and are reflected in the corresponding SmPCs. Other events such as rash were also more frequently reported in the combination arm compared to imlunestrant monotherapy, and rash is a known ADR for abemaciclib (plus endocrine therapy).

Of note, abemaciclib has already been approved in the EU in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy, and the safety profile of a CDK4/6i plus a SERD has been considered acceptable in case of clear patient benefit (EPAR Abemaciclib; EMEA/H/C/004302/0000).

As described above, the Applicant considered transaminases increased as the only **adverse event of special interest**. Similarly as for imlunestrant, abemaciclib also has an effect on the liver. It is therefore not unexpected that increase in AST and ALT were more frequently reported in the imlunestrant plus abemaciclib arm compared to the imlunestrant monotherapy in the EMBER-3 study, including more Grade ≥3 TEAEs. In the imlunestrant plus abemaciclib arm, an event of DILI was reported. This should be taken seriously, also considering the general hepatocellular injury reported. The cases of potential Hy's law are further discussed below.

The Applicant also emphasized several other, clinically important AEs, namely diarrhoea and nausea, neutropenia, infections and embolic and thromboembolic events.

As mentioned, diarrhoea and nausea were also common adverse events in patients treated with imlunestrant and were significantly higher with the addition of abemaciclib. In agreement with these data, the proportion of patients on concomitant antidiarrheal medication and antiemetics increases to 38% and 10% respectively with the addition of abemaciclib. Neutropenia was also an AE of special interest and was reported at a much higher rate in the combination arm than in the monotherapy arm (any grade: 48.1% vs 5.2%, grade 3: 19.8% vs. 1.8%), which also translated into somewhat higher rates of infection (30.8% vs. 22.0%) albeit without any clear pattern in types of infection. In addition, it did not lead to dose discontinuation or higher rates of febrile neutropenia, which were low in both the monotherapy and the combination arm (0.3% and 0.5% respectively) indicating a clinically manageable impact from neutropenia.

Embolic and thromboembolic events were mostly pulmonary embolisms and occurred more frequently in the monotherapy and the combination therapy groups compared to SOC. Events were low despite the metastatic cancer setting (0.9% in the SOC arm vs. 1.2% in the monotherapy arm and 2.9% in the combination therapy arm) with only one grade 3 episode and none above. Venous thromboembolism is part of the Orserdu and Faslodex SmPCs and the applicant has included it as an ADR for imlunestrant in section 4.8 of the SmPC .

Serious adverse events were reported slightly more frequently in the imlunestrant plus abemaciclib arm compared to the imlunestrant monotherapy arm (16.8% vs 10.4%). Nevertheless, the

percentages could be considered acceptable in case of clear benefit, also taking into consideration that patients are dealing with underlying disease and potential co-morbidities. Infections (incl. respiratory tract) events were reported in the imlunestrant plus abemaciclib arm. These events are known risks for abemaciclib and are adequately described in its SmPC. A couple of the other events are also consistent with known ADRs for abemaciclib, such as anaemia, diarrhoea and pyrexia, and are probably treatment-related (Verzenios SmPC). Three SAEs were fatal (also refer to the section "deaths" below).

Three patients died due to AEs (on treatment or up to 30 days after discontinuation from study treatment) in the imlunestrant plus abemaciclib arm. One patient died due to myocardial infarction and one due to pneumonia. For these **deaths** there were confounding factors and relevant history. Hence, it is agreed that these deaths are unlikely to be treatment-related. The remaining death due to unknown cause was considered related to treatment by the investigator (but not by the Applicant). It is agreed with the Applicant that this death (and the renal failure prior to this event) is unlikely to be related to imlunestrant. Moreover, from the patients who died due to study disease (on treatment or up to 30 days after discontinuation from study treatment), there was one case in which it remains uncertain whether this death was due to the study disease or due to an AE (pneumonia). The risk of infections, however, was proposed to be reflected in the SmPC in section 4.8 and therefore this issue is not further pursued.

Dose adjustments were more frequently reported for imlunestrant plus abemaciclib compared to abemaciclib monotherapy (60.6% vs 10.4%). In the combination arm, diarrhoea, nausea and neutropenia were the most common reasons for dose withheld and dose reduction. **Discontinuations** were infrequent and the most common reason was ALT increased in both arms. In short, dose adjustments were more often needed to manage the TEAEs in the combination arm compared to the imlunestrant monotherapy arm, but only a few patients eventually discontinued therapy, indicating a tolerable regimen even with the addition of a CDK4/6 inhibitor and comparable with the known safety profiles of CDK4/6 inhibitors.

Safety per **age** subgroups revealed numerical differences that deserve attention. Patients aged 65 years and older more often experienced grade ≥ 3 TEAEs compared to patients <65 years. Grade ≥ 3 TEAEs with a higher incidence in the elderly population were diarrhoea, neutrophil count decrease and fatigue. Furthermore, the treatment tolerability of patients aged 65 years or older was lower, as more patients discontinued treatment due to AE or experienced TEAEs leading to dose withheld or dose reduction. The lower treatment tolerability in the elderly population was partly related to the frequently reported TEAE diarrhoea. The differences in safety profile in elderly patients for the combination arm was proposed to be reflected in section 4.8 of the SmPC.

TEAEs were well balanced between racial groups. Other racial groups than Caucasians (Asians and Other) had higher rates of diarrhoea and nausea although the number of observations is too small to be conclusive.

Imlunestrant increases the concentration of digoxin, but also P-gp-substrates such as direct oral anticoagulants (DOACs), which are commonly used concomitantly in oncology. While the EMBER-3 study had very few patients using digoxin (n=3), the study had 33 patients on concomitant DOAC and imlunestrant. The limited data did not reveal an increased risk of bleeding in patients receiving imlunestrant and DOACs, but this should be interpreted with caution. The interaction between imlunestrant and P-gp substrates is reflected in section 4.5 of the SmPC, which is considered sufficient.

With regard to **laboratory findings**, cytopenia was more common in the imlunestrant + abemaciclib arm compared to the imlunestrant monotherapy arm. Cytopenias were observed during the total duration of treatment and were mostly low grade and did not result in study treatment discontinuation. The Applicant stated that the cytopenias were manageable, but did not provide further information how

cytopenias were managed (e.g. if patients were treated with transfusions). Due to the low grade of the observed cytopenia's, this issue is not further pursued.

Grade ≥3 neutrophil count decreased was common and frequently resulted in a dose withheld or dose reduction of both abemaciclib and imlunestrant. Neutropenia is a known adverse event of abemaciclib, and the observed incidence of neutropenia TEAEs is in line with the reported incidence for abemaciclib monotherapy. The incidence of febrile neutropenia was low (1 patient in the imlunestrant monotherapy arm; 1 patient in the combination therapy arm). However, as febrile neutropenia is a known ADR for abemaciclib and has been reported in the EMBER-3 trial, and therefore considered an ADR for the combination therapy.

The increased incidence of cytopenias is reflected in SmPC section 4.8 (ADRs: neutrophil count decreased, white blood cell decreased, haemoglobin decreased, lymphocyte count decreased, platelet count decreased). General recommendations for dose modification in case of adverse reactions are described in SmPC section 4.2 and are considered sufficient. There is no warning for neutropenia in SmPC section 4.4, which is considered acceptable as it is expected that an increased incidence of neutropenia can be attributed to abemaciclib. However, a cross-reference to the SmPC of abemaciclib has been proposed to be included in SmPC section 4.4, similarly to Fulvestrant (SmPC Fulvestrant).

Elevated transaminases were more frequent in the imlunestrant and abemaciclib combination arm, which is expected as AST/ALT increase are adverse drug reactions that are reported "very common" for abemaciclib (SmPC Abemaciclib).

There was one case of drug-induced liver injury. The Applicant argued that this case did not meet Hy's law case because hepatic steatosis was found on ultrasound which will have contributed to the observed liver injury. Furthermore, as the patient had positive hepatitis A serology when the total bilirubin was elevated it is agreed that this is not a Hy's law case. Because this was the only case of drug-induced liver injury, which is confounded by hepatic steatosis, drug-induced liver injury is not considered an ADR for imlunestrant.

An increased creatinine was observed in the imlunestrant and abemaclib combination arm. This can possibly be attributed to abemaclicb, as abemaciclib has been shown to increase serum creatinine (SmPC Abemaciclib). Furthermore, increased cholesterol and triglyceride levels were observed, which are also described for other SERDs (SmPC Orserdu). Overall, the incidence of Grade ≥3 serum chemistry findings was low and adverse reactions due to investigations was proposed to be described in SmPC section 4.8.

For **vital signs** results, please kindly refer to the subsection on the imlunestrant monotherapy above.

The ADRs are discussed above for the imlunestrant monotherapy. Several potential ADRs with lower occurrence (4-8% of patients) are not included namely pyrexia, insomnia, pruritus, peripheral oedema, decreased weight and dysgeusia. During the evaluation, the Applicant provided a justification on why these events should not be listed as ADR. It is agreed with the Applicant that insomnia should not be added to the list of ADRs. Although the applicant agreed to include pyrexia, pruritus, peripheral oedema, decreased weight and dysgeusia as ADRs, since the combination indication was withdrawn, this is not reflected in section 4.8 of the SmPC.

2.6.10. Conclusions on the clinical safety

The safety data from the EMBER-3 study are reasonably sufficient to characterise the safety profile of imlunestrant monotherapy and overall indicate an acceptable tolerability profile. Overall imlunestrant exhibits an AE profile comparable with other SERDs.

The most common adverse reactions with imlunestrant monotherapy were ALT increased, AST increased, joint and musculoskeletal pain, fatigue, diarrhoea, nausea, triglycerides increased and back pain. These ADRs are mostly consistent with the class effects of (oral) SERDs. Compared to standard of care (i.e. predominantly fulvestrant), there is a slight increase in risk of gastrointestinal disorders with imlunestrant. In the pivotal trial EMBER-3, most patients were able to continue therapy without any dose adjustments and few patients discontinued imlunestrant, indicating that the therapy was generally tolerated.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 111 summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Gastrointestinal bleeding
Missing information	None

2.7.2. Pharmacovigilance plan

Table 112 summary of pharmacovigilance activities planned by the Applicant

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

2.7.3. Risk minimisation measures

Table 113 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk		
Gastrointestinal bleeding	**Routine risk minimisation measures:** Not applicable. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Gastroinestinal bleeing has been included into the list of safety specifications for the PSUR and thus updates should be presented as part of the PSUR.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 25.09.2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Inluriyo (imlunestrant) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication reflecting the data evaluated is:

"*Inluriyo is indicated as monotherapy for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, with an activating ESR1-mutation, advanced or metastatic breast cancer, previously treated with an endocrine based regimen (for biomarker-based patient selection, see section 4.2).*

In pre- or perimenopausal women, or men, Inluriyo should be combined with a luteinising hormone-releasing hormone (LHRH) agonist."

3.1.2. Available therapies and unmet medical need

The standard-of-care first-line therapy for patients with oestrogen receptor-positive (ER+), HER2-negative locally advanced or metastatic breast cancer (mBC) is a CDK4/6 inhibitor (CDK4/6i) in combination with endocrine therapy (ET), with improved PFS and OS observed in several trials. After progression on a CDK4/6i, the optimal sequence of endocrine-based therapy is uncertain, underlining an unmet medical need. The choice of next-line treatment is dependent on which agents were used previously, duration of response to previous endocrine therapy, disease burden, patient preference and treatment availability. According to ESMO Guidelines (Gennari et al 2021, ESMO guideline), evidence-based available options for second-line therapy are fulvestrant-alpelisib (for PIK3CA mutated tumours), PARP inhibitors (for tumours harbouring genomic BRCA mutations), exemestane-everolimus, fulvestrant monotherapy, aromatase inhibitors (AI), elacestrant (for *ESR1* mutated tumours), trastuzumab deruxtecan (for HER2-low tumours), and chemotherapy. At least two lines of endocrine-based therapy are preferred before moving to chemotherapy (Gennari et al, Annals of Oncology, 2021). For several treatment options, data in CDK4/6-pretreated patients (e.g. alpelisib) is limited.

3.1.3. Main clinical studies

The application is based on the pivotal EMBER-3 study, a global, open-label phase 3, randomized, 3-arm study of imlunestrant (N=331) (arm A), investigator's choice of endocrine therapy of either fulvestrant or exemestane (SOC) (N=330) (arm B), and imlunestrant plus abemaciclib (N=213) (arm C) in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. Initially, patients were randomized 1:1 between the imlunestrant arm and the SOC arm. The imlun+abema arm was added in amendment (a) which was approved in October 2021 prior to first patient entering treatment. Randomization was stratified based on previous treatment with any CDK4/6 inhibitor (yes/no), presence of visceral metastases (yes/no), and region (East Asia versus North America/Western Europe versus Other). Baseline *ESR1*-mutation

status was determined by circulating tumour DNA analysis of plasma collected prior to initiating study treatment. Overall, 37% of patients had an *ESR1*-m-detected.

The studied dose of imlunestrant was 400 mg PO QD both as monotherapy and in combination with abemaciclib (150 mg PO BID). Study treatment was continued until disease progression or unacceptable toxicity.

The primary efficacy endpoint was PFS as assessed by investigator in the ITT and in the *ESR1*mutated population between arm A and arm B comparison, and PFS as assessed by investigator in the ITT between arm C and arm A. OS was the key secondary endpoint.

3.2. Favourable effects

As of the DCO date (24 June 2024), the study met one of its primary objectives for imlunestrant monotherapy, reporting a statistically significant improvement in investigator-assessed PFS in the *ESR1*m-detected population (N=256). Median PFS was 5.49 months (95% CI: 3.91, 7.39) in the imlunestrant arm versus 3.84 months (95% CI: 3.68, 5.52) in the SOC arm, HR:0.617 (95% CI: 0.464, 0.821; p = 0.0008). Regarding the key secondary endpoint, based on the OS (DCO: 18 August 2025), median OS was 34.50 months (95% CI: 25.43, NR) in the imlunestrant arm and 23.1 months (95% CI: 18.43, 28.94) for the SOC (HR: 0.603; 95% CI: 0.425, 0.856).

3.3. Uncertainties and limitations about favourable effects

The use of investigator-assessed PFS is prone to bias in the context of an open-label study, introducing uncertainty on the magnitude of the effect/true effect size.

Although a sensitivity analysis was performed using BIRC-assessed PFS, the majority of patients did not continue assessments after the investigator-assessed progression and therefore the BIRC-assessed PFS cannot be reliably estimated.

3.4. Unfavourable effects

Most patients experienced at least one treatment emergent adverse event (TEAE) in the pivotal study EMBER-3 (82.6%) and just above half of these were treatment-related.

Fatigue (22.6%), diarrhoea (21.4%), and nausea (17.1%) were the most common TEAEs, followed by arthralgia (14.1%), aspartate aminotransferase increased (12.5%), back pain (10.7%), and alanine aminotransferase increased (10.4%). These are known AEs for ET. Other AEs known for ET, such as hot flushes and musculoskeletal and joint pain, were observed at the same order of magnitude as for the SOC.

Only diarrhoea (21.4% vs 11.7%) and fatigue (22.6% vs 13.3%) were more frequently reported (differences >5%) in the imlunestrant monotherapy arm compared to the standard of care arm.

Grade ≥3 TEAEs were observed at comparable rates for imlunestrant and SOC (17.1% vs. 20.7%). Most frequently observed grade 3 or 4 AEs with imlunestrant were anaemia and neutropenia (2.1% each), and gamma-glutamyltransferase increased (1.5%). Grade ≥3 AEs for diarrhoea and nausea occurred in one patient (0.3%) each.

Serious adverse events (SAEs) were observed in 10.4% of subjects, comparable to the SOC (11.4%).

Overall, 19.0% of the patients had died in the imlunestrant arm, of which 12 (3.7%) on therapy or within 30 days of treatment discontinuation. Five patients (1.5%) died due to adverse events (single

events each). Three patients died from gastrointestinal bleedings in the imlunestrant monotherapy arm.

The overall discontinuation rate due to AEs in the EMBER-3 study was 4.3% in the imlunestrant monotherapy arm and 1.2% in the SOC arm. Most common AE leading to discontinuation was alanine aminotransferase increased (n=3; 0.9%) and the only event occurring in more than one patient. The incidence of dose adjustments (reduction or drug withheld) was 10.4% in the imlunestrant arm and 7.1% in the SOC arm. Dose reductions occurred in 2.4% (n=8) of patients.

The safety profile was independent of *ESR1*-mutation status.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 114 Effects Table for imlunestrant monotherapy for the treatment of adult patients with ER-positive, HER2-negative, advanced or metastatic breast cancer, previously treated with endocrine based regimen – EMBER-3 (data cut-off: 24-June 2024, OS IA3: 18 August 2025).

Effect	Short Description	Unit	Imlunestrant	Imlun + abema	SOC	Uncertainties/ Strength of evidence	References
Favourable Effects							
Imlunestrant monotherapy - ESR1m-detected population							
PFS	Progression-free survival by investigator	Median in months (95% CI)	5.49 (3.91, 7.39)		3.84 (3.68, 5.52)	HR: 0.617 (95% CI: 0.464, 0.821) Internal validity uncertain due to late study amendments Open-label study, PFS by BIRC not reliable	CSR
OS IA3	Overall Survival	Median in months (95% CI)	34.50 (25.43, NR)		23.10 (18.43, 28.94)	HR: 0.603 (95% CI: 0.425, 0.856) Immature; event rate 41.3% and 60.2%	CSR
Unfavourable Effects							
Grade≥3 AEs	Incidence	%	17.1	48.6	20.7		CSR
SAEs	Incidence	%	10.4	16.8	11.7		CSR
AES leading to discontinuation	Incidence	%	4.3	6.3	1.2		CSR
Transaminases increased	Incidence	%	15.6	20.2	14.8	One case of DILI reported (Arm C).	CSR
	Incidence (Grade≥3)		1.2	5.3	1.2		CSR
Diarrhoea	Incidence	%	21.4	86.1	11.7	Only one patient discontinued therapy (Arm C).	CSR
	Incidence (Grade≥3)		0.3	8.2	0		CSR
Nausea	Incidence	%	17.1	48.6	13.0	Zero patients discontinued therapy.	CSR
	Incidence (Grade≥3)		0.3	1.9	0		CSR

Abbreviations: BIRC = blinded Independent Review Committee; NR: not reached; HR: Hazard ratio; CI: confidence interval; AE: adverse event; SAE: serious adverse event
Notes: Unfavourable effects were based on the EMBER-3 safety population

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint of investigator-assessed PFS showed a statistically significant, but small difference in favour of **imlunestrant monotherapy** compared to SOC in the population with an *ESR1* mutation. The difference in PFS was only observed at and after the first scan at 8 weeks. While the investigator-assessed PFS in an open label study is concerning, based on the available information, it can be concluded that there are no strong signals of differential systematic bias for the investigator-assessed PFS that favoured Arm A compared with Arm B in the *ESR1*-m population. However, BIRC-assessed PFS cannot be reliably estimated. The improvement in mPFS of 1.7 months is in the same order of magnitude as previously shown for Orserdu (mPFS gain of 1.9 month) in a CDK4/6i-pretreated population based on IRC-assessed PFS. No PFS benefit of imlunestrant vs SOC was shown in the ITT population (*ESR1*m-detected and *ESR1*m-not detected).

Subgroup analyses were generally supportive of the primary analysis in the *ESR1*m-detected population, although the interpretation is hampered by small numbers in some subgroups in combination with the overall limited magnitude of effect.

The key secondary endpoint OS was not statistically different between the imlunestrant monotherapy and SOC arms in the *ESR1*-mutated population, though reassuringly the KM curve did not show a signal of a detriment and even separated in favour of imlunestrant monotherapy. A trend towards OS improvement at OS IA3 continues to be observed with imlunestrant monotherapy in the *ESR1*m-detected population.

Overall, the safety profile of the oral SERD **imlunestrant as monotherapy** in the proposed target population is similar to that known for endocrine therapies and especially fulvestrant and elacestrant. The main difference is an increase in GI toxicity which may be partly related to the difference in route of administration when compared to fulvestrant. Most events were mild to moderate and discontinuations or dose reductions occurred at low rates. Other AEs known for ET, like fatigue/asthenia, elevated hepatic enzymes, hot flushes and musculoskeletal and joint pain were observed at the same order of magnitude as for the SOC.

3.7.2. Balance of benefits and risks

The benefit-risk is positive for imlunestrant.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Inluriyo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Inluriyo is favourable in the following indication:

Inluriyo is indicated as monotherapy for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen (for biomarker-based patient selection, see section 4.2).

In pre- or perimenopausal women, or men, Inluriyo should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that imlunestrant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously

authorised within the European Union.