22 May 2025
EMA/CHMP/122122/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Itovebi

International non-proprietary name: inavolisib

Procedure No. EMEA/H/C/006353/0000

Note

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

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List of abbreviations

ADC	antibody-drug-conjugate
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-∞	AUC from 0 to infinity
BC	breast cancer
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BICR	blinded independent central review
BMI	body mass index
BOR	best objective response
BPI-SF	Brief Pain Inventory-Short Form
BSA	body surface area
CBR	clinical benefit rate
CCOD	clinical cutoff date
CDK	cyclin-dependent kinases
CDK4/6	cyclin-dependent kinase 4 and 6
CDx	companion diagnostic
CfDNA	cell-free DNA
CFU	colony forming units
CHMP	Committee for Medicinal Products for Human use
CL	clearance
Cmax	maximum concentration observed
CQA	critical quality attribute
CR	complete response
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
ctDNA	circulating tumour DNA
CYP	cytochrome P450
DDI	drug-drug interaction
DoE	design of experiments
DOR	duration of response
DSC	differential scanning calorimetry
EC	European Commission
ECG	electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life 5 Dimension, 5-Level questionnaire
ER	oestrogen receptor
ET	endocrine therapy

EU	European Union
F1CDx	FoundationOne® Companion Diagnostic
F1LCDx	FoundationOne® Liquid Companion Diagnostic
FAS	full analysis set
FMI	Foundation Medicine Inc
FT-IR	Fourier transform infrared spectroscopy
GC	gas chromatography
GDC-0077	inavolisib
GMP	good manufacturing practice
GMR	geometric mean ratios
HbA1C	glycosylated haemoglobin
HER2-negative /HER2-	human epidermal growth factor receptor 2-negative
HER2-positive /HER2+	human epidermal growth factor receptor 2-positive
HPLC	high performance liquid chromatography
HR	hazard ratio
HR-positive/HR+	hormone receptor-positive
HRQoL	health related quality of life
HS-GC	head space gas chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	in-process control
iPSP	initial paediatric study plan
IR	infrared
ITT	intent-to-treat
IV	intravenous
IVDR	in-vitro diagnostic regulation
KF	Karl Fischer titration
LA	locally advanced
LDPE	low density polyethylene
LoQ	list of questions
LT	less than
MAA	marketing authorisation application
MATE	multidrug and toxic compound extrusion
mBC	metastatic breast cancer
MRI	magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCA	non-compartmental analysis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	new drug application
NGS	next-generation sequencing
NLT	not less than
NMR	nuclear magnetic resonance
NMT	not more than

OAT	organic anion transporter
OATP	organic-anion-transporting polypeptides
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
p110α	catalytic subunit of PI3Kα complex
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
PDCO	Paediatric Committee
PFS	progression-free survival
PFS2	proxy for time to second objective disease progression
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	product information
PI3K	phosphatidylinositol 3-kinase
PI3Kα	complex of p110α with a p85 regulatory subunit (see also p110α)
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (gene name/acronym)
PK	pharmacokinetic
PO	Oral
popPK	population pharmacokinetic
PR	partial response
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
PT	preferred term
QbD	quality by design
QD	once daily
QOL	quality of life
QTc	corrected QT interval
QTPP	quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
RF	role functioning
RH	relative humidity
RMP	risk management plan
RSI	request for supplementary information
rwPFS	real-world PFS
SAEs	serious adverse events
SAP	statistical analysis plan
SAS	safety analysis set
SBP	summary of biopharmaceutical studies
SCE	summary of clinical efficacy
SCP	summary of clinical pharmacology
SCS	summary of clinical safety
SD	stable disease
SD	standard deviation
SERD	selective oestrogen receptor degrader

SmPC	summary of product characteristics
sPMA	supplemental premarket approvals
T1/2	half-life
TAMC	total aerobic microbial count
TDI	time-dependent inhibition
TMB	tumour mutational burden
TSE	transmissible spongiform encephalopathy
TTCD	time to confirmed deterioration
TYMC	total combined yeasts/moulds count
UV	ultraviolet
XR(P)D	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 29 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Itovebi, 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 26 April 2023.

The applicant applied for the following indication:

Itovebi in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

In pre- or perimenopausal women, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

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(s) P/0113/2020 on the granting of a (product-specific) 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(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active Substance status

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

Date	Reference	SAWP co-ordinators
25 July 2019	EMA/CHMP/SAWP/398206/2019	Serena Marchetti, Kristian Wennmalm

The scientific advice pertained to the following non-clinical and clinical aspects:

Non-clinical:

- Toxicology programme

Clinical:

- Clinical pharmacology programme
- Design of the Phase III Study, including target patient population, selection of the combination treatments and comparators, dose and schedule of inavolisib, primary and secondary endpoints, methods of statistical analysis and Type 1 error control, safety monitoring plan and risk mitigation strategy, central testing for *PIK3CA* mutation-positive patients, and PRO endpoints
- Overall development plan based on a single Phase III Study, and safety database to support registration

1.7. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Martin Mengel

The application was received by the EMA on	29 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 August 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	26 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 February 2025

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 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	March 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 April 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 Itovebi on	22 May 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	22 May 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication was:

Itovebi in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see SmPC section 5.1).

In pre- or perimenopausal women, endocrine therapy should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

2.1.2. Epidemiology and risk factors

Breast cancer is the most common cancer in the world, with an estimated 2.3 million new cases of female BC in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer globally, with an estimated 685,000 deaths. In Europe, an estimated 531,000 patients were diagnosed with BC in 2020, and 141,765 died from the disease (GLOBOCAN 2020).

2.1.3. Biologic features

BC is a molecularly diverse disease with several clearly defined molecular subgroups (Perou *et al*., 2000). Hormone receptor positive (HR+), HER2-negative (HER2-) BC is the most common BC subtype, accounting for approximately 70% of all BCs (Breast Cancer, Facts and Figures 2022-2024).

The PI3K signalling pathway is commonly dysregulated in HR+ BC, often due to activating *PIK3CA* mutations. *PIK3CA* mutations occur in approximately 35-40% of HR+ BC patients and are negative prognostic markers (Fillbrunn *et al.,* 2022).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Almost all newly diagnosed BC cases are localised to the breast tissue and regional lymphatics and are potentially curable with surgical resection and a variety of treatment modalities. Patients with HR+ BC are recommended adjuvant endocrine therapy (ET), with the goal of preventing both early and late recurrence and, subsequently, death due to BC.

Despite adjuvant ET, recurrences are still common. Approximately 30-60% of patients with stage II and III BC suffer from recurrent disease. The risk of recurrence in patients with HR+, HER2- early BC is highest during the first 5 years after diagnosis, but still more than half of those who recur experience late recurrences (≥ 5 years from diagnosis). The prognosis for HR+, HER2- BC with distant metastases is poor, with 5-year survival of 34% (SEER 2023).

2.1.5. Management

For locally advanced (LA) and metastatic BC (mBC), curative surgery is not a treatment option. Instead, for HR+, HER2- LA/mBC the current treatment options include endocrine therapy (ET), chemotherapy, and several targeted therapies. The treatment goal is to stabilise and decrease the tumour burden, aiming at delaying disease progression and death due to BC.

For advanced HR+, HER2- BC, sequential endocrine-based therapies to control the disease and delay chemotherapy are used in most cases. Standard of care first- and second-line treatment for LA/mBC is either an aromatase inhibitor (AI) or fulvestrant in combination with a CDK4/6 inhibitor, whereas ET monotherapy may be appropriate for frail patients with comorbidities. The treatment approach for men with LA/mBC is the same as for women. In pre- and perimenopausal women ovarian function suppression or ablation is recommended in addition to ET (ESMO 2023; NCCN 2024, Vasconcelos de Matos *et al.,* 2023).

For patients who relapse after ET plus a CDK4/6 inhibitor the treatment options are tailored depending on several factors including clinical (e.g., disease burden), molecular (e.g., presence of somatic *PIK3CA*, *AKT1*, *PTEN*, or *ESR1* mutations), response to prior agents (treatment resistance), patient preference, and treatment availability. For example, ET monotherapy (e.g., AIs, fulvestrant, and elacestrant for ESR1 mutated tumours), the PI3Kα inhibitor alpelisib plus fulvestrant for *PIK3CA* mutated tumours, the mTOR inhibitor everolimus plus ET, and the AKT inhibitor capivasertib plus fulvestrant for *PIK3CA/AKT1/PTEN* altered tumours. In some cases, a second-line CDK4/6 inhibitor + ET may be used (ESMO 2023; NCCN 2024).

Although other available therapies, not directed against PI3Kα, are efficacious in patients with *PIK3CA* mutated LA/mBC, these tumours may derive less benefit compared to *PIK3CA* wildtype tumours. Furthermore, this disease setting is incurable and inevitably leads to death. Thus, there is a high unmet need for further treatment enhancements in this patient population.

2.2. About the product

Inavolisib is an inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the *PIK3CA* gene). In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader). The PI3K signalling pathway is commonly dysregulated in HR-positive breast cancer, often due to activating *PIK3CA* mutations. With its dual mechanism of action, inavolisib inhibits the activity of downstream PI3K pathway targets, including AKT, resulting in reduced cellular proliferation and induction of apoptosis in *PIK3CA*-mutated breast cancer cell lines.

The finally approved indication was:

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In pre/perimenopausal women and in men, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

The recommended dose of Itovebi is 9 mg taken orally once daily with or without food.

Itovebi should be administered in combination with palbociclib and fulvestrant. The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. The recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, and 29, then once monthly thereafter.

Treatment of pre/perimenopausal women and men with Itovebi should also include an LHRH agonist in accordance with local clinical practice.

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment. The recommended first dose reduction is 6 mg daily and the second dose reduction is 3 mg daily. Treatment should be permanently discontinued if the 3 mg daily dose is not tolerated.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the lack of a demonstrated effect on OS (at time of the request for accelerated assessment), as it is not considered that, in a setting like this, a PFS effect of the present magnitude, in the absence of a demonstrated effect on OS, is sufficient to address an 'unmet medical need' in the sense required for accelerated assessment.

On 17/05 2019 the applicant Roche Registration GmbH requested scientific advice from the CHMP (EMEA/H/SA/4185/1/2019/III) for their product RO7113755 (now inavolisib). The advice regarded the preclinical and clinical development programme and registration strategy for inavolisib + the CDK4/6 inhibitor palbociclib + fulvestrant for the treatment of patients with *PIK3CA* mutant, HR+, HER2- LA/mBC following progression on or after adjuvant ET in the phase III study WO41554.

The development programme was considered generally acceptable. Further justifications for selection criteria and the proposed dose and administration schedule were requested. Specifically, inclusion of patients with well controlled type 2 diabetes with implementation of an adequate treatment algorithm in case of worsening of hyperglycaemia was recommended. The sample size, analysis populations, and other statistical methods including type I error control were considered acceptable, except for the applicant's plan to eventually introduce an additional interim analysis when the study was running, which was discouraged.

The applicant proposed to enrol patients with *PIK3CA* mutations identified through central testing with the blood-based clinical trial assay FoundationOne Liquid CDx or using pre-existing *PIK3CA* test results from local laboratories. Tumour tissue was proposed to be provided when feasible. It was stated in the advice that the test instrument, regardless of which used, should be validated. Although blood-based testing confers convenience benefits over tumour testing, the ctDNA assays do not capture all genomic

aberrations detected in tumour tissue. This might affect concordance evaluation between blood-based and tumour tissue testing and potentially impact evaluations of findings in the respective subgroups.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 3 mg or 9 mg of inavolisib.

Other ingredients are:

Tablet core: lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460), sodium starch glycolate.

Film-coating: polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), macrogol, talc (E553b), iron oxide red (E172) and iron oxide yellow (E172) (9 mg film-coated tablets only).

The product is available in Alu/Alu (aluminium/aluminium) perforated unit dose blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. *General information*

The chemical name of inavolisib is (2S)-2-[[2-[(4S)-4-(difluoromethyl)-2-oxo-oxazolidin-3-yl]-5,6-dihyroimidazo[1,2-d][1,4]benzoxazepine-9-yl]amino]propanamide corresponding to the molecular formula $C_{18}H_{19}F_2N_5O_4$. It has a molecular weight of 407.37 g/mol and the following structure:

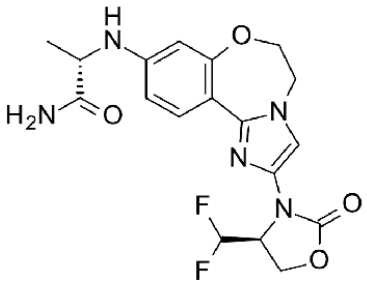


Figure 1. Active substance structure

The chemical structure of inavolisib was elucidated by a combination of elemental analysis, UV spectroscopy, IR spectroscopy, mass spectrometry, ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR and single crystal X-ray diffraction analysis. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD).

The active substance is a white to off-white, greyish pink, greyish orange, or greyish yellow powder or powder with lumps. The active substance is soluble in organic solvents and its aqueous solubility is pH-dependent with the greatest solubility at low pH, and solubility decreasing with increasing pH. The active substance is non-hygroscopic.

Inavolisib exhibits stereoisomerism due to the presence of two chiral centres, which originate from the starting materials. The crystal structure was studied by X-ray crystallography, which confirmed the absolute configuration of the two stereo-centres in inavolisib (S,S).

Polymorphism has been observed for inavolisib. All forms were characterised by various techniques: DSC, TGA, XRPD, IR spectroscopy, Raman spectroscopy, and DVS analysis. Form A is the most thermodynamically stable form at ambient conditions and was selected for the finished product development. Results from the stability studies performed on the active substance indicate that no change to the polymorphic form occurs during long-term and accelerated conditions. The active substance specification includes identity testing by XRPD for the confirmation of the correct polymorphic form.

2.4.2.2. *Manufacture, characterisation and process controls*

Satisfactory GMP documentation on the active substance manufacturer has been provided

The active substance is synthesised using well defined starting materials with acceptable specifications

The active substance manufacturing process consists of several transforming steps and one re-crystallisation step. Adequate description has been provided.

Adequate in-process controls (IPCs) are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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

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

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified.

The manufacturing process has been developed using elements of QbD such as risk assessment and design of experiment (DOE) studies. No design space has been claimed.

The active substance is packaged in a double LDPE bag placed in a metal drum, which complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. *Specification*

The active substance specification shown in Table 1 includes tests for appearance (visual), identification (FT-IR, HPLC, XRPD), assay (HPLC), impurities (HPLC), chiral impurities (HPLC), water content (KF), residual solvents (HS-GC), residue on ignition (Ph. Eur.), particle size (laser diffraction), microbial limits (Ph. Eur.).

The specification parameters for inavolisib were established based on applicable ICH guidelines, and information obtained during development; the proposed limits have been adequately justified.

The initially proposed assay acceptance criteria have been tightened as requested.

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 limits for other impurities are set below the relevant qualification threshold and in line with ICH Q3A requirements.

The active substance has two chiral centres and was developed as a single enantiomer of the S,S-configuration. Two chiral centres give the possibility to form four different stereoisomers. All three undesired stereoisomers are controlled in the specification of the active substance and their limits are acceptable per ICH Q3A or qualified.

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 the active substance and specified impurities has been presented.

Batch analysis data from six batches at commercial scale of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. *Stability*

Stability data from three pilot scale batches of active substance manufactured with a process representative of the commercial process from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Long-term conditions are different from those outlined in ICH Q1A guideline, however, this has been considered acceptable as the conditions applied represent worse case conditions. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions of high temperature, high temperature and humidity, neutral, acidic and basic solution at high temperature, peroxide-mediated oxidation, electron-mediated oxidation, and light in solution were also provided on one batch.

The following parameters were tested*:* description, XRPD, assay, organic impurities, chiral impurities, water content, particle size, and microbial quality. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no trends have been observed.

The active substance showed photosensitivity when exposed to ICH Q1B conditions. Therefore, the following storage conditions have been defined: "Store in the original container in order to protect from light."

Results from a stress study in solution showed that the active substance is stable in neutral conditions, but several degradation products were observed in all other conditions (basic, peroxide-mediated oxidation, electron-mediated oxidation, and light). The results from the forced degradation studies demonstrate the suitability and specificity of the release HPLC method to separate and identify potential degradation products in the active substance.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period and storage condition.

2.4.3. Finished Medicinal Product

2.4.3.1. *Description of the product and pharmaceutical development*

The finished product is a film-coated tablet containing either 3 mg or 9 mg of inavolisib active substance.

The 3 mg film-coated tablet is red, round convex shaped with an "INA 3" debossing on one side and approximate diameter of 6 mm.

The 9 mg film-coated tablet is pink, oval with an "INA 9" debossing on one side and approximate size of 13 mm (length), 6 mm (width).

The composition of the two finished product presentations has been provided.

The compositions of the 3 mg and the 9 mg tablet cores are proportional. The film-coating blends differ, with the total amounts being proportional.

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. One excipient (lactose monohydrate) is of animal origin and a TSE declaration has been provided.

The pharmaceutical development followed an enhanced approach including elements of a QbD and risk-based methodology. The Quality target product profile (QTTP) for the proposed product was defined during development as an immediate-release tablet, which is palatable and can be swallowed easily, and allows to achieve the required dosage.

The following Critical Quality Attributes (CQAs) were identified as being potentially impacted by the manufacturing process variables and were investigated in development studies: appearance, content, uniformity of dosage units, water content, and dissolution.

Polymorphic Form A has been selected for product development and its stability during finished product storage has been demonstrated.

The active substance aqueous solubility is pH dependent with the greatest solubility at low pH, and solubility decreasing with increasing pH. Inavolisib is highly soluble over the physiological pH range. Due to its moderate permeability, the active substance is considered as BCS Class 3.

Different formulations were evaluated during development and detailed information has been provided. The proposed commercial formulation has evolved from several clinical formulations, with adaptations implemented to address dosage strengths and active substance load. A film-coat was introduced to mitigate the light sensitivity of the active substance. The colour of the intended commercial formulation has been optimised.

Changes in the formulation during development have been bridged by in vitro dissolution studies. During the procedure, a Major Objection (MO) has been raised to question the in-vivo relevance of the dissolution method. In addition, it was requested to demonstrate the discriminatory power of the dissolution method. Also, it was requested to amend the finished product specification limits for dissolution testing based on representative batches used in the pivotal Phase III clinical studies. Although the dissolution method did not fulfil all formal requirements for formulation bridging or discriminatory properties, it is acknowledged that the core tablets of all formulations are of the same qualitative composition and the formulations do not contain any excipients that may affect active substance absorption and the relative amounts of excipients are very similar. Furthermore, the absorption is fast, independent from food, and comparable systemic exposure has been shown for the formulations. In relation to the dissolution specification limits based on dissolution data from relevant clinical batches, the initially proposed limit for the 3 mg tablets was considered acceptable and the revised limit for the 9 mg tablets was considered acceptable.

The manufacturing process for the finished product is considered to be a standard manufacturing process and consists of blending, sieving, roller compaction, tablet compression, film coating of tablets and packaging. The manufacturing process development has been described. During initial development the manufacturing process was similar compared to the proposed commercial process. Only minor adaptations have been applied to increase active substance load, modify filler composition, decrease tablet weight, and adapt film-coat colour. Development was conducted at both development and commercial manufacturing sites. The applicant has applied QbD elements in some development of the finished product manufacturing process. The manufacturing development has been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed in order to define critical process steps and process

parameters that may have an influence on the finished product quality attributes. The critical process parameters have been adequately identified. No design space has been claimed.

The primary packaging is Alu/Alu (aluminium/aluminium) perforated unit dose blisters. 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*

Satisfactory GMP documentation for the finished product manufacturer has been provided.

The manufacturing process consists of seven main steps: sieving, blending, roller compaction, final blending, tablet compression, film-coating and packaging.

The level of details included in the manufacturing process description is considered adequate. The IPCs are adequate for this type of manufacturing process and pharmaceutical form. Proven acceptable ranges have been defined for several manufacturing steps and considered acceptable.

A process validation scheme has been presented outlining the process validation to be conducted. As the process is considered to be standard, the proposal for prospective validation is considered acceptable.

The proposed bulk holding time is acceptable.

2.4.3.3. *Product specification*

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description (visual), identification (HPLC, FT-IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), water content (KF, Ph. Eur.), dissolution (HPLC), microbiological quality (Ph. Eur.).

The specification parameters are in line with relevant ICH guidelines and proposed limits have been adequately justified.

The degradation products limits during shelf life for specified and unspecified impurities are set in accordance with the ICH Q3B guideline, while tighter limits are applied at release. Total related substances acceptance criteria are tighter at release than during shelf life. All other limits are the same for release and shelf life.

No mutagenic degradation products was identified in the finished product. Nevertheless, considering the advanced cancer indication, applying ICH Q3B thresholds for the specification limits for degradation products is considered acceptable in line with ICH S9.

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. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active

substance or the related finished product exceeding levels allowed for ICH S9 indications. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for six primary stability batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. *Stability of the product*

Stability data from three primary batches of each finished product presentation stored for up to 12 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing (presenting a different imprint) and were packed in a primary packaging representative of that proposed for marketing. The selected long-term condition corresponds to worse case condition and, therefore, were considered acceptable. Supportive stability data have been provided for up to 36 months under long term conditions.

Samples were tested for description, assay, degradation products, dissolution, water content and microbial limit. The analytical procedures used are stability indicating.

Slight decrease in assay and increase in degradation products were observed at long term conditions. These changes were considered not significant.

The submitted post-approval stability protocol is considered acceptable. In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch of each product presentation was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed.

Forced degradation studies were performed on at the following conditions: exposure to acid, base, oxidation, high temperature, high temperature and humidity Degradation of the finished product was observed under dry heat. Inavolisib is stable in neutral solution, whereas degradation is observed in the presence of acid or base, oxidation reagents and metal ions. The finished product is very unstable in solution in the presence of light.

Based on available stability data, the proposed shelf-life of 2 years with no special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.5. *Adventitious agents*

One excipient of animal origin is used: lactose monohydrate.

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion 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.

During the procedure one major objection (MO) concerning quality aspects was raised. This concerned the dissolution method for bridging of formulations used during clinical development and the finished product specification limit for dissolution test. The applicant has provided satisfactory justification and the dissolution specification limit for the 9 mg tablet strength has been tightened, as requested.

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.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

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. Data has been presented to give reassurance on TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Inavolisib has been evaluated in a comprehensive non-clinical package of in vitro and in vivo studies that were designed to characterise its pharmacology, safety pharmacology, pharmacokinetics and toxicity. Pivotal toxicology studies were conducted in compliance with GLP.

2.5.2. Pharmacology

2.5.2.1. *Primary pharmacodynamic studies*

In vitro

The biochemical potency in an enzymatic assay for the PI3K isoforms (alpha, beta, delta, and gamma) of inavolisib was determined.

Table 1. PI3K Isoform Biochemical Selectivity of Inavolisib

	PI3Ka	PI3Kb	PI3Kd	PI3Kg
Ki (nM)	0.038 ± 0.003	101.7 ± 12.1	12.8 ± 2.15	21.8 ± 1.16
Fold Selectivity (relative to PI3Kα)	NA	2676	337	574

The selectivity of inavolisib in a panel of kinases was determined. Inavolisib inhibited 3 of 224 kinases in the Invitrogen kinase panel at > 80% at 1 μM.

Table 2. Kinase Selectivity of Inavolisib

Kinase	ATP Conc. (mM)	IC_{50} (mM)	Selectivity over PI3Ka
PI3Ka	40	0.0000283	NA
DNA-PK	$K_{m\ app}$	4.28	152857
PI3KC2a	$K_{m\ app}$	10	No inhibition at 10 mM
PI3KC2b	10	0.056	2000
PI3KC2b	10	0.0694	2479
PI3KC3_hVPS34	$K_{m\ app}$	10	No inhibition at 10 mM
PI4Ka	10	10	No inhibition at 10 mM
PI4Kb	$K_{m\ app}$	10	No inhibition at 10 mM

Inavolisib demonstrated a stronger effect in matched isogenic SW48 lines colon cancer cells H1047R and E545K (engineered to express H1047R or E545K hotspot alterations, respectively, knocked into one allele of the *PIK3CA* locus) than in SW48 WT. When assayed by the pPRAS40 assay, inavolisib was 2.4-fold more potent in E545K cells and 2.6-fold more potent in H1047R cells relative- to the *PIK3CA*-WT parental cells.

The treatment of cells with inavolisib leads to depletion of p110α protein, specifically in the HCC1954 human epidermal growth factor receptor (HER2)-positive cell line that contains the hotspot H1047R *PIK3CA* alteration. Inavolisib did not change the p110a protein level in the HDQ-P1 cell line that is WT for *PIK3CA*.

A study in ER-positive, HER2-negative *PIK3CA* E545K-mutated MCF7 cells was performed to determine whether inavolisib potentiates the activity of fulvestrant or palbociclib. Inavolisib showed modest synergy in combination with fulvestrant or palbociclib in MCF7 cells.

In vivo

Inavolisib was orally administered QD in SCID beige mice bearing orthotopic KPL4 human breast cancer xenografts at doses ranging from 1 to 50 mg/kg. Dose-dependent TGI was observed, with the greatest anti-tumour response of 153% TGI noted at the MTD of 50 mg/kg. Tolerability of PO QD administration of inavolisib was assessed by percent change in body weight during the course of- the study. Human KPL4 breast tumours- secrete interleukin 6 (IL6), which induces cachexia, and as a result body weight loss is commonly observed in the absence of treatment. Overall body weight loss was less pronounced with an increase in dose, likely related to the decrease in tumour- burden and associated IL-6 levels.

Inavolisib was administered PO QD at doses ranging from 0.5 to 50 mg/kg to NCr nude mice bearing orthotopic HCC1954X1 human breast cancer xenografts. Dose-dependent TGI was observed from 2.5 to 50 mg/kg, with the greatest anti-tumour response of 149% TGI observed in the highest-dose group of 50 mg/kg. All doses were well tolerated, with the exception of the 50 mg/kg dose.

Inavolisib (25 mg/kg), palbociclib (50 mg/kg), or the combination were administered PO QD to nu/nu mice bearing orthotopic MCF7 human breast cancer xenografts. On Day 21, inavolisib at 25 mg/kg resulted in 63% TGI, while palbociclib at 50 mg/kg resulted in 44% TGI. The combination of inavolisib with palbociclib resulted in increased TGI and PRs at the end of treatment on Day 21 (114% TGI, 4 PRs

out of 12 animals) when compared with each single agent alone. Oestrogen is required for growth of ER-positive MCF7 tumour cells in vivo, and toxicity associated with body weight loss is commonly observed in mice supplemented with oestrogen. Apart from the weight loss associated with oestrogen administration, the doses tested for inavolisib, palbociclib, and the combination of both drugs were tolerated.

Inavolisib was administered at 25 mg/kg PO QD, and fulvestrant was administered at 5 mg/mouse SC QW to nu/nu mice bearing orthotopic MCF7 human breast cancer xenografts. At the end of treatment on Day 21, inavolisib at 25 mg/kg resulted in 82% TGI, while fulvestrant at 5 mg/mouse resulted in 52% TGI. The combination of inavolisib with fulvestrant resulted in greater TGI on Day 21 (96% TGI) compared with each single agent alone. Apart from the weight loss associated with oestrogen administration, the doses tested for inavolisib, fulvestrant, and the combination of both drugs were tolerated.

A triple combination study was conducted to determine the efficacy of palbociclib, fulvestrant, or inavolisib dosed as single agents, the combination of inavolisib with palbociclib or fulvestrant, or the combination of all three drugs in the MCF7 *PIK3CA*-mutated breast cancer xenograft model established in nu/nu mice. At the end of treatment on Day 20, inavolisib at 25 mg/kg PO QD resulted in 61% TGI; palbociclib at 50 mg/kg PO QD resulted in 49% TGI; and fulvestrant at 5 mg/mouse QW SC resulted in 20% TGI. On Day 20, the combination of palbociclib with fulvestrant at the same doses as single agents resulted in 62% TGI; the combination of inavolisib with fulvestrant resulted in 79% TGI; and the combination of inavolisib with palbociclib resulted in 102% TGI. The triple combination of inavolisib, palbociclib, and fulvestrant resulted in greater TGI on Day 20 (119%) when compared with each single agent as well as the doublet combinations. With the exception of the weight loss associated with oestrogen, the doses tested for inavolisib, palbociclib, fulvestrant, and the combination of each drug were tolerated on the basis of < 10% body weight loss over the course of the study when compared with the vehicle control group.

2.5.2.2. *Secondary pharmacodynamic studies*

No significant off-target responses (> 50% inhibition or stimulation of control specific-binding) were identified when inavolisib was evaluated in radioligand binding and enzyme assays at a concentration of 10 μM against 88 targets (including those associated with abuse liability), including major classes of biogenic amine receptors, neuropeptide receptors, ion channels, neurotransmitter transporters, and enzymes.

2.5.2.3. *Safety pharmacology programme*

Cardiovascular

Inavolisib does not show significant inhibition of cardiac hERG, sodium, or calcium channels in vitro at clinically relevant concentrations. The IC_{50} for inhibition of hERG current was > 1700 times higher than the human plasma C_{max} [unbound] (0.116 μM) at the 9 mg dose.

In the single dose telemetry- instrumented dog safety pharmacology study, inavolisib-related cardiovascular (CV) effects included generally dose dependent, reversible and non-adverse decreases in heart rate, increases in arterial pressure and contractility, lengthening of PR and QT intervals (likely driven by the decreased heart rates), and minimally lengthened corrected QT (QTc) interval (+ 11 msec/+ 5%) at doses ≥ 0.3 mg/kg. The C_{max} [total] at the no observed- adverse- -effect level (NOAEL) of 3 mg/kg was 679 ng/mL (9.0 × the C_{max} of 75.1 ng/mL at 9 mg in the clinic).

Central nervous system

A general behaviour and neurobehavioral assessment (functional observation battery [FOB]) was integrated in the 4-week general toxicity study in rats, and no findings were attributed to inavolisib up to 10 mg/kg.

Respiratory system

Assessments of respiratory function were integrated into the GLP 1- and 3-month repeat-dose toxicity studies in dogs. No effects on respiratory rate were observed up to 1.5 mg/kg in dogs.

2.5.2.4. *Pharmacodynamic drug interactions*

No PD drug interaction studies have been conducted.

2.5.3. Pharmacokinetics

2.5.3.1. Analytical methods

In the GLP studies, inavolisib concentrations were quantified using LC-MS/MS assays that were developed and validated in both Sprague Dawley rat and beagle dog plasma.

2.5.3.2. Absorption

Table 3. Pharmacokinetics (Mean ± SD) of Inavolisib following Single-Dose IV and PO Administration to Mice, Rats, Dogs, and Monkeys

Parameters	CD-1 Mice (Female)	Sprague-Dawley Rats (Male)	Beagle Dogs (Male)	Cynomolgus Monkeys (Male)
Dose (mg/kg)	1 [a]	5 [b]	1 [a]	1 [b]
CL (mL/min/kg)	37.3 ± 4.24	86.2 ± 10.0	6.32 ± 1.69	10.2 ± 1.98
$t_{1/2}$ (hr)	0.727 ± 0.629	2.05 ± 0.664	4.75 ± 0.574	3.81 ± 1.45
V_{SS} (L/kg)	1.36 ± 0.454	3.74 ± 0.734	2.01 ± 0.571	1.96 ± 0.0239
Renal clearance (mL/min/kg)	ND [c]	15.6 ± 1.56	1.79 ± 0.0611	3.11 ± 0.657
Dose (mg/kg)	25 [d]	5 [a]	1 [a]	1 [b]
C_{max} (μM)	7.95 ± 3.83	0.641 ± 0.567	0.684 ± 0.123	0.270 ± 0.0956
t_{max} (hr)	0.833 ± 0.289	0.417 ± 0.144	1.67 ± 1.15	4.00 ± 1.73
AUC_{inf} (μM•hr)	32.8 ± 13.0	1.38 ± 0.985	4.53 ± 0.740	2.37 ± 0.311
F (%)	100 ± 47	57.6 ± 41.1	66.1 ± 10.9	57.5 ± 7.46

2.5.3.3. Distribution

The percent of inavolisib bound to proteins in mouse, rat, rabbit, dog, cynomolgus monkey, and human plasma was low to moderate, ranging from 27% to 75% bound and was independent of the concentration in the range tested (0.1–10 μM).

Following a single PO dose of 3 mg/kg [^{14}C]inavolisib to male and female pigmented and male nonpigmented rats, inavolisib-related radioactivity was extensively distributed in rat tissues and organs. The endocrine metabolic/excretory, and ocular tissues, as well as the tissues in the

gastrointestinal tract contained the highest distribution of [^{14}C]inavolisib-derived radioactivity. By 672 hours postdose, levels of radioactivity in all tissues were below quantifiable levels except in the adrenal gland, medulla and cortex, and uveal tract, where concentrations remained quantifiable at 1344 hours postdose. Concentrations in the CNS tissues were low or lower than the limit of quantitation for the entire duration of the study.

2.5.3.4. Metabolism

Inavolisib was the most abundant drug related component- in rat plasma, urine, feces, and bile. Metabolites M5 (imidazole ring cleavage) and M27 (−29 amu) accounted for 7.3% and 3.6% of the total drug related- plasma exposure, respectively. No human-specific metabolites (> 10% of total circulating radioactivity exposure) were observed in plasma upon comparison of metabolites from [14C] inavolisib in vivo studies in rat and humans.

2.5.3.5. Excretion

The primary route of elimination of inavolisib and drug-related radioactivity in rats was the feces (57%–64% of the dose), followed by elimination in urine (23%–35% of the dose) and bile (9%–15% of the dose).

2.5.4. Toxicology

Inavolisib was assessed in a series of non-clinical toxicology studies in rats and dogs.

The oral route of exposure was selected for these studies since the oral route is the intended clinical route of administration. The rat and dog were selected as the toxicology species based on high protein homology of the target, the demonstration of *in vivo* pharmacodynamics, adequate *in vivo* exposure, and comparable *in vivo* metabolic profile to humans.

2.5.4.1. *Single dose toxicity*

Non-GLP pilot single dose tolerability studies were conducted in a few rats and dogs following oral gavage administration. In rats, inavolisib caused dose-dependent body weight loss and transient increases in glucose at ≥15 mg/kg. The MTD was considered to be above 30 mg/kg, the highest dose tested, corresponding to a C_{max} of 611 ng/mL and AUC_{0-24} of 5051 ng·h/mL, respectively.

In dogs, dose-dependent body weight loss, increased glucose and inflammation were observed at ≥3 mg/kg. The MTD was determined to be 10 mg/kg, corresponding to a C_{max} of 1950 ng/mL and AUC_{0-24} of 16200 ng·h/mL.

2.5.4.2. *Repeat dose toxicity*

Preliminary and definitive GLP repeat-dose toxicity studies were conducted with inavolisib in rats and dogs up to 13 weeks of duration.

The findings identified include hyperglycaemia and body weight loss in rats and dogs, inflammation in dogs, bone marrow hypocellularity, atrophy of glandular and reproductive tissues and eye lens degeneration in rats; and lymphoid depletion and swelling of the lens fibres in the eye in dogs. Findings were generally dose-dependent and reversible. Lens fibre degeneration observed in some rats (≥3.6x the AUC exposure) was considered irreversible.

Body weight
Reversible effects on body weights attributed to inavolisib administration occurred in rats (decreased

body weight gain and body weight loss) and in dogs (body weight loss). In rats, a reversible, dose-dependent decrease in body weight gain was observed at ≥1 mg/kg/day, and body weight loss was observed at 10 mg/kg/day. In dogs, inavolisib-related decreases in body weight were observed in individual females at ≥0.5 mg/kg/day and individual males at ≥1.5 mg/kg/day.

Metabolic effects
Dose-dependent and reversible, minimal to marked, increases in glucose were observed in rats at ≥1 mg/kg/day and in dogs at ≥0.5 mg/kg/day. The hyperglycaemia was accompanied by increases in cholesterol and urine glucose at higher doses. Correlative microscopic adaptive changes in the pancreas included islet hypertrophy with vascular ectasia (angiectasia) in rats at 10 mg/kg/kg for 4 weeks and diffuse hypertrophy/vacuolation of islet cells in dogs at 1.5/1.0 mg/kg/day for 13 weeks. Other findings consistent with hyperglycaemia-related metabolic disturbances observed in one dog with persistent hyperglycaemia at 1.5/1.0 mg/kg/day included centrilobular vacuolation/degeneration of the hepatocytes in the liver, diffuse bilateral microvesicular vacuolation in the straight proximal tubules of the kidney, and vacuolation at the equatorial region of the lens cortex of the eyes.

Haematopoietic effects
Effects on haematopoiesis were observed in rats and included decreases in circulating monocytes at ≥1 mg/kg/day, decreases in reticulocytes, haematocrit, leukocytes, lymphocytes, and neutrophils at ≥1.5 mg/kg/day, decreased erythrocytes, haemoglobin concentrations, eosinophils, and basophils at 5 mg/kg/day, and decreased platelets at 10 mg/kg/day. These hematologic changes were likely correlated microscopically with decreases in bone marrow cellularity at ≥5 mg/kg/day and decreases in cellularity and haematopoiesis in the splenic red pulp at ≥3 mg/kg/day.

Inflammation
Inavolisib administration in dogs for up to 13 weeks was associated with dose-dependent and reversible inflammation in multiple organs and correlating clinical pathology changes of inflammatory markers of inflammation. The microscopic inflammation was limited to the oesophagus (1 female), rectum, and mandibular lymph node at 0.5 mg/kg/day and present in GI tract, blood vessels, urinary bladder, bone marrow, and eye at ≥1.0/1.5 mg/kg/day; and in lung, heart, liver, and testis at 5/3 mg/kg/day. Morbidity was associated with multi-organ inflammation in dogs at 5/3 mg/kg/day.

Microscopic inflammation was associated with clinical indicators of inflammation at all dose levels in dogs. At 0.5 mg/kg/day, subtle increases in inflammatory foci correlated with increased neutrophils and fibrinogen. At ≥1.0/1.5 mg/kg/day, correlating clinical pathology findings consistent with inflammation included decreased red cell mass, albumin and albumin/globulin ratio; increased globulins, leukocytes, neutrophil, lymphocyte, and monocyte counts; and increased fibrinogen.

Ocular findings
In rats administered 10 mg/kg/day for 4 weeks, minimal-to-slight lens degeneration of the eye was observed in 2 of 20 animals and in 1 of 10 recovery animals at the end of a 4-week recovery period. In the 13-week rat study, there were no ocular findings noted up to the highest dose of 5 mg/kg/day.

In dogs, ocular-related findings included inflammation and lens fibre swelling. In dogs administered inavolisib at 1.5/1.0 mg/kg/day for 13 weeks, ocular inflammation was limited to reversible, focal, minimal neutrophilic infiltrates in the stroma of the corneal-limbal junction of the eye and may have corresponded to reddish conjunctiva observed clinically. In the 4-week study at 5/3 mg/kg/day, reversible minimal or slight neutrophil or mixed cell inflammation in the limbus/sclera correlated with ophthalmic examination findings of anterior segment inflammation. In animals euthanised in moribund condition at 5/3 mg/kg/day, more extensive mixed cell endophthalmitis was observed, correlating with clinical observations indicative of persistent ocular inflammation. These inflammatory findings were considered to be part of the multi-organ inflammatory process observed in dogs at this dose level. The ocular inflammation dogs was reversible.

In the 13-week dog study, bilateral, reversible, very slight swelling of the fibres at the equatorial region of the lens was observed in 1 male and 1 female at 0.3 mg/kg/day, and 1 male and 1 female at 1.5/1.0 mg/kg/day. Lens opacity at the posterior capsule/cortex was noted during ophthalmology evaluations in 2 animals at 1.5/1.0 mg/kg/day; however, no histopathologic correlates for lens opacity were observed in the posterior lens of these animals.

Lymphoid depletion

Decreases in lymphocytes in lymphoid tissues were observed in dogs administered inavolisib for 4 weeks. The lymphoid depletion was dose-dependent, showed a trend toward recovery, and was present in the thymus, GALT/Peyer's patch, and mesenteric lymph node at ≥0.5 mg/kg/day and in the mandibular lymph node and spleen at 5/3 mg/kg/day. No microscopic changes in lymphoid populations were observed in dogs administered up to 1.5/1.0 mg/kg/day for 13 weeks.

Glandular atrophy

In rats administered inavolisib for up to 13 weeks, dose-dependent microscopic atrophy and/or decreased organ weights were present in the mammary gland, pituitary gland (pars distalis), and mandibular salivary gland at≥1 mg/kg/day; thyroid gland at ≥1.5 mg/kg/day; Harderian gland at ≥3 mg/kg/day; and pancreas and adrenal gland at ≥5 mg/kg/day. These glandular atrophy effects were relatively mild and reversible, considered non-adverse.

2.5.4.3. *Genotoxicity*

Genotoxicity of inavolisib was assessed *in vitro* and *in vivo* in a series of GLP studies. Inavolisib was negative in bacterial gene mutation assay (Ames). In the micronucleus assay conducted on human lymphocytes, inavolisib was found positive for *in vitro* clastogenic effects (NOEL 120-180 µg/mL). The effect was concentration related and spanned over four highest test concentrations, reaching up to 6.5x increase.

Chromosomal and DNA damage was assessed in rats *in vivo* using the micronucleus assay in polychromatic erythrocytes (PCE) in the bone marrow and using alkaline comet assay in the liver. The highest selected dose was MTD (40 mg/kg). The exposure was dose related and when compared with the exposure observed in patients in therapeutic application of inavolisib, the margin of exposure (MoE) of approximately 16x was obtained, with adequate exposure of target tissues. Taking the mid dose of 15 mg/kg as NOEL, still results in a MoE of 7x to the human exposure. In this study, inavolisib was found negative for *in vivo* genotoxicity (clastogenicity, aneugenicity and DNA damage).

2.5.4.4. *Carcinogenicity*

No carcinogenicity studies have been conducted with inavolisib.

2.5.4.5. *Reproductive and developmental toxicity*

According to ICH S9, no dedicated studies to investigate fertility and early embryonal development have been conducted. In repeat-dose studies, findings in male reproductive organs were observed in rats and dogs, and in female reproductive organs in rats only.

In male rats, decreased prostate gland weight was observed at ≥3 mg/kg/day and at 10 mg/kg/day, decreased weights of seminal vesicles, testes and epididymis were seen in the 4-week study. Minimal atrophy was present in the prostate and in the seminal vesicle at 10 mg/kg/day. These findings were reversible. In the 13-week study, prostate gland and epididymis weight were decreased at ≥1.5 mg/kg/day, and testis weight at 5 mg/kg/day. Microscopically a very slight decreased prostate lobular size/secretion was observed in 2/10 animals at 1.5 and 5/10 animals at 10 mg/kg/day.

In male dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed at ≥1.5 mg/kg/day in the 4-week study. There were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology in the 13-week study at similar exposures. However, a decrease in total sperm count was observed at 1.5/1.0 mg/kg/kg at the end of dosing phase compared with controls. The finding was not observed following the recovery period indicating reversibility. In dogs, no effects on male reproductive organs were observed at exposures of 456 ng·h/mL, corresponding to 0.4X the clinical therapeutic exposure.

In female rats in the 4-week study, a decreased ovary weight was observed at 10 mg/kg/day with no microscopic correlates. Minimal atrophy was present in the uterus and vagina at ≥3 mg/kg/day. In addition, at 10 mg/kg/day, the oestrus cycle stage could not be determined in 3/10 rats suggesting a possible interruption in the oestrus cycle. These findings were not observed following the recovery period, indicating reversibility. In the 13-week study, very slight atrophy was observed in the vagina at 5 mg/kg/day. At the same dose, the oestrus cycle stage could not be determined in several females and the remainder were in dioestrus or proestrus, suggesting an interruption/alteration of the oestrus cycle. No recovery period was included in the 13-week study. No effects in female reproductive organs or on oestrus cycling were observed at 1.5 mg/kg/day corresponding to an AUC of 545 ng·h/mL, corresponding to 0.5X the clinical therapeutic exposure. There were no findings in female reproductive organs in dogs treated for up to 13 weeks at exposures of 1560 ng·h/mL, corresponding to 1.6X the clinical therapeutic exposure.

A preliminary GLP study in rats to determine the initial embryo-foetal toxicities of inavolisib after administration by oral gavage QD during Gestation Days 6 through 17 was conducted, including a toxicokinetic assessment.

Inavolisib was well-tolerated up to 6 mg/kg/day, with maternal findings limited to non-adverse lower body weight gain and transient glucose increases at ≥ 2 mg/kg/day. Inavolisib-related effects on embryo-foetal development at 2 mg/kg/day included adverse decreases in foetal body weight and placental weight, and at 6 mg/kg/day higher post-implantation loss, lower foetal viability, and malformations. The most frequent findings of foetal external, visceral, and skeletal malformations were oedema, anasarca, absent eye bulge, microphthalmia, fused thoracic arch, and kyphosis of the vertebral column.

The NOAEL for maternal toxicity is considered to be 6 mg/kg/day. The NOAEL for embryo-foetal development is considered to be 0.6 mg/kg/day with maternal GD 17 AUC exposure levels of 256 ng·h/mL, corresponding to 0.2X the clinical therapeutic exposure.

2.5.4.6. *Toxicokinetic data*

Toxicokinetic data was obtained in the repeat-dose studies performed in rats and dogs and in the preliminary embryo-foetal development study in pregnant rats.

In rats and dogs, exposures (C_{max} and AUC_{0-24}) of inavolisib increased dose-proportionally and were generally similar on Day 1 and after multiple administrations. In rats, exposure was approximately 2-fold higher in females than in males. In dogs, no apparent differences were observed in inavolisib mean C_{max} and AUC_{0-24} values by sex.

The AUC exposure margins NOAELs in the 4- and 13-week repeat-dose rat and dog studies, and in the preliminary EFD study in rats were generally below 1 indicating a lack of exposure margins to the adverse effects observed in the non-clinical studies.

2.5.4.7. *Local tolerance*

No specific local tolerance studies were conducted.

2.5.4.8. *Other toxicity studies*

Two impurities in drug substance (RO7304383 and RO7304403) were specified at levels exceeding the ICH Q3A (R2) qualification threshold. Both were qualified for general toxicity *in vivo* in a 28-days GLP dog toxicity study. RO7304383 was qualified for genotoxicity *in vitro* (Ames, non-GLP) and declared negative. RO7304403, a stereoisomer of API, was analysed *in silico* for genotoxicity using Derek Nexus and Leadoscope models and the result was inconclusive. However, considering structural similarity to inavolisib, the absence of structural alerts, as well as the fact that the impurity was present (at 1.1%) in the batch of inavolisib tested in the Ames study and the *in vivo* genotoxicity study, this impurity is considered qualified for genotoxicity. In addition, several other potential drug substance-related mutagenic impurities were evaluated *in silico* and the results were inconclusive. These impurities are specified below the qualification limit, according to the ICH S9 guideline, and no further testing was performed.

Another impurity (RO7533297) was specified in the drug product at the ICH Q3B (R2) qualification threshold. The impurity was found positive in a GLP study of gene mutations in bacteria (Ames test). In the peripheral blood erythrocyte Pig-a gene mutation assay conducted in rats *in vivo* with inavolisib, RO7533297 was found negative in an *in vivo* mammalian system at clinically relevant exposure. Since this impurity is also a minor metabolite in repeated dose toxicity studies, it is considered qualified.

Inavolisib was found non-phototoxic in the *in vitro* neutral red uptake phototoxicity assay on BALB/c 3T3 fibroblasts conducted according to GLP.

2.5.5. Ecotoxicity/environmental risk assessment

Inavolisib has a partition coefficient lesser than 4.5 (log Dow = 0.93 at pH 7) and thus, a further PBT assessment is not warranted. However, a supplementary PBT assessment was submitted concluding that inavolisib is T, but not P and not B. To be classified as a PBT substance, all three criteria must be fulfilled, therefore, inavolisib is not a PBT nor a vPvB substance.

Predicted environmental concentration (PEC) – refined

Inavolisib is currently indicated for the treatment of adult patients with hormone receptor positive (HR+) metastatic breast cancer. The estimated prevalence is as follows:
• The 5-year prevalence of breast cancer in Europe within Globocan 2020 of the International Agency for Research on Cancer (IARC) amounts to 2,138,117 cases (https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf). According to the Cancer Genome Atlas Network (2012), HR+ metastatic breast cancer accounts for up to 70% of breast cancer.
• Considering a European population of 746,225,356 in 2020 according to Worldometer (https://www.worldometers.info/world-population/europe-population/) for Eastern, Western, Southern and Northern Europe, this results in 1,496,682 cases for HR+ metastatic breast cancer in Europe. Compared to the European population of 746,225,356 the 1,496,682 cases result in a 5-year prevalence for Europe of 0.002.

The $F_{PEN\text{-}REFINED}$ is calculated as follows:
$F_{PEN\text{-}REFINED}$ = (prevalence × duration of one treatment × treatments per year) ÷ number of days per year = (0.002 × 365 days × 1) ÷ 365 = 0.002

The refined Phase I PEC_{SW} is calculated as follows:
PEC_{SW} = (DOSEai × $F_{PEN\text{-}REFINED}$) ÷ (default wastewater per inhabitant × default dilution)
= (9000 µg/d × 0.002) ÷ (200 L/d × 10) = **0.009 µg/L**A refined PEC (based on a 5-year disease

prevalence for Europe of 0.002) amounts to 0.009 µg/L, a value lower than the action limit of 0.01 µg/L.

Table 4. Summary of main study results

Substance (INN/Invented Name): Inavolisib				
CAS-number (if available): 2060571-02-8				
PBT screening		Result		**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	$logD_{OW}$ = 0.95, pH 5 $logD_{OW}$ = 0.93, pH 7 $logD_{OW}$ = 0.95, pH 9		Potential PBT: N
PBT-assessment				
Parameter	**Result relevant for conclusion**			**Conclusion**
Bioaccumulation	log K_{ow}	0.93 (pH 7)		not B
Persistence	Not readily biodegradable			Potentially P or vP
	DT_{50}	<120 d		not P
Toxicity	CMR			T
PBT-statement:	The compound is not considered as PBT nor vPvB.			
Phase I				
Calculation	**Value**		**Unit**	**Conclusion**
PEC_{sw}	Default: 0.045 Refined: 0.009		µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)				N

2.5.6. Discussion on non-clinical aspects

The toxicology programme of inavolisib was performed in agreement with recommendations in ICH S9. The choice of rats and dogs as relevant toxicology species is agreed. No data were provided on the activity on PI3Kα in the animal species used in the toxicology programme (rat and dog). However, the demonstration of a pharmacodynamic effect (hyperglycaemia) at clinical exposures provides support for the pharmacological relevance of the toxicology species.

The *in vitro* and *in vivo* primary pharmacology of inavolisib have been adequately characterised.

In the single-dose telemetry dog safety pharmacology study, inavolisib-related cardiovascular effects included generally dose-dependent, reversible, and non-adverse decreases in heart rate, increases in arterial pressure and contractility, lengthening of PR and QT intervals (likely driven by the decreased heart rates), and minimally lengthened corrected QTc interval. The Cmax at the NOAEL level of 3 mg/kg was 9x the clinical Cmax.

In the 13-week repeat-dose toxicology studies in rats and dogs, only two inavolisib dose levels were included. As the toxicology profile of inavolisib is considered adequately characterised, the strategy is considered acceptable.

No clear dose-limiting toxicity was observed in rats indicating that higher dose levels may have been employed, at least in the short-term studies. In dogs, dose-limiting toxicity include body weight loss and multiorgan inflammation leading to termination for welfare reasons of three animals in the 4-week study. In the 13-week study, the high dose level was reduced due to adverse body weight loss in some animals.

The majority of findings identified in the repeat-dose studies were consistent with the anticipated pharmacologic effects of PI3K inhibition, including hyperglycaemia and body weight loss in rats and dogs, inflammation in dogs, bone marrow hypocellularity, atrophy of glandular and reproductive tissues and eye lens degeneration in rats; and lymphoid depletion and swelling of the lens fibres in the

eye in dogs. Findings were generally dose-dependent and reversible. Minimal lens fibre degeneration observed in some rats (at ≥ 3.6 times the exposure at a clinical dose of 9 mg) was considered irreversible. (see SmPC section 5.3)

The dose-related and reversible hyperglycaemia is considered related to the pharmacologic effect of PI3K inhibition on insulin signalling. Hyperglycaemia was very common in clinical trials (see SmPC section 4.8) and warnings are included in SmPC section 4.4. Hyperglycaemia is also included as an important potential risk (see RMP).

Several findings are considered secondary to the hyperglycaemia, such as increases in cholesterol and urine glucose and microscopic changes in pancreas in rats and dogs, and in liver, kidney and in the lens cortex of the eyes in one dog.

Dose-dependent and reversible decreases in all circulating hematopoietic cell lineages were observed in rats at exposures below the clinical therapeutic exposure and correlated with decreased cellularity in bone marrow and in splenic red pulp. In the dog 4-week study, dose-related decreases in lymphocytes in lymphoid tissues, including thymus, GALT/Peyer's patch, mesenteric lymph node, mandibular lymph node and spleen, were observed at exposures below the clinical therapeutic exposure. No microscopic changes in lymphoid populations were observed in the dog 13-week study at exposures around the clinical exposure. The effects on haematology and lymphoid compartments are likely related to inhibition of the PI3K pathway. Thrombocytopenia and anaemia are both listed as ADRs in SmPC section 4.8.

In dogs, dose-related and reversible inflammation was observed in multiple organs (including eyes), correlating with changes in clinical pathology markers of inflammation. This finding is also likely related to the pharmacology of inavolisib. The most common inflammation associated AEs in inavolisib clinical trials were stomatitis and oral mucositis as outlined in SmPC section 4.8.

Ocular findings included lens degeneration in rats and lens fibre swelling in dogs. In the rat 4-week study, minimal-to-slight lens degeneration of the eye was observed in 2 high dose rats and in 1 rat at the end of the recovery period indicating that this effect is not reversible. This finding was not observed in the 13-week study at AUC exposures 1.4X the clinical therapeutic exposure. Although lens degeneration can be a consequence of prolonged hyperglycaemia, no direct correlation with blood glucose level in individual animals was observed, and thus a direct effect of inavolisib cannot be ruled out. This observation is included in SmPC section 5.3 which is endorsed.

In dogs, dose-related and reversible, very slight swelling of the fibres at the equatorial region of the lens was observed in the 13-week study. Given the minimal nature and distribution, no effect on lens function is anticipated. The effect may be related to inhibition of the PI3K pathway. Dry eye is addressed in the SmPC section 4.8.

Inavolisib-related radioactivity was extensively distributed in rat tissues and organs. The extended exposure in the uveal tract could have relevance for the ocular toxicity seen in rat toxicology studies (see Toxicology section). Apart from this, distribution data do not indicate any issue of importance for the safety evaluation.

In genotoxicity studies, inavolisib was negative in the bacterial mutagenesis test (AMES), but positive in the *in vitro* micronucleus assay on human lymphocytes, showing clastogenic effects. In an *in vivo* study in rats, micronucleus assay was conducted in polychromatic erythrocytes in bone marrow, together with DNA damage assessed by alkaline comet test in the liver. Inavolisib was negative in both *in vivo* genotoxicity assays showing no relevant clastogenic, aneugenic or DNA damage effects, when tested up to MTD and at sufficient exposure of target organs (16 times the exposure at a clinical dose of 9 mg). Therefore, inavolisib is considered non-genotoxic. Relevant information is reflected in the SmPC section 5.3.

In line with ICH S9, no carcinogenicity studies have been performed with inavolisib, which is acceptable.

No dedicated study to investigate fertility and early embryonal development has been conducted. This is acceptable and in line with recommendations in ICH S9. In repeat-dose studies, findings in male reproductive organs were observed in rats and dogs, and in female reproductive organs in rats only. In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights without microscopic correlate in the epididymis and testis were observed (at ≥ NOAEL of 0.4 times the exposure at a clinical dose of 9 mg). These findings were reversible. In male dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed following 4 weeks of dosing (at ≥ 2 times the exposure at a clinical dose of 9 mg). In female rats, minimal to mild atrophy in the uterus and vagina, decreased ovarian follicles, and findings suggestive of an interruption/alteration of the oestrus cycle were observed (at ≥ 1.2 times the exposure at a clinical dose of 9 mg), with a NOAEL of 0.5 times the exposure at a clinical dose of 9 mg. These findings were not observed following the recovery period in the 4-week toxicity study. Recovery was not assessed in the 3-month study in rats. This is reflected in SmPC section 5.3. In addition, SmPC section 4.6 informs that based on non-clinical data, inavolisib may impact fertility in males and females.

In a preliminary embryo-foetal development study in rats, inavolisib caused dose-dependent adverse decreases in foetal body weight and placental weight, post-implantation loss, lower foetal viability, and external, visceral and skeletal malformations with the maternal exposure at NOAEL being 0.2 times the exposure at a clinical dose of 9 mg. Thus, inavolisib may cause foetal harm when administered to pregnant women, therefore, comprehensive contraception guidance is provided in the SmPC section 4.6. Female patients of childbearing potential and male patients with female partners of childbearing potential or pregnant female partners should use effective contraception while receiving inavolisib and for 1 week following the last dose of inavolisib. Correspondingly, as a risk to newborns cannot be excluded, breast-feeding should be discontinued during treatment and for 1 week after the last dose. Given the elimination half-life of inavolisib of 16.4 hours, the proposed time interval of 1 week following the last dose (5x16.4=82 hours ~3.4 days) is acceptable.

In rats and dogs, exposures (C_{max} and AUC_{0-24}) of inavolisib increased dose proportionally and were generally similar on Day 1 and after multiple administrations. In rats, exposure was approximately 2-fold higher in females than in males. In dogs, no apparent differences were observed in inavolisib mean C_{max} and AUC_{0-24} values by sex.

The AUC exposure margins NOAELs in the 4- and 13-week repeat-dose rat and dog studies, and in the preliminary EFD study in rats were generally below 1 indicating a lack of exposure margins to the adverse effects observed in the non-clinical studies.

No specific local tolerance studies were conducted. Inavolisib is intended for oral administration and the excipients are commonly used in pharmaceuticals and are standard ingredients in solid dosage formulations.

Since inavolisib is considered not genotoxic and assessed according to ICH S9, only impurities specified at levels exceeding qualification thresholds need to be tested for general toxicity and genotoxicity. Two impurities in the drug substance were specified at levels exceeding the ICH Q3A (R2) qualification threshold. Both were qualified for general toxicity *in vivo* in a 28-days GLP dog toxicity study. For genotoxicity, one impurity RO7304383 was tested in Ames test in a non-GLP study, whereas the other impurity, RO7304403, was investigated *in silico* analysis of genotoxicity and is considered qualified.

The PEC surfacewater value is below the action limit of 0.01 µg/L, and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, inavolisib is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The applicant has provided an adequate characterisation of the pharmacology, pharmacokinetics and toxicology of inavolisib. Relevant information has been reflected in SmPC sections 4.6 and 5.3.

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.

Table 5. Tabular overview of clinical studies

Study Number	Study Design	Population	No. of Patients Treated	Dose, Route, and Regimen
Study GO39374 (Phase I)[a]	Multicenter, first-in-human, open-label, dose escalation and expansion	Patients ≥ 18 years of age with locally advanced or metastatic *PIK3CA*-mutated solid tumors, including breast cancer	Stage I: Dose escalation (N=50): Arm A = 20; Arm B = 13; Arm C = 17 Stage II: Dose expansion[b]: (N = 140) Arm B = 20 Arm C = 20 Arm D = 60 Arm E = 20; Arm F = 20[c] Interim analysis [e]: 27 Mar 2023	**Dose Escalation:** Arm A: inavolisib QD PO (6-, 9-, 12 mg) Arm B: inavolisib QD PO (3-, 6-, 9 mg) + letrozole 2.5 mg QD PO + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm C: inavolisib QD PO (6-, 9 mg) + letrozole 2.5 mg QD PO **Dose Expansion[b]:** Arm B: inavolisib 9mg QD PO + letrozole 2.5 mg QD PO + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm C: inavolisib 9mg QD PO + letrozole 2.5 mg QD PO Arm D: inavolisib 9mg QD PO+ fulvestrant 500 mg IM Arm E: inavolisib 9mg QD PO+ fulvestrant 500 mg IM + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm F: inavolisib 9mg QD PO+ fulvestrant 500 mg IM + palbociclib 125 mg QD PO (3 weeks on/1 week off)+ metformin up to 2000 mg PO
Study WO41554 (Phase III)	Multicenter, randomized, double blinded, placebo controlled	Patients ≥ 18 years of age with locally advanced or metastatic *PIK3CA*-mutated, HR positive, HER2-negative breast cancer	N = 324 (Inavo + Palbo + Fulv: 162 patients; Pbo + Palbo + Fulv: 162 patients) Primary Analysis 29 Sep 2023	Inavolisib 9 mg/placebo QD PO + palbociclib 125 mg QD PO (21/7) + fulvestrant 500 mg Q4wk IM (Days 1 and 15 of first 28-day cycle, and then Day 1 of each following 28-day cycle)
Study GP42652	Single center, open-label, non-randomized study to assess mass balance and absolute bioavailability	Healthy male and female volunteers of non-childbearing potential	N = 8 Study complete. Final CSR 28 July 2022	Oral administration of 9 mg inavolisib and IV administration of approximately 100 µg of [$^{13}C_6$]-inavolisib in healthy volunteers

2.6.2. Clinical pharmacology

2.6.2.1. *Pharmacokinetics*

Methods

Human plasma (K2EDTA) concentrations of inavolisib were measured using validated and cross-validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. Plasma and urine samples were extracted by supported-liquid extraction. A qualified method was used for exploratory analyses of inavolisib in urine.

Evaluation and qualification of models

Population Pharmacokinetics

The objectives were to perform a PopPK analysis of inavolisib in patients and identify potential covariates effects that may explain the variability in PK parameters.

The PK analysis population consisted of patients who received inavolisib and who had at least one measurable serum concentration in Studies GO39374 and WO41554. The PopPK analysis included 3863 observations from 336 subjects. Arm G of Study GO39374 was excluded since it did not represent the target population. Of note, 170 observations were excluded due to post-dose samples below LLOQ (n=63, <1.5%) and various other reasons such as detectable concentration prior to the first dose, missing date/time and duplicate observations.

The median (range) age and body weight in the PK population was 56.6 years (27.0 to 85.0 years) and 65.0 kg (39.0 159 kg), respectively. Most subjects were White (i.e., 67% White and 18.5% Asian), female (98%) patients with normal (55%) or mild renal impairment (37%) and normal (67%) or mild (33%) hepatic impairment. A large majority of patients was assigned to a dose of 9 mg (93% overall). There were 42 subjects in phase 1 study that had more than 1 formulation (all from GO39374 study). All patients in phase 3 used phase 3 formulation.

The population PK analysis was performed using non-linear mixed effect model (NLME) in NONMEM (Version 7.5). The 1-, 2- and 3-compartment models were explored. Model evaluation and selection was based on the improvement in the objective function, model stability as measured by the condition number, a successful covariance step and standard model diagnostic plots. A covariate analysis explored the impact of several covariates on apparent clearance (CL/F), apparent central volume of distribution (Vc/F) and absorption rate constant (Ka). Covariates included renal function, hepatic function, sex, race, weight, age, food status, formulation and disease-related variables. Covariates were first evaluated graphically using scatter matrix plots and boxplots based on individual random effect of PK parameters (also known as eta-vs-covariate plots). Covariates that showed a trend were included in a stepwise analysis including forward addition process (significance level = 0.01) followed by backward elimination (significance level = 0.001).

The final model was a three-compartment model with linear elimination and absorption. The final model included eGFR on CL/F, body weight on Vc/F, Asian race effect on Vc/F and formulation on Ka. The parameter estimates for the final population PK model are presented in Table 8. The pcVPC over time after dose by study is presented in Figure 2.

Table 6. Final PK model parameter estimates for inavolisib

Parameters	Point Estimate	CV%	95% CI	Shrinkage%
Typical Values				
Clearance CL (L/h)	8.83	1.75	8.53 9.13	--
Central volume Vc (L)	155	3.45	145 166	--
Peripheral volume Vp (L)	68.1	17.5	44.7 91.5	--
Peripheral volume Vp2 (L)	31.4	7.08	27.0 35.7	--
Absorption rate constant Ka (h^{-1})	0.917	15.7	0.635 1.20	--
Intercompartmental clearance Q (L/h)	7.50	4.55	6.83 8.17	--
Intercompartmental clearance Q2 (L/h)	0.142	12.9	0.106 0.177	--
eGFR on CL ((eGFR/86)^{effect})	0.441	13.0	0.328 0.553	--
Body weight on Vc ((weight/65)^{effect})	0.635	14.4	0.456 0.815	--
Race on Vc (Asian exp^{effect})	-0.288	19.1	-0.396 -0.180	--
Formulation on Ka (Phase 1/Resupply exp^{effect})	-0.723	22.6	-1.04 -0.403	--
Random Effects				
On CL	0.0822	8.33	0.0688 0.0956	8.5
On Ka	0.632	13.7	0.462 0.802	28.7
On Vc	0.0671	23.1	0.0368 0.0975	24.5
On Vp	1.85	12.8	1.38 2.31	38.3
Covariance CL/Vc	0.0608	15.1	0.0428 0.0788	--
Residual Error				
Proportional (%)	33.1	0.898	32.5 33.7	--
Additive (ng/mL)	0.0759	17.9	0.0493 0.102	--

Abbreviations: CL=clearance of the central compartment; CI=confidence interval; CV=coefficient of variation; eGFR= estimated glomerular filtration rate; Ka=absorption rate constant; PK=pharmacokinetics; Q=intercompartmental clearance for the first peripheral compartment; Q2=intercompartmental clearance for the second peripheral compartment; Vc=volume of distribution of the central compartment; Vp=volume of distribution of the first peripheral compartment; Vp2=volume of distribution of the second peripheral compartment.

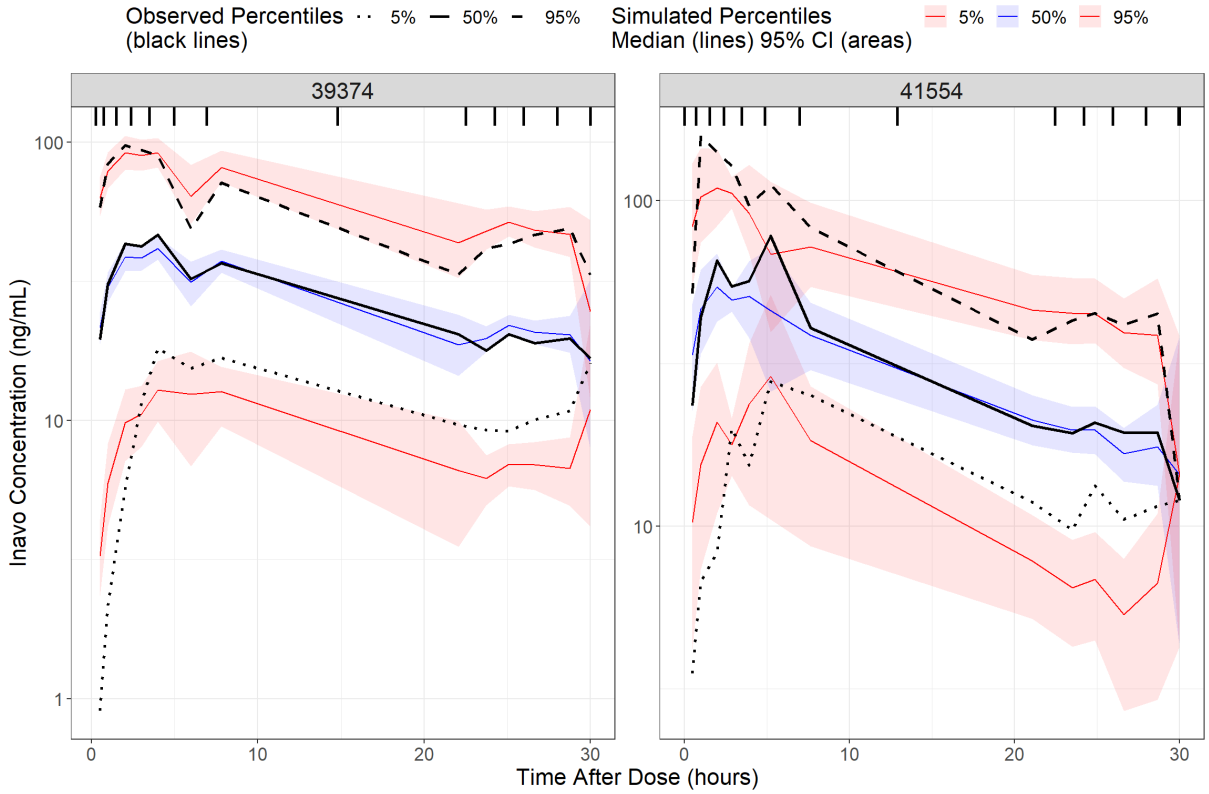


Figure 2. Prediction-corrected VPC by study for inavolisib (semi-log scale)

Notes: The x-axis was limited to the first 30 hours following the most recent dose. Black dash (small and large dashes) and solid lines represent observed 5th, 95th and 50th percentiles, respectively. Solid coloured lines represent the 5th (red), 50th (blue), and 95th (red) percentiles of the simulated data. Shaded areas represent 95% confidence intervals about the 5th, 50th, and 95th percentiles for the corresponding simulated data. The black vertical ticks on the top represent the edges of the bins for calculating the percentiles. Abbreviations: CI=confidence interval; VPC=visual predictive check.

Physiologically based pharmacokinetic model

A physiologically based pharmacokinetic (PBPK) model for inavolisib was developed to assess the cytochrome P450 (CYP) 3A4 (CYP3A4) perpetrator drug-drug interaction (DDI) risk from inavolisib. The PBPK model for inavolisib was developed using *in vitro* and clinical data. The *in vitro* CYP3A4 time-dependent inhibition (TDI) and rifampicin-calibrated induction data were incorporated into the model for DDI prediction. The inavolisib PBPK model was validated using clinical inavolisib PK data. The validated PBPK model was then applied to predict the effect of inavolisib on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate, together with sensitivity analysis to evaluate the magnitude of perpetrator DDI risk from inavolisib where the model predicted low likelihood of DDI, suggesting that inavolisib has a low risk of causing clinically relevant impact on the pharmacokinetics of sensitive CYP3A4 substrates.

Absorption

Based on the results of the Phase I study conducted in patients (GO39374), time to maximum concentration of inavolisib (T_{max}) occurred approximately 3 hours (range: 0.5 to 4 hours) after a single dose as well as at steady state after once-daily dosing.

Based on the *in vitro* results (study 19-1182), inavolisib is a substrate of P-gp and BCRP transporters. However, the clinical relevance for potential DDIs mediated via P-gp and/or BCRP is unlikely considering the overall clinical PK characteristics of inavolisib.

The absolute bioavailability of inavolisib following a single 9 mg oral capsule dose of [^{14}C] inavolisib was 76 % (90% CI: 69-83%) (GP42652 Report 1130181). Figure 3 shows the concentration time profile of inavolisib after iv and po administration.

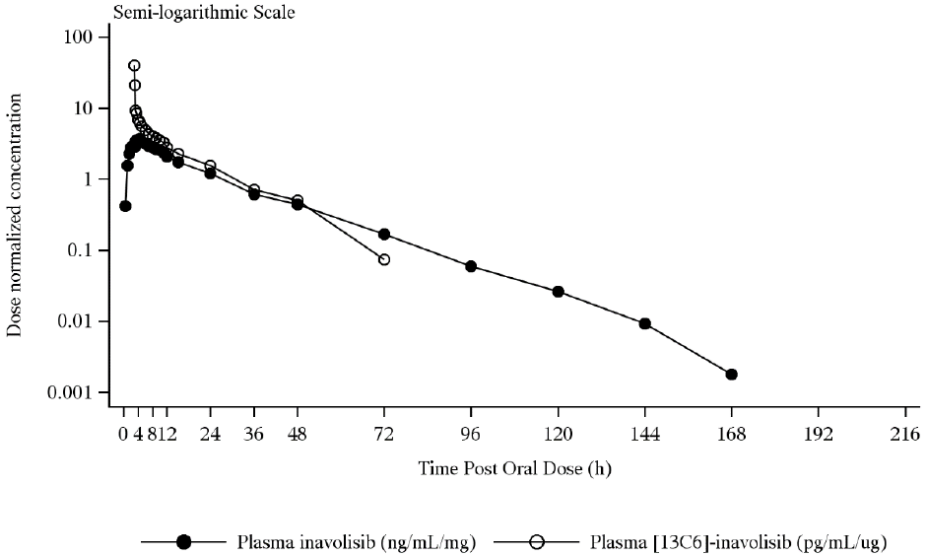


Figure 3. Arithmetic mean (+SD) concentration profiles of inavolisib and [$^{13}C_6$]-inavolisib in plasma (absolute bioavailability)

The estimate of systemic absorption of inavolisib following oral administration is at least 83.3%, based on the percentage of the dose excreted in urine (48.5%) and the metabolites excreted in the faeces. The percentage of metabolites in the excreta was 42% of the dose and the percentage of inavolisib excreted in urine was 40.4% of the administered dose (GP42652 Report 1130181).

No bioequivalence study was conducted between the different studied formulations. Their use in clinical studies is described in Table 7. Some minor changes (colour) have been made between the phase III and the intended commercial formulation.

Table 7. Summary of formulations and their use in respective clinical studies

Clinical Studies	Formulations used
GO39374	F01, F02, F04, F05, F08, F09, F14, and F15
WO41554	F08, F09, F14, and F15
GP42652	An intravenous solution of [$^{13}C_6$] labelled inavolisib at 100 µg/2 mL, A 9 mg powder-in-capsule comprised of [^{14}C] labelled inavolisib.

The influence of food on inavolisib absorption was studied in the treatment Arm D as a part of GO39374 Phase I study, (not performed in accordance with the bioequivalence guideline requirements). The geometric mean ratio (GMR) (90% CI) for AUC0-24 comparing the fed to the fasted state was 0.895 (0.737 – 1.09) after a single dose and 0.876 (0.701 – 1.09) at steady state. The GMR (90% CI) for Cmax comparing the fed to the fasted state was 0.925 (0.748 – 1.14) after a single dose and 0.910 (0.712 – 1.16) at steady state.

The absorption was estimated to be ~50% slower for the Phase 1 formulation than the Phase 3 formulation according to the PopPK analysis.

Distribution

According to the PopPK model, the oral volume of distribution of the central compartment is 155 L.

In an *in vitro* study 15-3820, the fraction unbound (fu) of inavolisib in human plasma was estimated to have a value of 63.3% (i.e., fraction bound to plasma proteins was 36.7%) and did not appear to be concentration- dependent over the concentration range tested (0.1 – 10 µM). Overall, the applied study design with a rapid equilibrium dialysis device, and obtained results appear acceptable. The binding of inavolisib to albumin fraction was low while binding to α1-acid glycoprotein was negligible. Albumin is likely the most relevant plasma protein for binding of inavolisib.

Elimination

There was minimal metabolism of inavolisib in the *in vitro* assay with HLM and recombinant CYPs.

In the mass balance study GP42652, a single 9 mg (approximately 200µCi) oral capsule dose of [^{14}C]-inavolisib was administered in a fasted state and followed 3 hours later by a single 100 µg intravenous (IV) dose of [$^{13}C_6$] inavolisib administered as an IV push over 2 minutes. Inavolisib plasma concentrations appeared to decline in a multiphasic manner, with geometric mean terminal $t_{1/2}$ of approximately 17.5 hours, while total radioactivity in plasma had a terminal t 1/2 of 52.9 hours, see Table 4. Following a single oral dose of 9 mg (200 µCi) [^{14}C]-inavolisib, the overall mean recovery of total radioactivity in urine and faecal samples was 96.5% over 336 h (range 92.6-99.2%). Most of the administered radioactivity was recovered in the first 120 hours postdose (87.8%). The amount of total radioactivity (expressed as a percentage of dose) eliminated in urine and faeces was similar with mean (SD) values of 48.5% (8.18) and 48.0% (7.22), respectively. The geometric mean renal clearance (CLR) of inavolisib was 5.54 L/h.

Table 8. Summary of PK parameters for inavolisib and [$^{13}C_6$] inavolisib in plasma and total radioactivity in plasma and whole blood

Parameter	Plasma inavolisib (N = 8)	Plasma [$^{13}C_6$]-inavolisib (N = 8)	Plasma Total Radioactivity (N = 8)	Whole Blood Total Radioactivity (N = 8)
AUC_{0-t} (h*ng/mL)[a]	695 (32.3) [8]	8930 (33.1) [7]	1120 (38.5) [8]	835 (39.2) [8]
$AUC_{0-\infty}$ (h*ng/mL)[a]	699 (32.0) [8]	9710 (31.9) [7]	1230 (38.7) [7]	1080 (24.2) [7]
$\%AUC_{extrap}$ (%)	0.576 (49.9) [8]	6.92 (46.8) [8]	12.3 (45.1) [8]	14.8 (38.8) [8]
C_0 (pg/mL)	NA	3510 (136.6) [7]	NA	NA
C_{max} (ng/mL)[a]	33.316 (52.2) [8]	3170 (69.9) [8]	33.3 (46.7) [8]	32.9 (43.6) [8]
t_{max} (h)	4.50 (2.00-10.0) [8]	0.0917 (0.0333-0.117) [8]	4.00 (2.00-10.0) [8]	4.00 (3.00-10.0) [8]
t_{last} (h)	132 (96.0-168) [8]	45.0 (45.0-69.0) [8]	132 (96.0-240) [8]	72.0 (48.0-96.1) [8]
λ_z (h^{-1})	0.0396 (16.7) [8]	0.0506 (20.1) [8]	0.0131 (66.0) [8]	0.0271 (39.2) [8]
$t_{1/2}$ (h)	17.5 (16.7) [8]	13.7 (20.1) [8]	52.9 (66.0) [8]	25.6 (39.2) [8]
CL (L/h)	NA	10.1 (30.1) [7]	NA	NA
V_z (L)	NA	204 (29.0) [7]	NA	NA
V_{ss} (L)	NA	182 (30.2) [7]	NA	NA
CL/F (L/h)	13.2 (32.6) [8]	NA	NA	NA
V_z/F (L)	334 (41.5) [8]	NA	NA	NA
V_{ss}/F (L)	320 (43.9) [8]	NA	NA	NA
$DAUC_{0-t}$ (h*ng/mL/mg)[a]	75.1 (32.9) [8]	90.8 (31.4) [7]	NA	NA
$DAUC_{0-\infty}$ (h*ng/mL/mg)[a]	75.5 (32.6) [8]	98.7 (30.1) [7]	NA	NA
F	0.756 (12.6) [7]	NA	NA	NA
CL_R (L/h)	5.54 (29.4) [8]	NA	NA	NA
$AUC_{0-\infty}$ Plasma inavolisib: Plasma TRA Ratio	0.588 (19.6) [7]	NA	NA	NA
$AUC_{0-\infty}$ Whole Blood: Plasma TRA Ratio	NA	NA	NA	0.794 (6.1) [6]

Units presented for Cmax, AUCs, and DAUCs are for plasma inavolisib. For plasma [$^{13}C_6$]-inavolisib the unit is pg/mL for C max, h*pg/mL for AUCs, and h*pg/mL/ug for DAUCs. For plasma and whole blood total radioactivity, the unit is ngEq/g for C max and h*ngEq/g for AUC. DAUC = dose normalised AUC.

Low extraction recovery (69 ± 14% after 3x extraction with acetonitrile) from the pooled plasma was observed, suggesting that drug-related material might have bound to proteins in the plasma and become unextractable. The extraction recovery of the pooled 6-hour plasma sample was 95.5%. The extraction recoveries for the faecal homogenates were in the range of 78-98%. Urine was injected directly after processing thus no recovery is applicable.

[^{14}C] inavolisib was stable in urine and plasma under the incubation conditions. In faeces, aerobic incubation for 3 hours increased the conversion of [^{14}C] inavolisib to M5, M6, M18, and M19. This conversion was not detected in the control samples involving only water. Under anaerobic incubation, M18 and M19 were both formed from [^{14}C] inavolisib; M5 and M6 were not formed. Faecal sample preparation introduced the artificial formation of M5, M6, M18, and M19. This was decreased after sample preparation improvements but not fully eliminated.

Figure 3 summarises the identified metabolites in plasma and excreta. Inavolisib represented 99.5% of extractable radioactivity in the plasma, with trace amounts of M5 (detected not quantified). In the pooled plasma at 6 hours, inavolisib represented 95.1% of the extractable radioactivity while M5 (imidazole ring cleavage) and M8 (hydrolysis) accounted for 1.3% and 1.5%, respectively.

Inavolisib in urine accounted for 40.4% of the dose. The minor metabolites identified in the urine accounted for 7.1% of the dose and included M5 (2.0% of the dose), M6 (1.3% of the dose), M8 (1.0% of the dose), and M10 (1.5% of the dose); together, M18 and M19 accounted for 1.3% of the dose.

Inavolisib in faeces accounted for 10.8% of the dose; M8, M14, and M15 accounted for 6.4%, 7.9%, and 6.8% of the dose, respectively. Together, M17, M18, and M19 accounted for 4.2% of the dose. M4, M11, M12, M13, and M16 accounted for 1.1, 1.4, 0.7, 2.2, and 1.7% of the total dose, respectively. Other minor metabolites were M5 (0.9% of the dose), M7 (0.8% of the dose), and M9 (0.8% of the dose).

Of the metabolites detected in the excreta, M8 (hydrolysis)-related metabolites (i.e., M4, M8, M9, M11, M12, M13, M14, and M15) accounted for 28.2% of the administered dose, suggesting that hydrolysis was the major metabolism pathway. Of note, no specific hydrolysis enzymes responsible for the metabolism of inavolisib could be identified. Other minor metabolism pathways include imidazole ring cleavage, oxidation, and conjugation of + 302 Da and + 304 Da, which were assumed to be mediated by the microbiota present in the intestine and faeces.

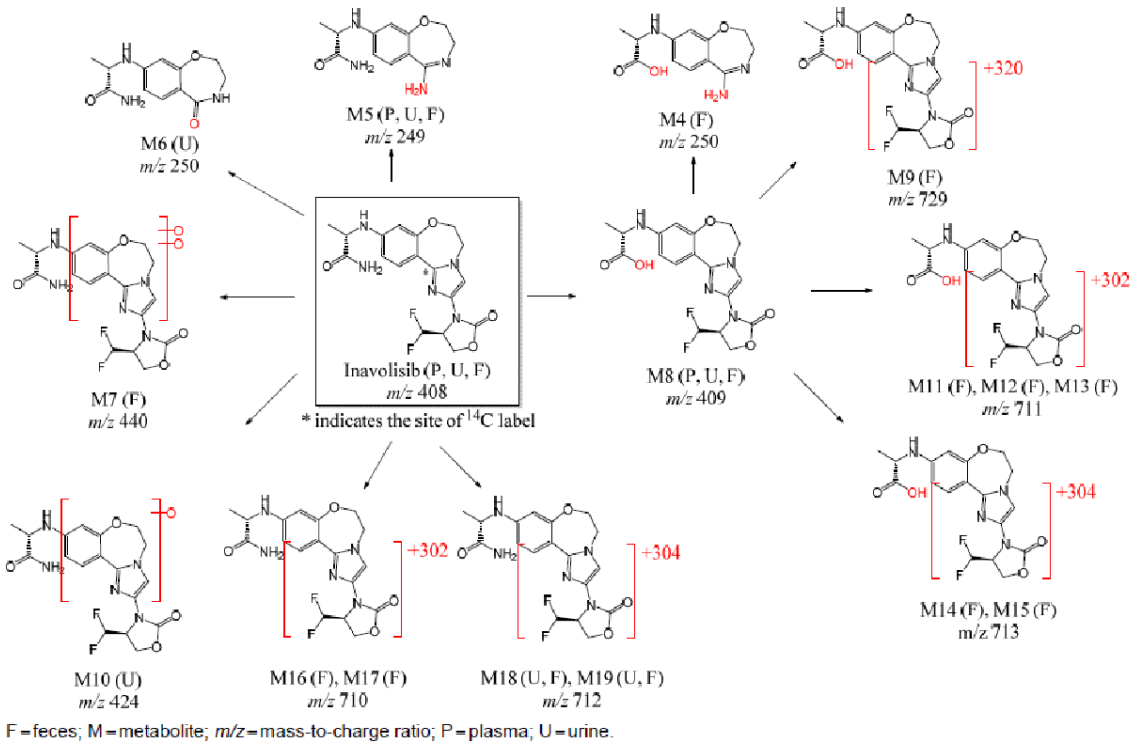


Figure 4. Proposed metabolic pathways of inavolisib in humans in vivo

The PopPK model was used to characterise PK in the target population, where CL/F was estimated to 8.83 L/h.

Dose proportionality and time dependencies

Analysis of dose linearity/proportionality was conducted as a part of the treatment arm A in the Phase I study GO39374, and has concluded that the single dose C_{max} and AUC_{0-24} as well as steady-state AUC_{0-24} of inavolisib increased proportional to the dose (tested doses were 6, 9 and 12 mg), while the steady-state C_{max} was not considered dose proportional (see "Pharmacokinetics in the target population" section).

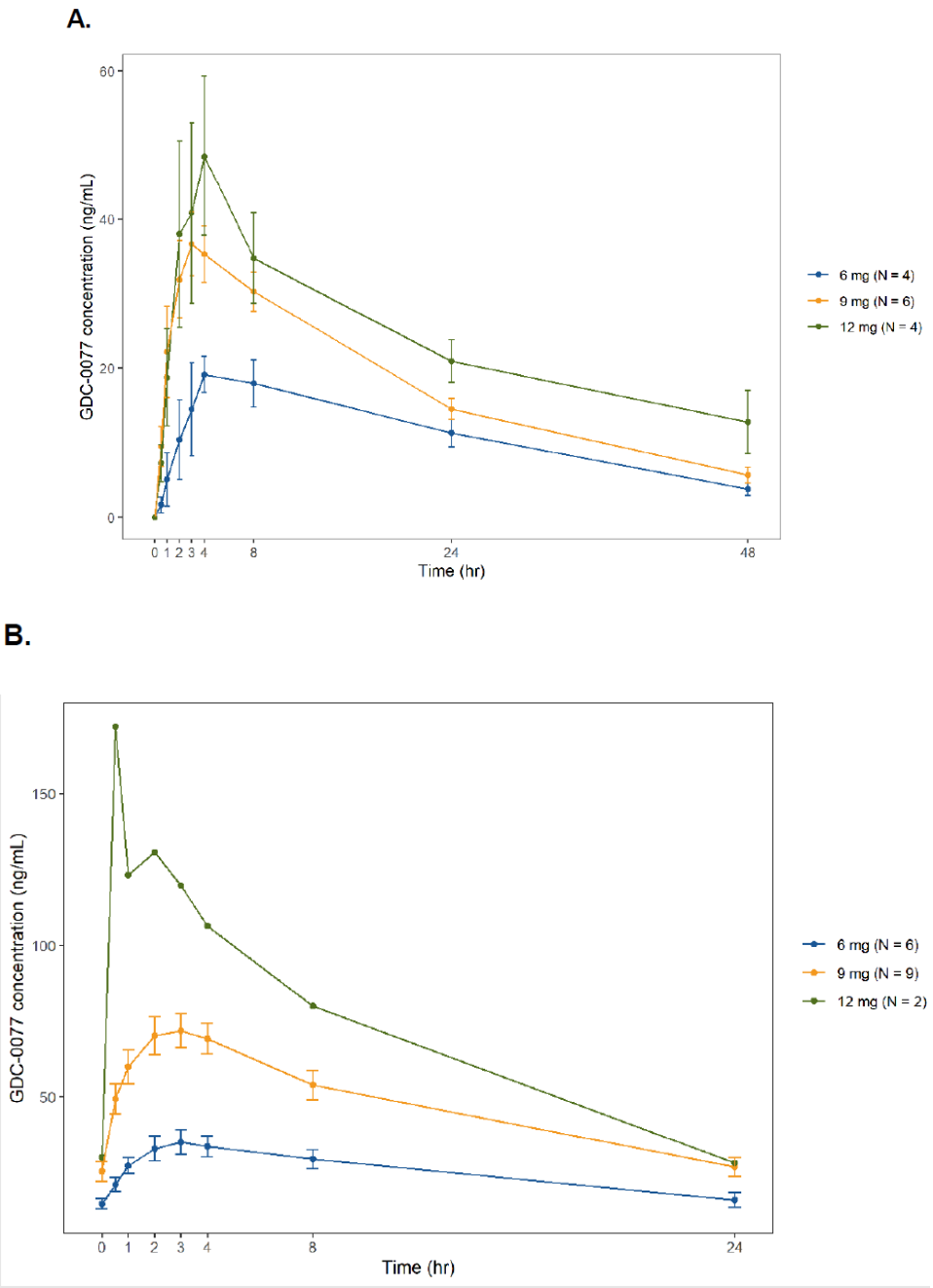
Repeated once-daily dosing of inavolisib applied for seven days in the treatment arm A is considered long enough to achieve steady-state conditions (considering the half-life of inavolisib of about 16 hours). Ratio of the obtained AUC_{0-24} values at steady-state and AUC_{0-24} after the single dose of inavolisib implied an accumulation ratio of about 2-fold. Moreover, AUC_{0-inf} after the single dose of inavolisib appears comparable to AUC_{0-24} at the steady state, thus implying no time-dependent pharmacokinetics.

Pharmacokinetics in the target population

The applicant has conducted two clinical studies which have provided clinical PK data for inavolisib in the patient population:

- Study GO39374 (Phase I)
- Study WO41554 (Phase III)

Treatment Arm A of the Phase I study GO39374 has provided PK data of inavolisib administered alone (i.e., without any concomitant therapies) at the following three dose levels: 6, 9 and 12 mg. Obtained PK profiles of inavolisib as well as tabulated summaries of the obtained PK parameters after single and repeated dosing are provided below.



QD=once a day.

Figure 5. Mean (± SE) plasma inavolisib concentration versus time profiles following a single dose (A) and at steady state (B) after 6, 9 and 12 mg QD dosing of inavolisib administered as a single agent in arm A (study GO39374)

Table 9. Summary of pharmacokinetic parameters for inavolisib following a single dose (C1D1) of inavolisib administered as a single agent in arm a (study GO39374)

Cohort (Dose)	N	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24hr} (ng • hr/mL)	AUC_{0-Inf} (ng • hr/mL)	$t_{1/2}$ (hr)
6 mg	4	4 (3-8)	21.6 (35%)	343 (29%)	590[a] (31%)	16.4 (16%)
9 mg	6	3 (2-8)	38.3 (22%)	570 (21%)	941 [b] (27%)	16.4[b] (16%)
12 mg	4	4 (4-4)	44.6 (53%)	683 (39%)	1430 (20%)	19.3 (37%)

Table 10. Summary of pharmacokinetic parameters for inavolisib at steady state (C1D15) following multiple QD doses of inavolisib administered as a single agent in arm a (study GO39374)

Cohort (Dose)	N	T_{max} (hr)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-24hr} (ng • hr/mL)	Accumulation Ratio (AR)
6 mg	6	3.5 (2-8)	34.7 (27%)	15.3 (33%) [A]	578 [B] (26%)	1.70 (21.6)
9 mg	9	3.0 (0.5-4)	75.1 (22%)	23.7 (42%)	1060 [C] (23%)	2.04 (20.3%)
12 mg	2	1.75 (0.5-3)	131 [D]	29.9 [E]	1610 [D]	2.33 [D]

PK objectives in the phase III study WO41554 were to characterise the pharmacokinetics of inavolisib, palbociclib, and fulvestrant, when administered in combination in the target population and a China-specific objective was to characterise the PK in patients enrolled in China. Inavolisib/Placebo was administered at 9 mg PO QD on Days 1-28 of each 28-day cycle without regard to the timing of food; palbociclib was administered with food at 125 mg PO QD on Days 1-21 of each 28-day cycle; fulvestrant was administered at 500 mg by intramuscular injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks. The results are presented in Table 11.

Table 11. Summary table of inavolisib plasma concentrations (ng/ml) in the presence of palbociclib and fulvestrant (study WO41554)

Visit	Timepoint	Inavo+Palbo+Fulv
Cycle(C)1Day(D)1	Predose	NE (ND)
	3 hr post-dose	36 (223); n=151
C1D8	Predose	17.8 (134); n=121
C1D15	Predose	13.6 (240); n=117
	3 hr post-dose	59.2 (119); n=120
C2D15	Predose	16.9 (124); n=115

ND = Not Derived; NE = Not Estimable;
Note: Geometric mean (%CV geo mean) are presented in the table.

PK parameters following single dose and at steady state of inavolisib from 28 patients from China are summarised in Table 12.

Table 12. Summary table of inavolisib PK parameters following a single 9 mg dose (C1D1) and at steady state (C1D15) after 9 mg QD dosing of inavolisib administered in combination with palbociclib and fulvestrant in patients from China with intensive PK in the Inavo+Palbo+Fulv arm (study WO41554)

	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng··hr/mL)	C_{min} (ng/mL)	Accumulation Ratio
Cycle(C)1Day(D)1	2.06 (1.03 - 7.68); n=14	57.4 (46); n=14	766 (39); n=11	NA	NA
C1D15	2.75 (1.00 – 3.08); n=9	104 (43); n=9	962 (35); n=8	17.4 (41); n=8	1.45 (23); n=8

AUC_{0-24}=area under the concentration-time curve from 0 to 24 hours after dosing; C_{max} = maximum plasma concentration observed; NA = Not Applicable
Values are reported as geometric mean (geometric %CV) with the exception of T_{max} which was reported as median and range.

The PopPK model predicted a mean Cmax,ss of 66.8 ng/mL (26.8%CV) and a mean AUC0-τ of 1050 ng*h/mL (30.5%CV) at steady-state following once daily administration of 9 mg inavolisib.

Inter-individual variability was estimated in clearance and volume in the PopPK analysis (log-normal distribution). The typical value of CL/F was 8.83 L/h and the inter-individual variability was 28.7%CV. The typical value of Vc/F was 155 L and the inter-individual variability was 25.9%CV. Of note, the PopPK model included covariance between CL and Vc.

Special populations

Given that urinary excretion is a major route of elimination for inavolisib (Study GP42652), patients with impaired renal function are likely to have elevated plasma levels of inavolisib. A dedicated renal impairment study (GP44944) in subjects with moderate and severe renal impairment is ongoing. The study portion for subjects with moderate renal impairment (RI) and their matched controls is completed (Interim CSR date 23 July 2024), while the study portion with severe RI subject and their matched controls is currently ongoing and the final CSR will be available in Q3 2025. Based on the presented data of this RI study (GP44944 study), the geometric mean ratios (90% CIs) for $AUC_{0-\infty}$ and C_{max} were 1.73 (1.49, 2.02) and 1.11 (0.992, 1.25) for the moderate renal impairment group versus the normal renal function group, respectively.

The applicant proposes the recommended starting dosage of inavolisib for patients with moderate renal impairment (eGFR ≥ 30 to <60 mL/min based on CKD-EPI) to be 6 mg QD orally. This dose recommendation was proposed to ensure that the total inavolisib exposure in patients with moderate renal impairment match those with normal renal function.

eGFR was identified as a statistically significant covariate on CL/F according to the PopPK analysis. However, PopPK model predictions suggested that mild renal impairment has no clinically significant impact on the exposure of inavolisib. The GMR (90% CI) of inavolisib PK in patients with mild renal impairment (n = 124) vs. normal renal function (n = 185) for AUC was 1.10 (1.05 -1.16), C_{max} is 1.11 (1.06 -1.17), and C_{min} is 1.11 (1.03 -1.18).

Hepatic markers (albumin, alanine transaminase, aspartate transaminase and bilirubin) were explored as covariates on inavolisib PK during the PopPK analysis. None of the explored hepatic markers were significant covariates for inavolisib PK.

Sex was explored as a covariate during the PopPK analysis and was not a statistically significant covariate for any PK parameter.

Race was explored as a covariate during the popPK analysis. Race was a statistically significant covariate on Vc and predicted ~25% lower Vc in Asian vs non-Asian patients.

Body weight was explored as a covariate during the PopPK analysis. Body weight was a statistically significant covariate on Vc. Body weight was implemented on Vc using allometric scaling with an estimated allometric exponent (0.635).

Age was explored as a covariate during the PopPK analysis and was not a statistically significant covariate for any PK parameter.

Table 13. Overview of elderly patients in clinical studies

	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*	73/336	12/336	1/336

*Including studies GO39374 and WO41554 (inavolisib-treated arm only). Only patients in the popPK dataset were included (n=336).

Pharmacokinetic interaction studies

There are no dedicated clinical DDI studies conducted in the Clinical Pharmacology programme of inavolisib.

In general, the positive *in vitro* DDI signals were addressed by using the clinical data obtained in the Phase I (GO39374) and Phase III (WO41554) study.

"Perpetrator" aspects of inavolisib towards CYP3A substrates

The potential for inavolisib for DDI as "perpetrator" was addressed in the Phase I study GO39374 (no dedicated clinical DDI studies were conducted), i.e., its potential to affect exposure of concomitant therapies, namely palbociclib (CYP3A4 substrate), fulvestrant and letrozole. PK samples taken in the treatment arms B-F (of the GO39374 study) were used to quantify concomitant therapies and to characterise their respective plasma PK profiles. However, GO39374 study did not provide clinical PK data with these drugs as single agents (i.e., there are no PK data generated without the concomitant inavolisib). Therefore, DDI comparisons were done together with published literature data/studies (and drug label data, e.g., fulvestrant) in which these drugs were administered without inavolisib. Based on the GO39374 study results and the provided literature data, there were no indications that inavolisib could impact PK of palbociclib (CYP3A4 substrate), fulvestrant and letrozole.

In the phase III study WO41554, the plasma concentrations of palbociclib for each visit were in the same range between the Inavo+Palbo+Fulv arm and the Pbo+Palbo+Fulv arm, see Table 16.

Table 14. Summary table of palbociclib plasma concentrations (ng/ml) in the presence (Inavo+Palbo+Fulv arm) or absence (Pbo+Palbo+Fulv arm) of inavolisib (study WO41554)

Visit	Timepoint	Inavo+Palbo+Fulv	Pbo+Palbo+Fulv
Cycle(C)1Day(D)1	Predose	NE (ND)	NE (ND)
	3 hr post-dose	20.7 (182); n=154	22.9 (251); n=153
C1D8	Predose	73.9 (56); n=134	74.5 (50); n=138
C1D15	Predose	69.9 (78); n=136	73.3 (65); n=134
	3 hr post-dose	96.7 (55); n=138	98.0 (62); n=131
C2D15	Predose	58.5 (111); n=130	66.9 (90); n=122

ND = Not Derived; NE = Not Estimable.

Note: Geometric mean (%CV geo mean) are presented in the table.

"Victim" aspects of inavolisib with proton pump inhibitors

Inavolisib exhibits pH-dependent solubility with reduced solubility at higher pH conditions. Therefore, concomitant medications that can increase gastric pH, like proton pump inhibitors (PPI), have a potential to reduce the exposure of inavolisib.

The effect of PPI on inavolisib was evaluated in the Phase I Study GO39374 by comparing the steady state (C1D15 for Arms A, B, and D and C2D1 for Arm C) PK of inavolisib in patients who self-reported PPI use at steady state of inavolisib with individuals who reported no PPI use during that time. Similarly, for Study WO41554, inavolisib steady state PK (C1D15) was compared between patients who self-reported PPI use at steady state of inavolisib with individuals who reported no PPI use at steady state. The PPIs considered for this analysis included omeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole, and esomeprazole. Based on this approach, no relevant impact of PPIs on inavolisib exposure was concluded.

Table 15. Statistical analysis of PPI effects on inavolisib PK based on data from Phase I (GO39374) and Phase III (WO41554) study

Study	Steady State Parameter	Treatment	n	GMR (90% CI) Test vs. Reference
GO39374	C_{max}	No PPI group (reference)	56	0.754 (0.549 – 1.03)
		PPI group (test)	19	
	AUC_{0-24}	No PPI group (reference)	54	0.845 (0.624 – 1.14)
		PPI group (test)	19	
WO41554	3 hour post-dose	No PPI group (reference)	107	0.981 (0.696 – 1.38)
		PPI group (test)	12	

AUC_{0-24} = area under the plasma concentration-time curve over the last 24-h dosing interval; CI = confidence interval; C_{max} = maximum concentration; GMR = Geometric mean ratio; PPI = proton pump inhibitor.

Source: GO39374 CSR, Report 1125233, Note to File and l_pkcl01_INAV_PKFL_29SEP2023_41554 and l_cm_CNCM_PPI_SAS_29SEP2023_41554 of CSR WO41554, Report 1126696

Additional "victim" aspects of inavolisib with common concomitant therapies

Phase I study (GO39374) also investigated some additional DDI aspects of inavolisib as a potential "victim" drug. Treatment arms B-F included concomitant administration of inavolisib together with one or more of the following medications: letrozole, palbociclib, fulvestrant and metformin. The applicant has collected plasma samples to quantify PK of inavolisib in arms B-F and to compare it to treatment arm A (i.e., PK of inavolisib alone) in order to investigate if inavolisib could be a "victim" of drug-drug interactions (i.e., if inavolisib exposure changes as a consequence of these concomitant medications). The applied analysis suggested no relevant changes in inavolisib systemic exposure as a consequence of concomitant therapies.

Pharmacokinetics using human biomaterials

Perpetrator aspects

The applicant has tested inavolisib at sufficiently high concentrations *in vitro* to investigate its potential to be a perpetrator of enzyme- and transporter-mediated interactions.

Table 16. Cut-offs for the evaluation of interaction potential of inavolisib

	50×Cmax(u) (µM)	25×Inlet Cmax(u) (µM)	0.1×dose/250 ml (µM)
Inavolisib	8.08	24.96	8.84

Inavolisib did not demonstrate inhibitory potential towards CYP enzymes *in vitro* except for CYP3A4 for which a time-dependent inhibition (TDI) was observed. Inactivation parameters k_{inact} and K_I of inavolisib had values of 0.077 ± 0.006 min^{-1} and 88 ± 10 µM, respectively, for midazolam 1'-hydroxylation.

When it comes to CYP induction, inavolisib has demonstrated positive *in vitro* induction signals (i.e., more than 2-fold increase in mRNA enzyme levels with concentration-dependent effect) towards following CYP enzymes: CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP3A4.

There were no positive inhibitory signals of inavolisib towards relevant drug-transporters *in vitro* (i.e., P-gp, BCRP MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2).

Victim aspects

Inavolisib did not appear to be a relevant substrate of CYP enzymes *in vitro* which implies no risk for clinically relevant interactions with concomitant medications that affect activity of CYP enzymes.

Moreover, inavolisib did not appear to be a substrate of SLC transporters *in vitro* (MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2) while inavolisib was a substrate of efflux transporters P-gp and BCRP *in vitro*. However, the clinical relevance for potential DDIs mediated via P-gp and/or BCRP is unlikely considering the overall clinical PK characteristics of inavolisib.

2.6.2.2. *Pharmacodynamics*

Mechanism of action

Inavolisib is an inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the PIK3CA gene). Inavolisib also promotes the degradation of mutated p110α. Inavolisib inhibits the activity of downstream PI3K pathway targets, including protein kinase B (AKT), resulting in reduced cellular proliferation and induction of apoptosis in PIK3CA-mutated breast cancer cell lines.

Primary and Secondary pharmacology

See also section 2.5.2.1 and 2.5.2.2.

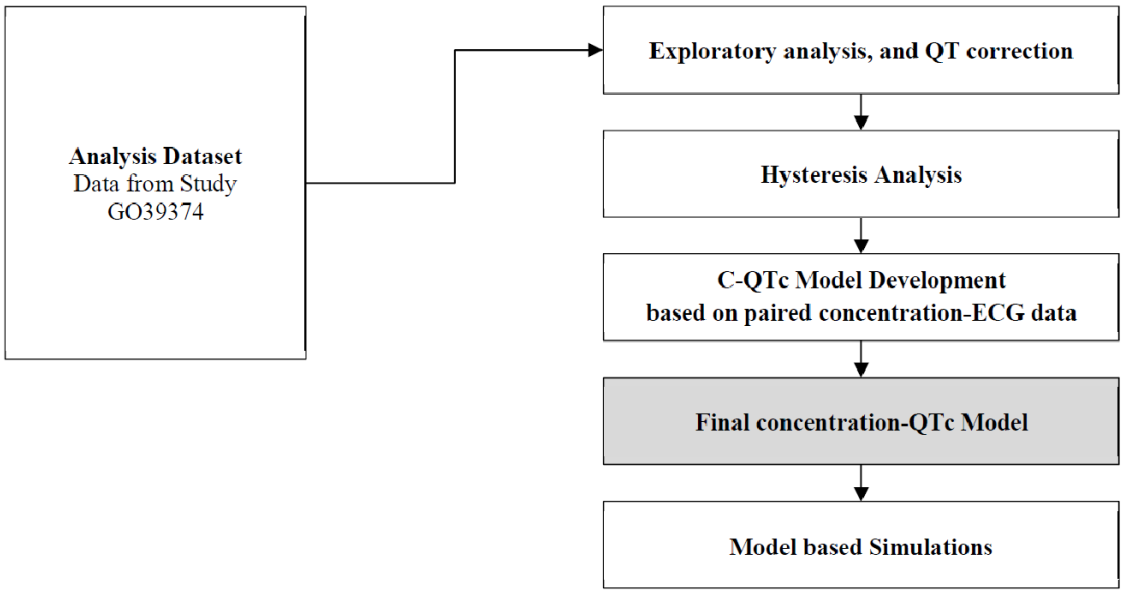
Relationship between concentration and effect

(a) Concentration-QTc analysis

The objectives of the concentration-QTc analysis were to develop a concentration-QT (C-QTc) model and to predict the mean and 90% confidence interval (CI) at the clinically relevant plasma concentrations.

The analysis included Study GO39374 where treatment arm G was excluded since it did not represent the target population. Triplicate digital ECGs were taken both before and after dosing on Day 1 and Day 15 for Stage I patients. Additional triplicate ECGs were captured during steady-state exposure in Stage II. 1476 post-dose pairs C-QTc from 172 unique patients were used in the C-QTc analysis (921 samples were excluded due to no paired inavolisib concentration, poor time-match and no post-baseline values). The population included 99.4% female and 0.6% male subjects. Mean age was 59.2 years, ranging from 31 to 85 years. Mean weight was 70.3 kg, ranging from 43 to 159 kg.

The workflow of the present C-QTc analysis is presented in Figure 6.



QTc = corrected QT interval.

Figure 6. Concentration-QTc model analysis workflow

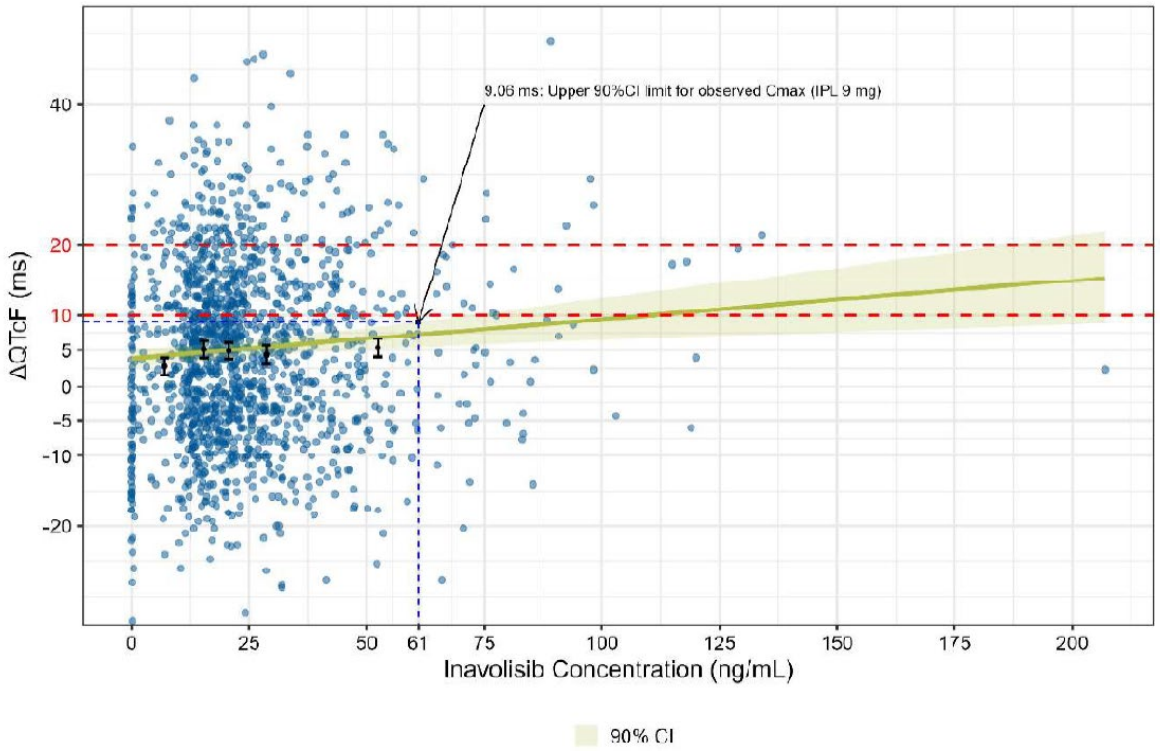
No clear hysteresis or time delay between inavolisib concentrations and ΔQTc was observed. The final model included a linear relationship between inavolisib concentrations and ΔQTc, which gave better fit than power and Emax models. The final model included steady state and nominal time (descriptors of time) as predictors for QT prolongation. Adjusted baseline QTcF was a covariate in the final model. The estimated parameter values of the final inavolisib-ΔQTcF model are presented in Table 17.

Table 17. Inavolisib concentration-ΔQTcF model parameters

Parameter	Estimate	SE	RSE (%)	95% CI
Intercept (θ_0, ms)	-1.85	0.913	49.4	(-3.64, -0.064)
Slope of Inavolisib [θ_1, ms.ng^{-1}.mL)]	0.0556	0.0207	37.2	(0.0151, 0.0961)
Steady State (Other vs Cycle 1 Day 1)	6.29	0.674	10.7	(4.97, 7.61)
Time Parameters (vs Other)				
6h post-dose	-5.79	1.96	33.9	(-9.62, -1.96)
8h post-dose	-2.61	0.849	32.5	(-4.27, -0.944)
Covariates				
adjusted Baseline QTcF	-0.255	0.0362	14.2	(-0.326, -0.184)
Between-Subject Variability				
BSV Intercept (η_0, ms)	7.3	0.529	7.25	(6.34, 8.42)
BSV Slope (η_1, ms)	0.12	0.0216	18	(0.0852, 0.169)
Error Model				
Residual error (σ, ms)	8.52	0.173	2.03	(8.19, 8.87)

Adjusted Baseline QTcF = effect of subject's baseline QTcF adjusted for averaged baseline QTcF measurements over the sample; BSV = between subject variability; CI = confidence interval; ΔQTcF = QTcF change from baseline; QT = ECG QT interval; QTcF = Fridericia's corrected QT; RSE = relative standard error; SE = standard error

The final model demonstrated a good fit to the individual ΔQTcF values. The final model was used to simulate ΔQTcF at a Cmax,ss of 61.2 ng/mL which is associated with the 9 mg once daily dose regimen. Typical inavolisib Cmax,ss value of 61.2 ng/mL was associated with mean (90% CI) ΔQTcF of 7.26 ms [5.45 to 9.06] considering the average effect of all time points. Observed values and predictions of 90% confidence interval on mean estimated ΔQTcF values at steady state as function of inavolisib concentrations are presented in Figure 7.



ΔQTcF = QTcF change from baseline; QT = ECG QT interval; QTcF = population corrected QT;
IPL 9 mg = Inavolisib 9 mg + Palbociclib + Letrozole.
Note: The dashed horizontal red lines represent 10 and 20 ms. The bold green line represents simulated C-QTc profile. Black box-plots present observed ΔQTcF binned into inavolisib concentration quartiles.

Figure 7. Observed values and simulated mean and 90% confidence interval of ΔQTcF values at steady state based on inavolisib concentration

The simulated values of the popPK simulated geometric means of Cmax,ss for special populations including race and different renal impairment conditions predicted slightly higher ΔQTcF ms, see below:

Table 18. Simulation scenarios for simulated Cmax,ss of inavolisib 9 mg by race and renal impairment

Simulated Scenarios	Inavolisib $C_{max,ss}$ (ng/mL)	ΔQTcF (ms)	90% Confidence Interval (ms)
Scenario one			
Non-Asian, Normal Renal Impairment	60.4	7.22	[5.43, 9.01]
Non-Asian	64.6	7.46	[5.55, 9.36]
Asian	77.5	8.17	[5.89, 10.45]
Normal Renal Impairment	62.7	7.35	[5.50, 9.20]
Mild Renal Impairment	69.8	7.75	[5.69, 9.80]
Moderate Renal Impairment	84.6	8.57	[6.07, 11.06]
Asian, Moderate Renal Impairment	96.7	9.24	[6.37, 12.11]
Scenario two			
Non-Asian, Normal Renal Impairment	60.4	7.56	[5.74, 9.37]
Non-Asian	64.6	7.79	[5.86, 9.72]
Asian	77.5	8.51	[6.20, 10.81]
Normal Renal Impairment	62.7	7.69	[5.81, 9.56]
Mild Renal Impairment	69.8	8.08	[6.00, 10.16]
Moderate Renal Impairment	84.6	8.9	[6.38, 11.42]
Asian, Moderate Renal Impairment	96.7	9.57	[6.68, 12.47]

ΔQTcF= QTcF change from baseline; QTcF = Fridericia's corrected QT; QT = ECG QT interval.
Scenario one: The average effect at the overall observed time points.
Scenario two: The average effect at time points other than 6- and 8-hours post-dose.

(b) Exposure-response analyses

The objectives were to perform exposure-response (ER) for several safety/efficacy endpoints and to assess potential impact of dose intensity on exposure parameters.

The analysis population consisted of patients who received inavolisib in Study GO39374 and Study WO41554, analysed separately. In Study GO39374, Arm F was not part of the safety analysis because anti-hyperglycaemic medication was given; Arm G (Inavolisib in combination with trastuzumab and pertuzumab) was not included since this combination is not intended for this regulatory filing. Patients having within-patient dose escalation in Study GO39374 were excluded from the ER population for efficacy and safety endpoints, because the assigned dose was lower than the actual dose taken.

The efficacy datasets (Study GO39374: 183 patients; Study WO41554: 149 patients) included several endpoints as defined by RECIST criteria v1.1 such as PFS and OS (only for Study WO41554).

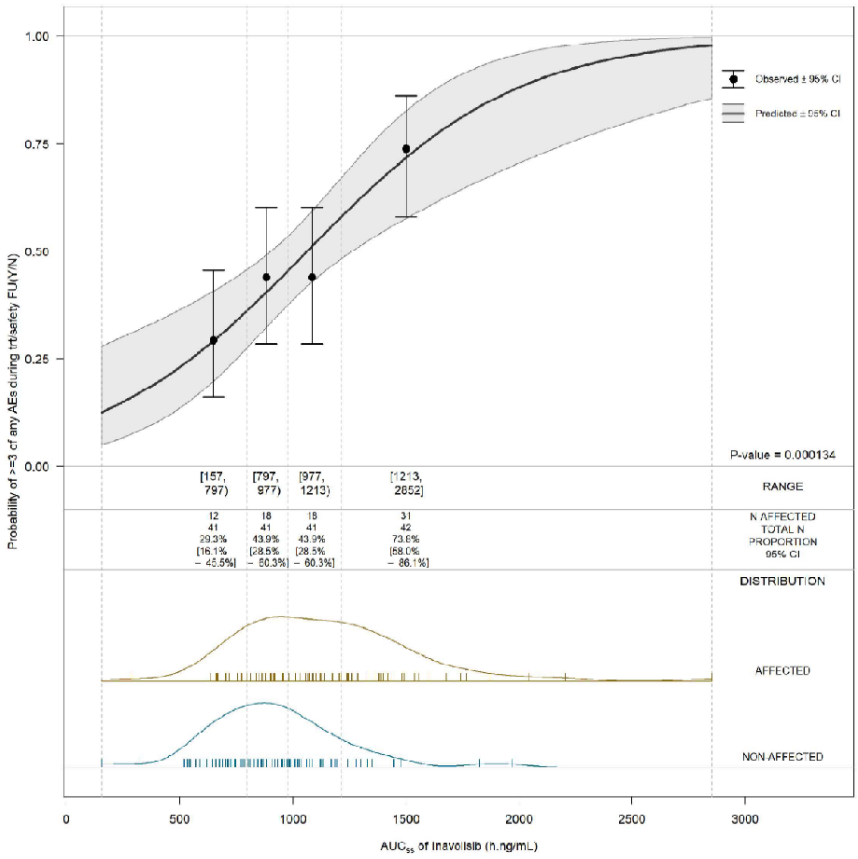
The safety datasets (Study GO39374: 165 patients; Study WO41554: 149 patients) included several adverse events (AE) of interest such as hyperglycaemia and any AE grade ≥3.

Data were analyses as binary variables using logistic regression and as time-to-event endpoints using Cox regression.

None of the explored exposure-efficacy relationships were statistically significant apart from the time-to-event analysis of OS. For the time-to-event exposure-OS analysis, only the highest quartile of exposure was significant and led to worse OS outcome compared with the lower quartiles. The logistic regression for exposure-OS did not identify a statistically significant exposure-response relationship.

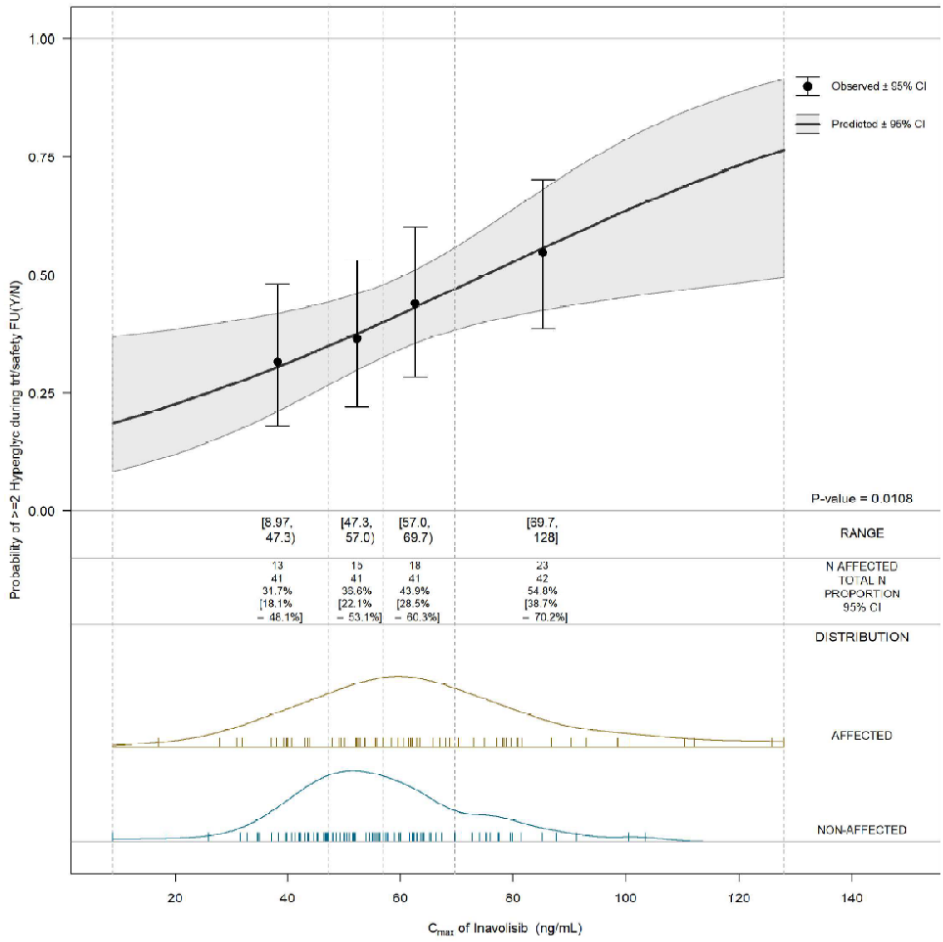
For Study GO39374, exposure-safety relationships were statistically significant for hyperglycaemia grade ≥ 2, any AE grade ≥3 and inavolisib dose modification due to AE. This was the case both for the logistic regression and time-to-event analyses.

The exposure-response relationship for the probability of AE grades ≥ 3 as a function of AUC is presented in Figure 9. The exposure-response relationship for the probability of hyperglycaemia grade ≥ 2 as a function of Cmax is presented in Figure 8.



AE= adverse event; AUC= area under the concentration-time curve over a dosing interval; CI= confidence interval; N= number of subjects.

Figure 8. GO39374 probability of AE grade ≥ 3 by quartiles of AUC



AE= adverse event; CI= confidence interval; C_{max}= maximum concentration; N= number of subjects

Figure 9. GO39374 probability of hyperglycaemia grade ≥ 3 by quartiles of Cmax

For Study WO41554, no exposure-safety relationships were statistically significant apart from grade ≥ 2 anaemia according to the logistic regression (the time-to-event analysis of grade ≥ 2 anaemia did not identify any statistically significant exposure-response relationship).

Dose justification

A dose of 9 mg QD is the recommended dose for oral administration of inavolisib in combination with palbociclib and ET for the treatment of adult patients with PIK3CA- mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer (LA/mBC).

- Inavolisib at 9 mg QD dose demonstrated substantial clinical benefit in the target population. Within the range of exposures observed at 9 mg QD dose for WO41554, efficacy endpoints of PFS, DOR, BOR, ORR, and CBR did generally not correlate with the exposure, indicating patients benefited similarly across the range of inavolisib exposures.
- High dose intensity (>90%) seen across all exposure quartiles of inavolisib supports the 9 mg QD dose from a safety and tolerability perspective. The higher risk for hyperglycaemia (GO39374) and anaemia (WO41554) was observed with higher inavolisib exposure, but these AEs were manageable with standard clinical measures. The discontinuation rate of inavolisib due to AEs was low (6.2% in WO41554).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

All analytical assays for PK were adequate.

Evaluation and qualification of models

The objectives of the PopPK analysis are considered reasonable. The PopPK model was used for descriptive purposes and is used to support statements in SmPC Section 5.2.

The PopPK dataset is considered overall acceptable.

An overall standard workflow has been used to develop the PopPK model. One limitation that was noted is the visual evaluation of eta-vs-covariates, which is a suboptimal method in case of parameters with high eta-shrinkage (> ~30%) and in this analysis, both Vc/F and Ka had high eta-shrinkage. However, this is acceptable since the final model did not include any highly correlated covariates and relevant covariate-parameter relationships were evaluated.

The 3-compartment model structure was chosen, including three distribution phases. Scrutiny of the predicted PK curve from the final model (data not shown) revealed that the third distribution phase occurs at ~200 hours post-dose, which is an extremely late transition given the proposed once daily dose regimen. From practical and parsimony aspects, this is redundant and a 2-compartment model may have sufficed. Nevertheless, the PopPK model is acceptable for supporting the proposed PopPK-based SmPC statements (mainly covariate effects).

The PopPK model performance was assessed using VPCs which indicated acceptable description of the observed data.

A PBPK model was developed by the applicant to assess the DDI risk for inavolisib as a potential perpetrator towards sensitive CYP3A4 substrates. However, as it was very difficult to qualify the PBPK model for the intended use, the conducted PBPK analysis is not acceptable for supporting SmPC statements in section 4.5. In a regulatory setting for perpetrator DDI scenarios, PBPK modelling may be used to support SmPC statements in section 4.5 for CYP substrates provided that the PBPK model has been qualified for its intended use using a clinical DDI study of a sensitive substrate (for instance midazolam for CYP3A4).

Absorption

The fraction absorbed estimation to 83.3% is not agreed. A part of the metabolites may have arisen in the GI tract or upon sample preparation, thus they should not be included in the estimation of the fraction absorbed. F_{abs} is however at least 76%, based on the oral bioavailability, which would denote a compound of moderate permeability. Given its high solubility, inavolisib may be considered as BCS class III.

Numerous formulations were used across the development of inavolisib. In the phase III study WO41554, the final strengths (3 and 9 mg) were used. The effect of some minor changes (colour) between the phase III and the commercial formulation is addressed by *in vitro* dissolution, see Quality assessment aspects. Since the formulation of the 3 and 9 mg is qualitatively and quantitatively proportional, PK is linear and both were used in the phase III study, the available PK data is acceptable.

Inavolisib was taken without regard to the timing of food in the Phase III study WO41554. The obtained results from treatment Arm D as a part of GO39374 Phase I study have overall not implied a clinically significant impact of food on the absorption of inavolisib. Therefore, the currently proposed SmPC 4.2 recommendation that inavolisib can be taken with or without food is acceptable.

Characterisation of the inavolisib absorption characteristics in the target population using a PopPK approach is supported.

Distribution

The PopPK model estimated the apparent central volume of distribution to 155 L.

Fraction bound to plasma proteins *in vitro* was 37%, and this parameter value is considered acceptable in SmPC section 5.2.

Elimination

Given the minimal metabolism of inavolisib in the *in vitro* assay with HLM and recombinant CYPs, the potential for inavolisib to be affected by inducers and inhibitors of CYP3A4/5 or other CYPs is negligible.

The recovery in the mass balance study was over 90%, denoting a sufficiently long sampling of excreta. 93.1% of the radioactive dose in excreta has been identified, which is adequate.

Inavolisib related radioactivity is excreted in faeces and in urine at similar amounts (48 and 48.5%). Renal excretion is a major elimination pathway. Considering that fu*GFR is smaller than CLR (5.54 L/h), there is some extent of renal secretion.

Total radioactivity has a longer t1/2 than inavolisib in plasma (14h (iv) to 18h (po) for inavolisib and 53h for total radioactivity). In plasma, the main extracted entity was inavolisib, however the extraction recovery in pooled samples for the whole interval was only 69%, thus up to 31% of the plasma radioactivity are not identified. It is unclear whether the lower recovery is time or concentration dependent. Recovery of total radioactivity in excreta is high, suggesting that any protein-bound or metabolite-related radioactivity is eventually excreted. It is also considered unlikely that there would be a major metabolite that has not been identified, since the majority of metabolites in excreta are formed by hydrolysis (28% M8 related).

Inavolisib is unstable in faeces and during faecal sample extraction, generating M5, M6, M18 and M19 (sum in excreta ca 9.7% of the dose). M5, M18 and M19 were also found in urine and plasma where inavolisib was stable. An uncertainty remains thus on how much of these metabolites is formed *in vivo* and how much their amount increases due to instability in faeces or during sample preparation. Thus, they should not be included in the calculation of Fabs (see absorption section).

The M8 related metabolites (i.e., M4, M8, M9, M11, M12, M13, M14, and M15, 28.2% of the dose) are not part of the metabolites detected in stability experiments. Overall, this indicates that hydrolysis is a major elimination pathway of inavolisib. Furthermore, additional *in vitro* experiments were conducted by the applicant in which carboxylesterase 1 (CES1), carboxylesterase 2 (CES2), and aldehyde oxidase (AO) hydrolysis enzymes did not seem to be involved in the metabolism of inavolisib. In conclusion, no specific hydrolysis enzymes responsible for the metabolism of inavolisib could be identified. Therefore, no specific enzyme inhibitors are expected to cause clinically relevant interactions with inavolisib (i.e., with inavolisib as a "victim" drug).

Overall, data indicates that major elimination pathways (>25%) of inavolisib are renal excretion and hydrolysis. Biliary excretion of unchanged inavolisib is likely a minor pathway, considering that 10.8% of inavolisib was recovered in faeces, along with 9.7% of the potentially instable metabolites.

To evaluate the possibility of inter-conversion *in vivo* (enzymatic conversion), the applicant has re-analysed samples collected in the mass-balance study (Study GP42652) to investigate whether the inavolisib isomers could be detected in human plasma, urine, and faeces. This study indicated that 3 inavolisib isomers (G03050264, G03044276, and G03050263) were not detected in plasma, urine, or faeces from human volunteers following a single oral dose (9 mg) of [^{14}C] inavolisib. Therefore, these reanalysed data imply that chiral interconversion of inavolisib is unlikely to occur *in vivo* in humans.

Pharmacokinetics in the target population

The inter-individual variability in inavolisib PK is considered moderate. No intra-individual variability in PK parameters was included in the PopPK model, which is considered acceptable.

Dose proportionality and time dependencies

The applicant did not include any dose-dependent PK parameters and/or PK non-linearity in the PopPK model. However, the PopPK model over-predicted the 3 mg dose level (data not shown), which is not considered an issue since 3 mg is considerably lower than the recommended starting dose (9 mg) and only three subjects were randomised to the 3 mg dose in Study GO39374.

Special populations

Based on the currently presented/available data from the ongoing renal impairment (RI) study (GP44944 study), the geometric mean ratios (90% CIs) for $AUC_{0-\infty}$ and C_{max} were 1.73 (1.49, 2.02) and 1.11 (0.992, 1.25), respectively, for the moderate renal impairment group versus the normal renal function group. The recommended starting dosage of inavolisib for patients with moderate renal impairment (eGFR ≥ 30 to <60 mL/min based on CKD-EPI) is 6 mg QD orally. No dose adjustment is required in patients with mild renal impairment (eGFR 60 to < 90 mL/min). There are no data in patients with severe renal impairment (see SmPC 4.2 and 5.2). The study portion with severe RI subjects and their matched controls is currently ongoing and the final CSR of GP44944 will be available in Q3 2025 (REC).

A dedicated study in patients with moderate or severe hepatic impairment is not considered warranted for inavolisib because hepatic impairment in general is unlikely to have a clinically significant impact on the PK of inavolisib based on its low metabolic turnover, low extraction ratio and low protein binding.

Based on the PopPK analysis, none of the hepatic markers were significant which indicates limited impact of hepatic impairment on inavolisib PK. No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN and total bilirubin ≤ ULN) as reflected in SmPC section 4.2. However, in the observed PopPK dataset most subjects had either normal hepatic function (62%) or mild hepatic impairment (37%) which means that no firm conclusions can be drawn from the PopPK analysis for patients with moderate or severe hepatic impairment (see SmPC section 4.2 and 5.2).

A popPK approach is acceptable for exploring sex, race, weight and age as covariates on inavolisib PK where neither of these covariates were considered clinically relevant, which is acceptable.

Pharmacokinetic interaction studies

As no dedicated clinical DDI studies were conducted, some of the positive *in vitro* DDI signals are addressed by the clinical data from the Phase I (GO39374) and Phase III (WO41554) study.

According to the EPAR of Ibrance, palbociclib is mainly eliminated through CYP3A4 and SULT2A1 metabolism, with itraconazole inhibiting about half the elimination *in vivo* [AUCR 1.87]. Palbociclib is thus a CYP3A4 substrate, however it cannot be considered a sensitive substrate. At all timepoints in the phase III study, there is no sign of an impact of inavolisib on the PK of palbociclib. Thus, for a moderately sensitive CYP3A4 substrate, the net effect of the CYP3A4 TDI and induction indicates no relevant interaction. These aspects are reassuring that not all concomitant administration with CYP3A4 substrates may be affected, however, as extrapolation to sensitive CYP3A4 substrates is not possible, appropriate warnings were included in section 4.5 of the SmPC to highlight that inavolisib should be used with caution in combination with sensitive CYP3A4 substrates with a narrow therapeutic index as inavolisib may increase or decrease the systemic exposure of these substrates.

Also, despite the current data indicating the lack of CYP3A4 DDI, this cannot be extrapolated to other PXR-mediated enzymes and transporters. Overall, the provided data is not considered sufficient to exclude an interaction, and the applicant was recommended to submit a DDI study with sensitive substrates of CYP3A4, CYP2B6 and CYP2C enzymes (PAM-REC) (see further below).

The impact of PPIs on inavolisib exposure was evaluated from data from GO39374 and WO41554 from those patients who have self-reported the use of PPIs. However, this approach is not considered robust enough (e.g., a parallel study design, small number of individuals taking PPIs, uncertainties in self-reporting, etc) to draw relevant conclusions on clinically relevant interaction. A possibly, somewhat lower exposure might, however, be acceptable taking into account that PPI use was not excluded in the pivotal study. Importantly, based on the quality data which have indicated high solubility of inavolisib (i.e., sufficiently high solubility even at higher pH values) a dedicated clinical DDI study between inavolisib and PPIs is not required.

Study GO39374 also investigated some additional DDI aspects of inavolisib as a potential "victim" drug. Treatment arms B-F of this study included concomitant administration of inavolisib together with one or more of the following medications: letrozole, palbociclib, fulvestrant and metformin. PK data from these treatment arms were then compared to treatment arm A (i.e., PK of inavolisib alone). Overall, data implied no interaction effects on inavolisib exposure (i.e., as a "victim" drug) with these common concomitant therapies. However, there are several drawbacks with the applied analysis approach, e.g., the parallel group design is generally not recommended due to the confounding inter-individual variability. Therefore, (according to the EMA DDI guideline) a dedicated clinical DDI study with a cross-over design would be considered as a more appropriate and reliable approach in investigating such DDI scenarios. Nevertheless, since there were no positive *in vitro* data/signals which would imply interaction risks, no such dedicated clinical DDI study (i.e., with letrozole, palbociclib, fulvestrant and metformin) are required with inavolisib as a potential "victim".

No dedicated DDI study was conducted between inavolisib and oral contraceptive, which is acceptable considering the proposed indication (e.g., patient population, combination with palbociclib and fulvestrant).

Pharmacokinetics using human biomaterials

Overall, the applicant has conducted all the necessary *in vitro* DDI experiments to investigate inavolisib as a potential "perpetrator" and "victim" of different DDI scenarios involving CYP enzymes and transporters. However, there are still several issues regarding *in vitro* DDI aspects/results which need to be addressed further.

In vitro study 16-0131 has indicated a significant induction potential of inavolisib towards CYP3A4 enzyme (more than 30-fold increase in mRNA levels), and also implied interaction potential due to the induction of CYP2B6 enzyme (reflected in mRNA increase of this enzyme). Moreover, considering that inavolisib also acts as time-dependent inhibitor of CYP3A4 (as demonstrated in the *in vitro* study 15-2967), the applicant is recommended to conduct a dedicated clinical DDI study with sensitive CYP3A4 substrate (midazolam) and sensitive CYP2B6 substrate (REC). Such clinical study should implement a suitable study design with sufficiently long repeated dosing of inavolisib in order to adequately capture the net effect of simultaneous induction and TDI inhibition of CYP3A4 enzyme.

In vitro data have also implied positive induction signals of inavolisib towards CYP2C8, CYP2C9 and CYP2C19 enzymes. The applicant is also recommended to evaluate the potential clinical relevance of the impact of inavolisib on sensitive substrates of CYP2C8, CYP2C9, and CYP2C19. Generation of new clinical data with sensitive CYP2C substrates is especially relevant because these PXR regulated enzymes might demonstrate induction only (unlike CYP3A4 for which simultaneous induction + TDI is expected). SmPC 4.5 reflects examples of representative sensitive CYP3A4, CYP2C and CYP2B6

substrates which are likely to be co-administered with inavolisib in the patient population and highlights that inavolisib should be used with caution in combination with sensitive substrates of these enzymes as it may decrease their systemic exposure and consequently lead to decreased efficacy.

Pharmacodynamics

Concentration-QTc analysis

The concentration-QTc analysis is considered supportive to the assessment on the inavolisib QT prolonging potential. The analysis supports that inavolisib does not cause clinically relevant QT prolongation at therapeutic exposures. However, an important limitation is that there were limited data from patients with supratherapeutic exposure. Furthermore, the model included empirical time elements (steady state vs single dose, different ΔQTcF for the 6- and 8 hr time-point) which is a limitation since it seems mechanistically implausible that certain time-points would be associated with different QT prolongation, and it is unclear how this translates to an actual clinical situation. This may be an artifact of the heterogenous nature of the study (open-label, multi-centre study in patients, etc). However, sensitivity analyses simulating both with and without time-effects ensured that the most conservative scenarios were reported, which is reassuring (data not shown).

The predictions of QT prolongation at various exposures of interest seems overall reasonable, although the data should be interpreted with caution due to the highlighted limitations of the analysis. Simulations for the typical patient indicate that the mean and 90% CI of the predicted increase in QT is generally below 10 ms. The upper end of the 90% confidence interval for patients with renal impairment slightly intersected with 10 ms but this is not considered a relevant concern given the totality of data relating to QT prolongation.

The overall conclusion that inavolisib does not cause clinically relevant QT prolongation is based on the totality of evidence also including pre-clinical data and the clinical (cardiovascular) safety database, in addition to the concentration-QT analysis.

Exposure-response analyses

In the current submission, the exposure-response analyses are considered exploratory and supportive only, with limited impact on the overall benefit/risk assessment.

For Study GO39374, exposure-response trends were identified for the safety endpoints hyperglycaemia grade ≥ 2 and any AE grade ≥3, whereas no statistically significant exposure-response trends were evident for the efficacy endpoints. In Study GO39374, data from different dose levels were available. However, apart from the 9 mg dose level, the data are scarcer; only 2 patients were in the 3 mg arm, 16 patients were in the 6 mg arm, and only 4 patients were in the 12 mg arm. This means that the amount of data at the lower and higher doses are very limited. Furthermore, the study was open-label and patients were subject to dose reductions which could also have confounded the analysis. Despite the outlined limitations, the exposure-safety relationships support the fact that dose reductions are useful due to AEs.

For Study WO41554, a key limitation is that the observed exposure range is narrow since only a single inavolisib dosing regimen was included. Furthermore, in Study WO41554, patients were subject to dose reductions which could confound the results. These are considerable limitations which make it difficult to characterise the underlying exposure-response trends. The identified exposure-response relationships for Study WO41554 (OS and anaemia) are not considered clinically significant.

Dose justification

The proposed starting dose of 9 mg is considered acceptable. The exposure-response analyses and dose intensity statistics to support the 9 mg dose have several limitations which means that they are not suitable for firmly concluding the most appropriate dose. However, an important consideration is

that study WO41554 was a placebo-controlled study, which makes it possible to evaluate the benefit/risk of the 9 mg dose.

2.6.4. Conclusions on clinical pharmacology

The Clinical Pharmacology of inavolisib is generally well-described. Relevant information is reflected in the SmPC.

2.6.5. Clinical efficacy

Table 19. Summary of studies contributing to the efficacy evaluation

Study No. (Phase)	Population	Study Design	Number of Patients Enrolled	Dose, Route, and Regimen	Efficacy Endpoints	CCOD
Pivotal Study						
WO41554 (Phase III)	Patients ≥ 18 years of age with locally advanced or metastatic *PIK3CA*-mutated, HR-positive, HER2- negative breast cancer	Multicenter, randomized, double blinded, placebo-controlled	N = 325 (Inavo + Palbo + Fulv: 161 patients; Pbo + Palbo + Fulv: 164 patients)	Inavolisib 9 mg/placebo QD PO + palbociclib 125 mg QD PO (21/7) + fulvestrant 500 mg Q4W IM (Days 1 and 15 of first 28-day cycle, and then Day 1 of each following 28-day cycle)	**Primary Endpoint:** INV-PFS **Secondary Endpoints:** OS, ORR, BOR rate, DOR, CBR, PRO **Exploratory Endpoints:** Proxy for PFS2, SRE, PRO	Primary analysis: 29 Sep 2023
Supportive Study						
Study GO39374 (Phase I) [a]	Patients ≥ 18 years of age with locally advanced or metastatic *PIK3CA*-mutated solid tumors, including breast cancer	Multicenter, first-in-human, open-label, dose-escalation and expansion	Stage I: Dose escalation (N=50): Arm A=20 Arm B=13 Arm C=17 Stage II: Dose expansion [b]: (N = 141) Arm B=20 Arm C=20 Arm D=60 Arm E=20 Arm F=21 [c]	**Dose Escalation:** Arm A: inavolisib QD PO (6-, 9-, 12 mg) Arm B: inavolisib QD PO (3-, 6-, 9 mg) + letrozole 2.5 mg QD PO + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm C: inavolisib QD PO (6-, 9 mg) + letrozole 2.5 mg QD PO **Dose Expansion [b]:** Arm B: inavolisib 9 mg QD PO + letrozole 2.5 mg QD PO + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm C: inavolisib 9 mg QD PO + letrozole 2.5 mg QD PO Arm D: inavolisib 9 mg QD PO + fulvestrant 500 mg IM Arm E: inavolisib 9 mg QD PO + fulvestrant 500 mg IM + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm F: inavolisib 9 mg QD PO+ fulvestrant 500 mg IM + palbociclib 125 mg QD PO (3 weeks on/1 week off) + metformin up to 2000 mg PO	**Activity (Efficacy) Endpoints [d]:** ORR, BOR rate; DOR, CBR, PFS	Interim analysis [e]: 27 Mar 2023

BOR = best overall response; CBR = clinical benefit rate; CCOD = clinical cutoff date; DOR = duration of response; Fulv = fulvestrant; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IM = intramuscular; Inavo = inavolisib; INV = investigator; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = proxy for time to second objective disease progression; Palbo = palbociclib; PO = per oral; PRO = patient-reported outcome; QD = once daily; Q4W = every 4 weeks; SRE = Time to first skeletal-related event.

a. Study design for Arms A through F for Study GO39374 is provided in this table for complete information. Only Arm B, Arm E and Arm F efficacy data are provided in this SCE.

b. Phase I Study GO39374 Stage II Arm G (inavolisib in combination with trastuzumab and pertuzumab) is not included in the dossier as this arm was still enrolling at the time of CCOD and the treatment combination studied and the population enrolled differ from the proposed indication in the application.

c. One patient in Arm F withdrew consent and discontinued from the study prior to receiving any study treatment.

d. The primary objective of Study GO39374 was safety.

e. Given the hypothesis-generating nature of Study GO39374, there was no protocol-specified interim analysis.

Source: WO41554 CSR, Report 1126696 and GO39374 CSR, Report 1125233.

2.6.5.1. *Dose response study(ies)*

Study GO39374 is an ongoing phase I, multicentre, first-in-human, open-label, dose-escalation and expansion study of:

- inavolisib monotherapy in patients with locally advanced (LA) or metastatic *PIK3CA*-mutated solid tumours and
- inavolisib + endocrine and targeted therapies in patients with LA or metastatic *PIK3CA*-mutated breast cancer (BC).

The study consisted of six treatment arms (A-F) and two stages (stage I dose escalation, stage II dose expansion).

Data from arms B (stage I + II), E (stage II), and F (stage II) were submitted as supportive for the current application.

In stage I arm B, the patients received inavolisib at 3, 6, or 9 mg.

In stage II arms B, E, and F all patients received inavolisib at the proposed recommended dose (9 mg).

Eligibility criteria

Key inclusion criteria for arms B, E, and F included:

- Female patients >18 years, with ECOG performance status 0-1, adequate haematologic and organ function (see protocol), and histologically documented locally advanced or metastatic breast cancer measurable according to the RECIST criteria.
- Verified *PIK3CA* mutation (H1047R/Y/L, E542K, E545K/D/G/A, Q546K/R/E/L, N345K, C420R, G1049R, R88Q, or M1043I.
- HR+ and HER2- tumour according to specified criteria (see protocol).

In arm B, only postmenopausal women were enrolled (see protocol for definition of postmenopausal status). In arms E and F, female patients regardless of menopausal status were enrolled, but pre- and perimenopausal patients had to be treated with a GnRH or LHRH agonist at least four weeks prior to cycle 1 day 1 of study treatment and throughout the study treatment.

In arm F, all patients had risk factors for hyperglycaemia (either BMI $\geq$30 kg/m^2 or HbA1C $\geq$5.7% and <7% at baseline) and all patients in this study arm received metformin.

Key exclusion criteria for arms B, E, and F included:

- Prior treatment with a PI3K inhibitor.
- For stage II arms B and E prior treatment with a CDK4/6 inhibitor and prior treatment with >1 cytotoxic chemotherapy regimen in the metastatic setting.
- Type 1 diabetes, or Type 2 diabetes requiring antihyperglycemic medication.
- Significant cardiac co-morbidity (history of or active ventricular dysrhythmia, congestive heart failure requiring medication, or symptomatic coronary heart disease), congenital long QT syndrome or QT interval corrected (QTcF > 470 ms), family history of sudden, unexplained death or long QT syndrome, or current treatment with medications that prolong the QT interval.

Objectives and endpoints

Objectives

The objectives of study GO39374 were to determine objective response, clinical benefit, duration of response, and progression-free survival for safety-evaluable patients by dose level and cohort.

Efficacy endpoints

The key endpoint which could isolate efficacy, given the study design, was objective response rate (ORR). DOR, BOR, CBR, and PFS were also assessed.

All efficacy endpoints were assessed by the investigator according to RECIST v 1.1.

Results

In total, 74 patients were included in the three study arms: n=33 patients in arm B (inavolisib + palbociclib + letrozole, of which n=13 in stage I and n=20 in stage II), n=20 patients in arm E (inavolisib + palbociclib + fulvestrant), and n=21 patients in arm F (inavolisib + palbociclib + fulvestrant + metformin).

All but one patient in arm F, who withdrew consent and discontinued the study, received study treatment.

As of the clinical cut-off date (CCOD) of 27 March 2023, most of the patients in arm B (84.8%), arm E (70.0%), and arm F (95.2%) had discontinued from the study, mostly due to progressive disease (arm B 69.7%, arm E 50.0%, and arm F 61.9%).

The median age of patients in arms B, E, and F were 57 years (range 37−80 years) in arm B, 55 years (range 33−73 years) in arm E, and 65 years (range 33-77 years) in arm F. In all three study arms, $\geq$50% of the patients in all three arms had self-reported race recorded as White.

A high proportion of patients in arm F had a baseline HbA1C ≥5.7% (50%) and BMI ≥30 kg/m^2 (75%) reflecting the inclusion criteria for that study arm (see inclusion criteria above).

The majority of patients had received prior systemic anti-cancer treatment (arm B 97%, arm E 60%, arm F 100%). Prior CDK4/6 inhibitor treatment was received by 7/33 (21.2%) of patients in arm B (stage I), and 14/21 (66.7%) of the patients in arm F. All but two patients received palbociclib (one received ribociclib, one received palbociclib + abemaciclib). No patients in arm E received a prior CDK4/6 inhibitor (per eligibility requirement, see above). Most of the patients had also received prior aromatase inhibitors (arm B 73%, arm E 80%, arm F 95%), mostly letrozole.

The efficacy endpoints in arms, B, E, and F were analysed in all 73 treated patients.

Table 20. Overview of study GO39274 efficacy: Arm B, Arm E, Arm F (patients with measurable disease)

	Inavo+Palbo+Letro Arm B	Inavo+Palbo+Fulv Arm E	Inavo+Palbo+Fulv+Metf Arm F
ORR [a]	25	15	18
Responders, n (%)	13 (52.0%)	6 (40.0%)	3 (16.7%)
95% CI	30.42, 73.58	11.87, 68.13	0.00 33.66
DOR [a]	13	6	3
Patients with event, n (%)	8 (61.5%)	5 (83.3%)	3 (100%)
Median (months) (95% CI)	42.3 (14.7, NE)	11.9 (7.6, 33.4)	9.2 (9.1, NE)
BOR rate [a]	25	15	18
Responders, n (%)	15 (60.0%)	6 (40.0%)	3 (16.7%)
95% CI	38.80, 81.20	11.87, 68.13	0.00, 36.66
CBR [a]	33	20	20
Responders, n (%)	24 (72.7%)	18 (90.0%)	10 (50.0%)
95% CI	57.53, 87.92	76.85, 100.00	28.09, 71.91
PFS [a]	33	20	20
Patients with event (%)	24 (72.7%)	9 (45.0%)	14 (70.0%)
Median (months) (95% CI)	23.3 (9.2, 44.4)	35.0 (17.7, NE)	10.8 (3.4, 12.5)

BOR=best overall response; CBR=clinical benefit rate; CI = confidence interval; DOR=duration of response; ORR= confirmed objective response rate; NE= not estimated; PFS=progression free-survival.

a. ORR and BOR rate were summarized for safety analysis set with measurable disease. DOR was summarized for safety analysis set with measurable disease and a confirmed response. CBR and PFS were summarized in safety analysis set.

Source: GO39374 CSR, Report 1125233, Table 22, Table 23, Table 24, Table 25, Table 26.

Based on the submitted documentation, it is unclear how many patients in the supportive study GO39374 that received the proposed recommended inavolisib dose of 9 mg and how many that received other doses. It is noted, though, that other doses than 9 mg only pertain to patients in stage I arm B dose escalation, i.e., 13/74 (17.6%) of the patients. Thus, this missing information is of little consequence.

In total 21/74 (28.4%) had received CDK4/6 inhibitor (CDK4/6i) treatment prior to study inclusion and were, thus, exposed to CDK4/6i re-challenge. All but two had received prior palbociclib.

2.6.5.2. *Main study(ies)*

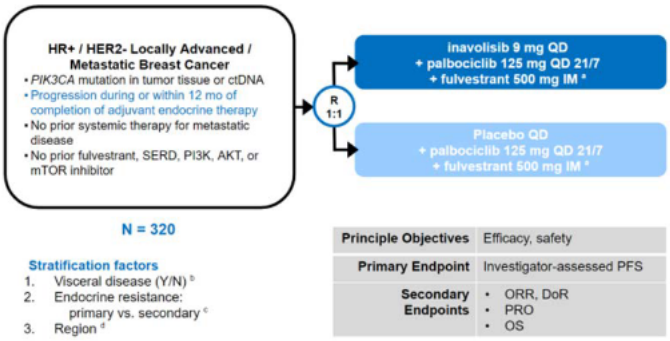
Study WO41554 (INAVO120), a phase III, randomised, double-blind, placebo-controlled, multi-centre, global study of inavolisib + palbociclib + fulvestrant (inavo + palbo + fulv) vs. placebo + palbociclib + fulvestrant (pbo + palbo + fulv) in patients with *PIK3CA*-mutated, HR+, HER2-, LA or metastatic breast cancer (mBC) whose disease progressed during or within 12 months of completing adjuvant ET and who had not received prior systemic therapy for LA/mBC.

As per protocol, study treatment continued until unequivocal disease progression as determined by the investigator, unacceptable toxicity, patient withdrawal of consent, or study termination.

For biomarker eligibility (i.e., positive for a study-eligible *PIK3CA* mutation) please refer to section `In vitro biomarker test for efficacy´ below.

Enrolment started on 29 January 2020 and was completed on 14 September 2023. The CCOD for the primary analysis was 29 September 2023. The study is ongoing.

Table 21. Study schema



AKT = protein kinase B; ctDNA= circulating tumor DNA; DOR = duration of response; HER2 – = human epidermal growth factor 2-negative; HR + = hormone-receptor positive; IM = intramuscular; mTOR =mammalian target of rapamycin; ORR = objective response rate; OS= overall survival; PFS= progression-free survival; PI3K= phosphatidylinositol 3-kinase; PRO= patient-reported outcome; QD = once daily; SERD = selective estrogen-receptor degrader.

a. Fulvestrant was administered on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.
b. "Visceral" (Yes/No) refers to lung, liver, brain, pleural, and peritoneal involvement.
c. Primary endocrine therapy resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy. Secondary endocrine therapy resistance was defined as relapse while on adjuvant endocrine therapy but after the first 2 years or relapse within 12 months of completing adjuvant endocrine therapy (4th European School of Oncology [ESO]–European Society for Medical Oncology [ESMO] International Consensus Guidelines for Advanced Breast Cancer [ABC4], Cardoso et al. 2018).
d. Region was stratified by site location: i) North America/Western Europe, ii) Asia/Pacific, iii) Other.

Methods

- **Study Participants**

According to the current version of the protocol (version 8), the study planned to enrol approximately 320 patients. A total of 590 patients were screened to enrol 325 patients, who were randomly assigned 1:1 to either inavo + palbo + fulv (n=161) or pbo + palbo + fulv (n=164).

Selected key inclusion criteria

- Histologically or cytologically confirmed adenocarcinoma of the breast that was locally advanced or metastatic and was not amenable to surgical or radiation therapy with curative intent.
- Documented ER+ and/or progesterone receptor (PR) + tumour and documented HER2- tumour (according to guidelines specified in the protocol)
- Confirmed *PIK3CA* mutation(s) by either central testing of blood or local testing of blood or tumour tissue.
- Tumour progression during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen.
- If a CDK4/6 inhibitor (CDK4/6i) was received as part of (neo-)adjuvant therapy, progression had to be >12 months since completion of the CDK4/6i portion of the (neo-)adjuvant or adjuvant therapy.
- Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1C <6.0% (<42 mmol/mol). For patients with fasting glucose >100 mg/dL (>5.5 mmol/L) at baseline, lifestyle changes according to American Diabetes Association guidelines and consultation with an endocrinologist or diabetologist was recommended.

- Pre- or perimenopausal female participants had to be treated with luteinizing hormone-releasing hormone (LHRH) agonist therapy. Male participants were recommended the same LHRH agonist therapy.

Selected key exclusion criteria

- Any prior systemic therapy for metastatic breast cancer
- Prior treatment with fulvestrant or any selective oestrogen-receptor degrader (SERD), except for patients that had received fulvestrant or any SERD as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months.
- Prior treatment with any PI3K, AKT, or mammalian target of rapamycin (mTOR) inhibitor, or any agent whose mechanism of action was to inhibit the PI3K-AKT-mTOR pathway.
- Known and untreated, or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases were eligible, provided they met the protocol criteria.
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry.
- Any history of type 1 diabetes.
- Daily dose of chronic corticosteroid therapy of ≥10 mg prednisone or equivalent anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.

- **Treatments**

Inavolisib/placebo was administered at 9 mg oral (PO) once daily (QD) on days 1-28 of each 28-day cycle.

Palbociclib was administered at 125 mg PO QD on days 1-21 of each 28-day cycle.

Fulvestrant was administered at 500 mg by intramuscular (IM) injection on days 1 and 15 of cycle 1 and then on day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.

Pre- or perimenopausal female participants and male participants also received LHRH agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to day 1 of cycle 1 and continuing for the entire duration of study treatment.

Patients at risk for developing hyperglycaemia (e.g., pre-diabetes, body mass index ≥30 kg/m2, HbA1c ≥5.7%, >45 years of age, family history of diabetes, history of gestational diabetes, and any other factor that may lead to increased risk of developing hyperglycaemia, including certain ethnicities and inactive lifestyle) may initiate treatment with metformin on day 1 of the study, where allowed by local regulations.

Table 22. Objectives/endpoints

Objectives	Endpoints
Primary Efficacy Objective • To evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant	• Progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression as determined by the Investigator according to RECIST v1.1 or death from any cause (whichever occurred first).
Secondary Efficacy Objective • To evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the bases of the following endpoints:	• Overall survival (OS), defined as the time from randomization to death from any cause • Objective response rate, defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions 4 weeks apart, as determined by the Investigator according to RECIST v1.1 • Best overall response rate, defined as the proportion of patients with a CR or PR, as determined by the Investigator according to RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a CR or PR to the first occurrence of disease progression as determined by the Investigator according to RECIST v1.1 or death from any cause (whichever occurred first) • Clinical benefit rate, defined as the proportion of patients with a CR, PR, and/or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1 • Time to confirmed deterioration (TTCD) in pain, defined as the time from randomization to the first documentation of a 2-point increase from baseline on the "worst pain" item from the Brief Pain Inventory- Short Form (BPI-SF) held for at least two consecutive cycles, or an initial increase followed by death or treatment discontinuation within three weeks from the last assessment. • TTCD in Physical Function, defined as the time from randomization to the first documentation of a ≥ 10-point decrease from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30) Physical Function scale (items 1–5), held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment • TTCD in Role Function, defined as the time from randomization to the first documentation of a ≥ 10-point decrease from baseline in the EORTC QLQ-C30 Role Function scale (items 6 and 7), held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment • TTCD in Global health status/Health-related quality of life (HRQoL), defined as the time from randomization to the first documentation of a ≥ 10-point decrease from baseline in the EORTC QLQ-30 GHS/QoL scale (items 29 and 30), held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment
Exploratory Efficacy Objective • To evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant	• Time to end of next-line treatment (proxy for time to second objective disease progression [PFS2]), defined as the time from randomization to end or discontinuation of next-line treatment, or death from any cause (whichever occurred first) • Time to first skeletal-related event (SRE), defined as the time from randomization to the first occurrence of an SRE. An SRE is a pathologic fracture, radiation therapy to bone, cancer-related surgery to bone, or spinal cord compression • Mean and mean change from baseline scores in function (Physical, Role, Cognitive, Emotional, and Social), HRQoL, and disease- and treatment-related symptoms, as measured by the scales of the EORTC QLQ-C30 and EORTC QLQ–Breast Cancer Module 23 Questionnaire (EORTC QLQ-BR23)
Safety Objective • To evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant	• Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Change from baseline in ECG parameters
Exploratory Safety Objective • To evaluate the tolerability of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant from the patient's perspective	• Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms) as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument • Overall bother from treatment side effects as assessed through the single bother item • Change from baseline in symptomatic treatment toxicities and treatment side-effect bother, as assessed via the PRO-CTCAE and the single bother item
Pharmacokinetic Objective • To characterize the pharmacokinetics of inavolisib, palbociclib, and fulvestrant, when administered in combination in this population	• Plasma concentration of inavolisib at specified timepoints • Plasma concentration of palbociclib at specified timepoints • Plasma concentration of fulvestrant at specified timepoints
China-Specific Pharmacokinetic Objective • To characterize the pharmacokinetics of inavolisib in all patients enrolled in China	• Plasma concentration of inavolisib at specified timepoints • Plasma concentration of palbociclib at specified timepoints • Plasma concentration of fulvestrant at specified timepoints

BPI-SF = Brief Pain Inventory–Short Form; CR = complete response ; ECG = electrocardiogram; EORTC QLQ-BR23 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Breast Cancer Module 23; EORTC QLQ-C30 = EORTC QLQ–Core 30; GHS = global health status; HRQoL = health-related quality of life; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; SRE = skeletal-related event; TTCD = time to confirmed deterioration

Note: Secondary efficacy endpoints were tested in a hierarchical manner as detailed in the statistical analysis plan (SAP)

Note: Exploratory pharmacokinetic, biomarker, and health status utility objectives are not analyzed in this Primary CSR. Details on these objectives and endpoints can be found in Study Protocol, Section 2.

- **Sample size**

- Estimates of the number of events required to demonstrate efficacy with regard to PFS were based on the following assumptions:
- Two-sided log-rank test at the 0.05 level of significance
- Eighty-five percent power to detect a hazard ratio for inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant of 0.65, corresponding to an improvement of 5.9 months (from 11 to 16.9 months) in median PFS for the treatment arm over the control arm
- Exponential distribution of PFS
- An annual dropout rate of 15%.

With these assumptions, 194 PFS events were required to achieve 85% power for the primary analysis. The 320 patients were to be enrolled over approximately 43 months and the primary analysis was expected to occur approximately 50 months after the first patient randomised.

The median OS in the control arm was assumed to be 35 months and the median OS in the experimental treatment arm was assumed to be 50 months, equating to a hazard ratio of 0.7. At the time of the primary PFS analysis, on the basis of the above assumptions, 105 OS events were expected to have occurred and 153 OS events for the final analysis of OS are expected to have occurred 19 months later. With the above assumptions, the cumulative power at the interim and final OS analysis was 25% and 59%, respectively.

- **Randomisation and Blinding (masking)**

Randomisation occurred in a 1:1 ratio using a permuted-block randomisation method to ensure a balanced assignment and stratified according to the following factors:

- Visceral disease (yes or no)
- Endocrine resistance (primary or secondary according to ESMO ABC4 guidelines [Cardoso et al. 2018])
- Geographic region (North America/Western Europe, Asia, Other).

This was a double-blind study. Study site personnel and patients were blinded to treatment assignment during the study.

Blinded Independent Central Imaging Review

A blinded independent central review (BICR) of tumour assessment data was performed to support the primary endpoint of investigator assessed PFS. To facilitate BICR for PFS, all radiological data (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan) and photographs for skin lesions obtained at baseline, during the treatment period, at the time of disease progression, and at the time of study treatment discontinuation (if not the same as disease progression) were to be sent to a central imaging vendor (contracted by the Sponsor) within 2 weeks of imaging to enable retrospective BICR.

- **Statistical methods**

Analysis sets

Table 23. Participant analysis sets

Participant Analysis Set	Description
FAS	All randomized participants; participants will be included in the analyses according to the treatment they were assigned.
SAS	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
PK-evaluable	All randomized participants in the inavolisib arm who have at least one evaluable inavolisib plasma concentration.

FAS = full analysis set; SAS = safety analysis set; PK = pharmacokinetic

Main analysis methods

The primary efficacy objective for this study was to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the Investigator-assessed PFS endpoint.

The statistical hypothesis was as follows:

- H0: PFS inavolisib plus palbociclib and fulvestrant = PFS placebo plus palbociclib and fulvestrant
- H1: PFS inavolisib plus palbociclib and fulvestrant ≠ PFS placebo plus palbociclib and fulvestrant

The null and alternative hypotheses were tested at a two-sided 0.05 significance level. The primary trial objective was to demonstrate superiority of the experimental over the control treatment.

The primary estimand handled ICEs (start of non-protocol anticancer therapy and early discontinuation from study treatment) with a treatment policy approach, in accordance with EMA censoring rules.

Data for participants without the occurrence of disease progression or death as of the clinical cutoff date (CCOD) were censored at the time of the last tumour assessment prior to the CCOD (or at the time of randomisation if no tumour assessment was performed after the baseline visit).

PFS were compared between treatment arms using the two-sided stratified log rank test at the 0.05 level of significance. The hazard ratio was estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio was provided. The stratification factors used were the same as the randomisation stratification factors (as entered in IxRS).

For each treatment arm, Kaplan-Meier methodology was used to estimate the median PFS, and the Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS. Kaplan-Meier curves were also produced.

Sensitivity and supplementary analyses

The following sensitivity analysis to the primary estimand of the primary PFS after randomisation will be performed:

- PFS assessed by Blinded Independent Central Review (BICR): PFS analysis were repeated based on BICR assessment. The BICR cannot evaluate patients if the baseline scans were missing hence, in such cases, data were censored at randomisation.

- PFS assessed by investigator based on unstratified analysis: To assess the impact of stratification the main analysis was repeated without stratification factors.
- PFS assessed by investigator in patients with *PIK3CA* mutation-positive status by the central test.
- Handling of missing scheduled tumour assessments: Patients who missed two or more scheduled assessments immediately prior to the date of disease progression were censored at the last tumour assessment prior to the missed visits.

Two supplementary analyses based on differing strategies of handling ICE were planned for PFS. Note that the attributes of population, variables, and population level summary remained the same as the primary estimand. The analysis for the supplementary estimands were conducted only on the primary endpoint investigator assessed PFS.

- PFS assessed by investigator based on hypothetical strategy for use of any non-protocol anti-cancer therapy (NPT) prior to disease progression: According to this strategy, patients who started NPT prior to disease progression were censored at the time of the last disease status assessment before the initiation of NPT. If patients started any NPT before starting study treatment, then the data of those patients were censored at the time of randomisation. Approaches to handle other ICE (discontinuation of study treatment prior to disease progression) and the analysis methods were the same as for primary analysis.
- PFS assessed by investigator based on composite strategy for use of any NPT prior to disease progression: According to the composite strategy, use of any NPT prior to disease progression was considered as a PFS event (progression) at the time of initiation of NPT. If patients started any NPT before starting study treatment, then the data of those patients were censored at the time of randomisation. Approaches to handle other ICE (discontinuation of study treatment prior to disease progression) and the analysis methods were the same as for primary analysis.

Analysis of important secondary endpoints

OS was defined as the time from randomisation to death from any cause. Data for patients who are alive at the time of the analysis data cutoff were censored at the last date they were known to be alive. Data from patients without post-baseline information were censored at the date of randomisation. Analysis methodology was as outlined for the primary endpoint, PFS.

Patients not meeting the criteria for Objective Response Rate (ORR), including patients with no response assessments (for whatever reason) were considered non-responders. An estimate of the response rate and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.

Analysis methodology for Best Overall Response (BOR) and for Clinical Benefit Rate (CBR) was as for ORR.

The analysis of Duration of Objective Response (DOR) included only patients who achieved an objective response. Analysis methodology was as outlined for the primary endpoint, PFS.

Planned subgroup analyses

The generalizability of PFS results were investigated as a part of an exploratory analysis by estimating the treatment effect in subgroups based on the following baseline prognostic factors (including stratification factors): Age (<65, ≥65), Age (<65, ≥65 to <75, ≥75), Sex (Male, Female), Ethnicity (Hispanic or Latino; Not Hispanic or Latino), Race (White, Black or African American, Asian, American

Indian or Alaska Native, Native Hawaiian or other Pacific Islander), Visceral disease (yes/no), Liver metastasis (yes/no), Number of organs of disease (<3 vs ≥3), Region (North America/Western Europe; Asia; Other), Endocrine resistance (primary resistance, secondary resistance), Menopausal status at randomisation (not post-menopausal, post-menopausal), ECOG (0, 1), Hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR+). Prior treatment in the adjuvant/neo-adjuvant setting: Endocrine treatment (aromatase inhibitor only/ tamoxifen only/aromatase inhibitor and tamoxifen), CDK4/6 inhibitor (yes/no), chemotherapy (yes/no).

Un-stratified analysis results were presented for subgroup analyses due to the potentially limited number of patients in each subgroup.

Interim analysis

One interim analysis for futility of the primary endpoint was planned to be conducted by iDMC after 75 PFS events (33% of information) were observed. The futility boundary was non-binding. The futility boundary (point estimate of PFS HR >1.1) were chosen so that the probability of stopping for futility when the study would be positive at primary analysis was small (<3%).

One interim analysis was performed for OS at the time of the primary PFS analysis. The type I error probability were controlled by using a Lan-DeMets (O'Brien Fleming) α-spending function for the secondary endpoint, OS, at a 5% overall level of significance.

If appropriate, additional exploratory analyses of OS may be conducted after the final analysis at time points defined through study milestones such as Health Authority interactions.

Table 24. Stopping boundaries for efficacy at the interim or final OS analysis

Analysis	p-Value Stopping Boundary (Effect Scale)	Estimated Time from FPI (months)	Information Fraction	Power
First interim analysis	0.0132 (or HR 0.615)	50	68% (105/153)	25%
Final analysis	0.0460 (or HR 0.724)	69	100% (153/153)	59%

The actual boundaries were calculated at the time of OS analysis based on the observed information fraction (i.e., actual number of events observed at time of analysis over the total planned target number of events).

Type I error control

The type I error-controlled secondary endpoints of this study were to be tested hierarchically according to the following pre-specified and fixed order of endpoints only if the primary endpoint, PFS, was statistically significant at the primary PFS analysis:

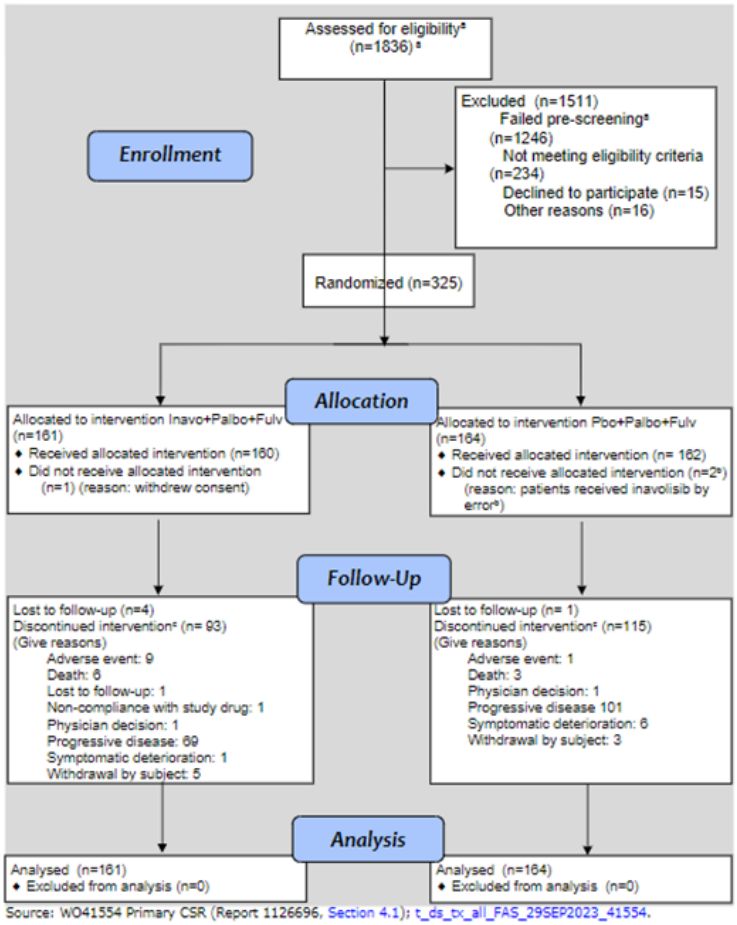
1. Overall survival (OS)
2. Objective response rate (ORR)
3. Best overall objective response rate (BOR)
4. Clinical benefit rate (CBR)
5. Time to confirmed deterioration (TTCD) in pain
6. TTCD in physical functioning (PF)
7. TTCD in role functioning (RF)

8. TTCD in Global Health Status/Quality of Life (GHS/QoL).

To adjust for multiple statistical testing of the key secondary efficacy endpoints, thereby controlling the overall type I error rate at a two-sided significance level of 5%, the fixed-sequence testing procedure were used, where each subsequent endpoint was formally tested at a two-sided significance level of 0.05 only if all previously tested hypotheses were statistically significant.

Results

- **Participant flow**



Source: WO41554 Primary CSR (Report 1126696, Section 4.1): t_ds_tx_all_FAS_29SEP2023_41554.

Patient disposition data reported as of the CCOD of 29 September 2023.

[a] A total of 1,836 patients were assessed for eligibility (prescreened) during the optional pre-screening period, of whom a total of 1,246 patients failed pre-screen, due to either having no detectable *PIK3CA* mutation or otherwise not qualifying for screening and therefore not moving forward into the screening period. A total of 590 patients were then screened for entry into the study.

[b] Two patients randomized to Pbo+Palbo+Fulv arm received inavolisib by error, these patients were included in efficacy analysis per their assigned treatment (Pbo+Palbo+Fulv), and in safety analysis per actual treatment received (Inavo+Palbo+Fulv).

[c] Reasons for intervention discontinuation are reasons collected at discontinuation visit in eCRF.

Figure 10 Study WO41554 participant flow diagram (CCOD 29 Sep 2023)

A total of 590 patients were screened for enrolment in study WO41554. Screen failures were reported for 265/590 (44.9%) whereas 325/590 (55.1%) were enrolled and randomised.

The most common reasons for screen failure were biomarker ineligibility (n=81), did not have adequate haematological and organ function (n=65), measurable disease per RECIST 1.1, patients with bone-only disease are not eligible even if bone qualifies as a measurable lesion (n=31), entered in error (n=16), and withdrew consent (n=15). Some patients had more than one reason for screen failure.

Reasons for discontinuation of individual study treatments are available from the CCOD of the primary analysis (29 Sep 2023). Updated reasons for study discontinuation were provided together with the final OS analysis results (CCOD 15 Nov 2024).

Table 25. Reasons for discontinuation of individual study treatments by trial treatment, FAS (CCOD 29 Sep 2023)

	Inavo+Palbo+Fulv (N=161)			Pbo+Palbo+Fulv (N=164)		
	Inavo	Palbo	Fulv	Pbo	Palbo	Fulv
Received Study Drug	160 (99.4%)	160 (99.4%)	160 (99.4%)	164 (100%)	164 (100%)	164 (100%)
Discontinued Treatment	94 (58.4%)	94 (58.4%)	93 (57.8%)	115 (70.1%)	115 (70.1%)	115 (70.1%)
ADVERSE EVENT	11 (6.8%)	8 (5.0%)	5 (3.1%)	1 (0.6%)	0	0
DEATH	6 (3.7%)	6 (3.7%)	6 (3.7%)	3 (1.8%)	3 (1.8%)	3 (1.8%)
NON-COMPLIANCE WITH STUDY DRUG	1 (0.6%)	1 (0.6%)	1 (0.6%)	0	0	0
PHYSICIAN DECISION	1 (0.6%)	2 (1.2%)	2 (1.2%)	0	0	0
PROGRESSIVE DISEASE	68 (42.2%)	69 (42.9%)	71 (44.1%)	102 (62.2%)	102 (62.2%)	102 (62.2%)
SYMPTOMATIC DETERIORATION	1 (0.6%)	1 (0.6%)	1 (0.6%)	6 (3.7%)	6 (3.7%)	6 (3.7%)
WITHDRAWAL BY SUBJECT	6 (3.7%)	6 (3.7%)	6 (3.7%)	3 (1.8%)	4 (2.4%)	4 (2.4%)
LOST TO FOLLOW-UP	0	1 (0.6%)	1 (0.6%)	0	0	0

Note: This output is presented per patient study drug assignment at randomization. Note that 2 patients randomized to the Pbo+Palbo+Fulv arm received at least one dose of inavolisib in error and were included in the Inavo+Palbo+Fulv SAS population for the purposes of the safety analyses.

Reasons for discontinuing individual trial treatments reported at Study Drug Early Discontinuation.
For patients who are missing discontinuation information from the individual drug early discontinuation eCRF page, but discontinued all three treatments at the same time, the information for discontinuation is pulled from the study disposition eCRF page.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Git repository: https://ssh.code.roche.com/studies/clinicalreporting/WO41554_CSR.git
Git hash: 01a8a971cc8a9eee1780816b4125917029aa443e
06 DEC 2023 19:14 GMT
Output:/ocean/harbour/CDT70123/WO41554/csr-primary/prod/output/t_ds_tx_FAS_29SEP2023_41554.out Page 1 of 1

Table 26. Reasons for study discontinuation, FAS (CCOD 15 Nov 2024)

Protocol: WO41554, CCOD: 15NOV2024, Data Snapshot: 10JAN2025

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)	All Patients (N=325)
Received Any Study Drug	160 (99.4%)	164 (100%)	324 (99.7%)
On-study status	75 (46.6%)	65 (39.6%)	140 (43.1%)
Alive: On Treatment	49 (30.4%)	20 (12.2%)	69 (21.2%)
Alive: In Follow-up	26 (16.1%)	45 (27.4%)	71 (21.8%)
Discontinued the study	86 (53.4%)	99 (60.4%)	185 (56.9%)
ADVERSE EVENT	1 (0.6%)	0	1 (0.3%)
DEATH	71 (44.1%)	79 (48.2%)	150 (46.2%)
LOST TO FOLLOW-UP	4 (2.5%)	5 (3.0%)	9 (2.8%)
PHYSICIAN DECISION	1 (0.6%)	0	1 (0.3%)
PROGRESSIVE DISEASE	1 (0.6%)	0	1 (0.3%)
SYMPTOMATIC DETERIORATION	1 (0.6%)	0	1 (0.3%)
WITHDRAWAL BY SUBJECT	7 (4.3%)	15 (9.1%)	22 (6.8%)

Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Git repository: https://code.roche.com/studies/clinicalreporting/WO41554_Overall_Survival_Reporting_Event_8219953
Git hash: 142631781fc0b756fa9e2423146b60eb622e69aa
03 FEB 2025 14:44 GMT
Output:/ocean/harbour/CDT70123/WO41554/CSRInterim_Ovrl_Surv/prod_srep_v1/output/t_ds_FAS_15NOV2024_41554.out Page 1 of 1

At the time of final OS analysis CCOD (15 Nov 2024), the median duration of follow-up was 34.2 months (range 30.2, 38.0) in the inavo + palbo + fulv arm vs. 32.3 months (range 26.7, 36.8) in the pbo + palbo + fulv arm.

- **Recruitment**

First patient enrolled: 29 January 2020

Last patient enrolled: 14 September 2023

CCOD of the primary analysis (final PFS analysis): 29 September 2023

CCOD of the final OS analysis: 15 November 2024

Study status: the study is ongoing. Enrolment is completed.

The study was conducted in 123 centres across the following 28 countries: China, Russia, Spain, Republic of Korea, Thailand, United States, Canada, Italy, Poland, Turkey, France, Taiwan, Ukraine, Australia, Greece, Hungary, Singapore, Hong Kong, Germany, Malaysia, United Kingdom, Argentina, Portugal, Georgia Republic, Belgium, Denmark, Brazil, New Zealand.

- **Conduct of the study**

Protocol amendments

The original global study protocol was finalised on 12 August 2019 and was amended seven times. The current protocol version is version 8, finalised on 8 March 2023.

The first study participant was enrolled on 29 January 2020, i.e., when protocol v2 was effective. All protocol versions were made before the primary analysis. The current protocol version (v8) was finalised approximately six months before CCOD of the primary analysis.

With **protocol amendment v2** (16 October 2019) v2, the protocol was amended with new information about interstitial lung disease (ILD)/pneumonitis, with palbociclib based upon a label update. palbociclib and/or GDC-0077 (inavolisib). The pneumonitis management guidelines were updated to align with the updated label.

Protocol amendment v3 (04 August 2020) was made to address the feedback from the Voluntary Harmonisation Procedure (VHP). The main amendments were addition of an interim safety analysis of the firs 25 enrolled patients and clarifications regarding the exclusion criteria for significant and active liver disease and known HIV infection, respectively. It was also clarified that prophylactic metformin may be initiated on day 1 of cycle 1 for patients at high risk of hyperglycaemia.

With protocol amendment v4 (3 November 2020) the protocol was amended to merge the VHP version (v3) and global protocol version 2.

Protocol amendment v5 (21 May 2021) was primarily made to allow for mobile nursing in Canada, to address the COVID-19 restrictions, and to improve access and convenience for study participants. Protocol v5 replaced v4 only in Canada.

Protocol amendment v6 (30 August 2021) included changes from both global version 4 and the Canada version 5. The main amendment was that a) the eligible threshold for HbA1C was changed from 5.7% [39 mmol/mol] to 6.0% [42 mmol/mol] to align with the eligible threshold more closely for fasting glucose of 126 mg/dL defining prediabetes per the American Diabetes Association and b) the eligibility criterion for measurable disease per RECIST v1.1 was extended to include bone-only disease with a measurable soft tissue component.

With **protocol amendment v7** (21 October 2022) the protocol was amended to correct the creatinine clearance threshold in the inclusion criteria and to clarify that mobile nursing may only be conducted by a sponsor-selected vendor.

With **protocol amendment v8** (8 March 2023) study design changes were introduced. The protocol was amended with a change in sample size due to an unanticipated slow enrolment during the COVID-19 pandemic. The intention was to minimise the risk of `last patient in´(LPI) occurring after reaching the number of planned events for the primary PFS analysis. Changes are summarised below:

- The total planned enrolment of 400 participants has been reduced to 320 to minimise the risk of LPI occurring after the number of planned events for the primary PFS analysis is reached.

- The number of progression free survival events to trigger primary study readout has been reduced from 227 to 194, resulting in a change in the power of PFS from 90% to 85%, which is considered adequate for the primary endpoint.
- An interim and a final OS analysis were added to preserve the integrity of this key secondary study endpoint.

Protocol deviations

Major protocol deviations were reported in four categories: procedural, medication, inclusion criteria, and exclusion criteria. All patients with protocol deviation(s) were included in the pre-defined analysis sets.

As of the CCOD, 28.3% of patients of the FAS had at least one major protocol deviation (26.1% of patients in the inavo + palbo + fulv arm vs. 30.5% in the pbo + palbo + fulv arm). The main reason for major protocol deviation in both study arms was procedural (labs not done per protocol; 5.0% and 7.9% in the inavo + palbo + fulv and pbo + palbo + fulv arms, respectively).

There were 35 major deviations that were upgraded as `major´ post-CCOD. They were all assessed by the applicant and resolved.

- **Baseline data**

Table 27. Demographic and baseline characteristics, FAS (CCOD 29 Sep 2023)

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)	All Patients (N=325)
Age (years)			
n	161	164	325
Mean (SD)	53.8 (10.9)	54.1 (11.2)	54.0 (11.1)
Median	53.0	54.5	54.0
Min - Max	27 - 77	29 - 79	27 - 79
Age group (years)			
n	161	164	325
< 65	136 (84.5%)	130 (79.3%)	266 (81.8%)
65 - 74	19 (11.8%)	28 (17.1%)	47 (14.5%)
>= 75	6 (3.7%)	6 (3.7%)	12 (3.7%)
Sex			
n	161	164	325
Male	5 (3.1%)	1 (0.6%)	6 (1.8%)
Female	156 (96.9%)	163 (99.4%)	319 (98.2%)
Race			
n	161	164	325
Asian	61 (37.9%)	63 (38.4%)	124 (38.2%)
Black or African American	1 (0.6%)	1 (0.6%)	2 (0.6%)
White	94 (58.4%)	97 (59.1%)	191 (58.8%)
Unknown	5 (3.1%)	3 (1.8%)	8 (2.5%)
Ethnicity			
n	161	164	325
HISPANIC OR LATINO	10 (6.2%)	10 (6.1%)	20 (6.2%)
NOT HISPANIC OR LATINO	145 (90.1%)	149 (90.9%)	294 (90.5%)
NOT REPORTED	2 (1.2%)	3 (1.8%)	5 (1.5%)
UNKNOWN	4 (2.5%)	2 (1.2%)	6 (1.8%)
Geographic region (per IxRS)			
n	161	164	325
Asia	58 (36.0%)	62 (37.8%)	120 (36.9%)
North America/Western Europe	62 (38.5%)	63 (38.4%)	125 (38.5%)
Other	41 (25.5%)	39 (23.8%)	80 (24.6%)
Baseline ECOG			
n	161	164	325
0	100 (62.1%)	106 (64.6%)	206 (63.4%)
1	60 (37.3%)	58 (35.4%)	118 (36.3%)
Missing	1 (0.6%)	0	1 (0.3%)
Post-menopausal status at randomization			
n	161	164	325
NOT POST-MENOPAUSAL	65 (40.4%)	59 (36.0%)	124 (38.2%)
POST-MENOPAUSAL	91 (56.5%)	104 (63.4%)	195 (60.0%)
Missing	5 (3.1%)	1 (0.6%)	6 (1.8%)
Visceral Disease (per IxRS)			
n	161	164	325
Yes	127 (78.9%)	126 (76.8%)	253 (77.8%)
No	34 (21.1%)	38 (23.2%)	72 (22.2%)
Endocrine Resistance (per IxRS)			
n	161	164	325
PRIMARY	57 (35.4%)	59 (36.0%)	116 (35.7%)
SECONDARY	104 (64.6%)	105 (64.0%)	209 (64.3%)

Endocrine resistance (primary or secondary according to European Society for Medical Oncology Advanced Breast Cancer 4 guidelines [Cardoso et al. 2018]).
HbA1c, hemoglobin A1c values by DCCT (Diabetes Control and Complications Trial) unit and by IFCC (International Federation of Clinical Chemistry) unit: 5.7% (DCCT) = 39 mmol/mol; 6.5% (DCCT) = 48 mmol/mol.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Table 28. Breast cancer history and baseline disease characteristics, FAS (CCOD 29 Sep 2023)

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)	All Patients (N=325)
Status of disease at Study entry			
n	161	164	325
Locally Advanced	1 (0.6%)	2 (1.2%)	3 (0.9%)
Metastatic	160 (99.4%)	162 (98.8%)	322 (99.1%)
Number of Organ Sites***			
n	161	164	325
1	21 (13%)	32 (19.5%)	53 (16.3%)
2	59 (36.6%)	46 (28%)	105 (32.3%)
>=3	81 (50.3%)	86 (52.4%)	167 (51.4%)
Visceral Disease (eCRF)**			
n	161	164	325
Yes	132 (82%)	128 (78%)	260 (80%)
No	29 (18%)	36 (22%)	65 (20%)
Liver**			
n	161	164	325
Yes	77 (47.8%)	91 (55.5%)	168 (51.7%)
No	84 (52.2%)	73 (44.5%)	157 (48.3%)
Lung**			
n	161	164	325
Yes	66 (41%)	66 (40.2%)	132 (40.6%)
No	95 (59%)	98 (59.8%)	193 (59.4%)
CNS**			
n	161	164	325
Yes	0	2 (1.2%)	2 (0.6%)
No	161 (100%)	162 (98.8%)	323 (99.4%)
Bone**			
n	161	164	325
Yes	107 (66.5%)	94 (57.3%)	201 (61.8%)
No	54 (33.5%)	70 (42.7%)	124 (38.2%)
Bone Only**, §			
n	161	164	325
Yes	5 (3.1%)	6 (3.7%)	11 (3.4%)
No	156 (96.9%)	158 (96.3%)	314 (96.6%)
Prior (neo)-adjuvant chemotherapy			
n	161	164	325
Yes	132 (82%)	137 (83.5%)	269 (82.8%)
No	29 (18%)	27 (16.5%)	56 (17.2%)
Prior (neo)-adjuvant CDK 4/6 inhibitor			
n	161	164	325
Yes	3 (1.9%)	1 (0.6%)	4 (1.2%)
No	158 (98.1%)	163 (99.4%)	321 (98.8%)
Prior (neo)-adjuvant Endocrine Therapy			
n	161	164	325
Yes	160 (99.4%)	163 (99.4%)	323 (99.4%)
No	1 (0.6%)	1 (0.6%)	2 (0.6%)
HER2 Status			
n	161	164	325
HER2-	161 (100%)	164 (100%)	325 (100%)
Hormone receptor status			
n	161	164	325
ER+/PR-	45 (28%)	45 (27.4%)	90 (27.7%)
ER+/PR+	113 (70.2%)	113 (68.9%)	226 (69.5%)
Other	3 (1.9%)	6 (3.7%)	9 (2.8%)
Endocrine Resistance (eCRF)			
n	161	164	325
Primary	53 (32.9%)	58 (35.4%)	111 (34.2%)
Secondary	108 (67.1%)	105 (64%)	213 (65.5%)
Missing	0	1 (0.6%)	1 (0.3%)

* at initial diagnosis
** at screening
§ Patients with evaluable bone-only disease are not eligible; disease that is limited to bone but has lytic or mixed lytic/blastic lesions and at least one measurable soft-tissue component per RECIST v1.1 may be eligible.
"Visceral Disease" (Yes/No) refers to lung, liver, brain, pleural, and peritoneal involvement.
*** "Number of Organ Sites" involved have been derived from target and non-target lesions at baseline.
"Endocrine Resistance" according to European Society for Medical Oncology Advanced Breast Cancer 4 guidelines [Cardoso et al. 2018]).
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Concomitant and rescue treatment

Most of the patients in both study arms received one or more concomitant medications initiated before randomisation (75.2% in the inavo + palbo + fulv arm vs. 72.0% in the pbo + palbo + fulv arm, respectively). Goserelin (8.7% inavo + palbo + fulv, 9.8% pbo + palbo + fulv, respectively), goserelin acetate (8.1% and 7.9%), and paracetamol (9.3% and 7.9%) were the most commonly used concomitant medications.

The majority of patients also received one or more concomitant medications initiated during study treatment (93.8% inavo + palbo + fulv, 87.8% pbo + palbo + fulv). Concomitant medications initiated in >10% of all patients during study treatment in both study arms included dexamethasone (33.5% inavo + palbo + fulv, 20.1% pbo + palbo + fulv, respectively), metformin (28.0% and 3.7%), and metformin hydrochloride (19.9% and 1.2%).

Concomitant medications initiated during study treatment for the treatment of adverse events was received by the majority of patients (89.4% vs. 79.9%, respectively). The most frequently reported such concomitant medications (>10% of all patients) were paracetamol (20.5% and 13.4%, respectively), dexamethasone (22.4% and 6.7%), metformin (26.7% and 0.6%), and metformin hydrochloride (18.6% and 0.6%).

Concomitant insulin for treatment of adverse event hyperglycaemia was initiated for 12.1% of the patients in the inavo + palbo + fulv arm vs. 0 in the pbo + palbo + fulv arm.

Subsequent anticancer therapy

Table 29. Key anti-cancer treatments administered during study after treatment discontinuation (for all lines post progression therapies), FAS (CCOD 15 Nov 2024)

	Inavo+Palbo+Fulv (N = 161)		Pbo+Palbo+Fulv (N = 164)	
	2nd Line	3rd Line or Later	2nd Line	3rd Line or Later
Discontinued Treatment	111 (68.9%)	111 (68.9%)	144 (87.8%)	144 (87.8%)
No Subsequent Therapy - Death	17 (10.6%)	17 (10.6%)	22 (13.4%)	22 (13.4%)
Patient with Subsequent Therapy	83 (51.6%)	48 (29.8%)	109 (66.5%)	56 (34.1%)
Chemotherapy (any)	46 (55.4%)	41 (85.4%)	79 (72.5%)	49 (87.5%)
Capecitabine	26 (31.3%)	14 (29.2%)	37 (33.9%)	24 (42.9%)
Antihormonal therapy (any)	26 (31.3%)	14 (29.2%)	31 (28.4%)	18 (32.1%)
Aromatase inhibitor	16 (19.3%)	10 (20.8%)	20 (18.3%)	14 (25.0%)
ADC (any)	1 (1.2%)	8 (16.7%)	1 (0.9%)	20 (35.7%)
PI3K inhibitor (any)	5 (6.0%)	2 (4.2%)	11 (10.1%)	3 (5.4%)
Alpelisib	5 (6.0%)	2 (4.2%)	9 (8.3%)	2 (3.6%)
mTOR kinase inhibitor (any)	8 (9.6%)	4 (8.3%)	10 (9.2%)	9 (16.1%)
Everolimus	8 (9.6%)	4 (8.3%)	10 (9.2%)	8 (14.3%)
CDK inhibitor (any)	8 (9.6%)	3 (6.2%)	5 (4.6%)	3 (5.4%)
Abemaciclib	2 (2.4%)	2 (4.2%)	0 (0.0%)	2 (3.6%)
Ribociclib	1 (1.2%)	1 (2.1%)	5 (4.6%)	0 (0.0%)
Palbociclib	5 (6.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)

Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant
Note: Only a selective therapies is presented in the table.

- **Numbers analysed**

All 325 randomised patients were included in the full analysis set (FAS), consisting of all patients randomised to the study (n=161 randomised to inavo + palbo + fulv and n=164 randomised to pbo + palbo + fulv). The FAS equals the intention to treat (ITT) population.

The FAS was used for all efficacy analyses except duration of response (DOR).

- **Outcomes and estimation**

Primary endpoint progression-free survival (PFS)

At CCOD of the primary PFS analysis, the PFS HR was 0.43 (95% CI 0.32, 0.59) with 2-sided p-value <0.0001, The overall PFS maturity rate was 60.0% (n=195 events).

Table 30. Time to event summary for PFS by investigator, FAS (CCOD 29 Sep 2023)

Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)
Patients with event (%)	82 (50.9%)	113 (68.9%)
Earliest contributing event		
Death	7 (8.5%)	8 (7.1%)
Disease Progression	75 (91.5%)	105 (92.9%)
Patients without event (%)	79 (49.1%)	51 (31.1%)
Time to Event (months)		
Median	15.0	7.3
95% CI	(11.3, 20.5)	(5.6, 9.3)
25% and 75%-ile	8.0, 30.1	3.2, 14.9
Range (censored)	0.0 to 37.6	0.0 to 38.8
Range (event)	0.1 to 30.1	0.1 to 27.4
Stratified Analysis		
p-value (log-rank)	<0.0001	
Hazard Ratio	0.43	
95% CI	(0.32, 0.59)	
Unstratified Analysis		
p-value (log-rank)	<0.0001	
Hazard Ratio	0.50	
95% CI	(0.38, 0.67)	
6 months		
Patients remaining at risk	111	77
Event Free Rate (%)	82.93	55.92
95% CI	(75.60, 88.23)	(47.55, 63.48)
Difference in Event Free Rate	27.01	
95% CI	(16.87, 37.15)	
p-value (Z-test)	<0.0001	
12 months		
Patients remaining at risk	66	40
Event Free Rate (%)	55.89	32.61
95% CI	(46.87, 63.98)	(24.86, 40.57)
Difference in Event Free Rate	23.28	
95% CI	(11.59, 34.97)	
p-value (Z-test)	<0.0001	
18 months		
Patients remaining at risk	41	19
Event Free Rate (%)	46.24	21.10
95% CI	(37.07, 54.90)	(14.26, 28.84)
Difference in Event Free Rate	25.14	
95% CI	(13.52, 36.76)	
p-value (Z-test)	<0.0001	

Summaries of PFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Hazard ratios and log-rank p-values are using stratified methods by stratifying Visceral Disease, Endocrine Resistance, and Region
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

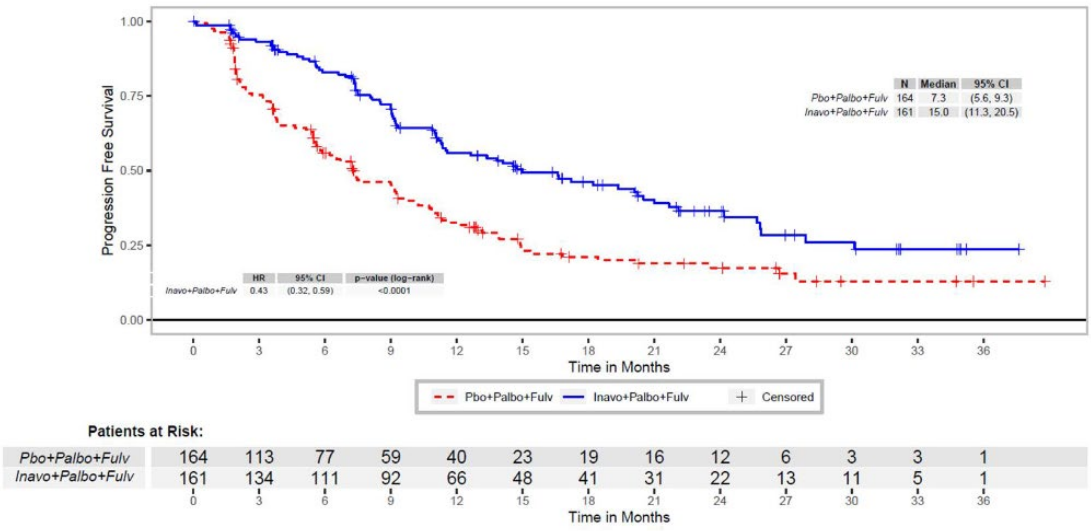


Figure 11. Kaplan-Meier plot for PFS by investigator, FAS (CCOD 29 Sep 2023)

Supplementary investigator-assessed PFS analyses and a sensitivity analysis based on blinded independent central review (BICR) were consistent with the primary analysis.

Time to response (TTR) was defined as the time from the date of randomisation to the date of first occurrence of a CR or PR, whichever status was recorded first, as determined by the investigator using RECIST v1.1.

In the descriptive TTR analysis, all patients from the FAS who had an objective response (CR or PR) on two consecutive occasions ≥4 weeks apart were included.

Table 31. Summary of time to first response by investigator in study WO41554

Summary for Time to First Response by Investigator, Full Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)
Time to First Response by Investigator(months)		
n	94	41
Mean (SD)	3.6 (3.5)	4.0 (2.9)
Median	1.9	3.6
25% and 75%-ile	1.8 - 3.7	1.9 - 3.8
Min - Max	1.7 - 18.6	1.6 - 12.9

Time to first response is defined as the time from the date of randomization to the date of first occurrence of a CR or PR (whichever status is recorded first) as determined by the investigator using RECIST v1.1, for patients with an objective response.
Objective responses correspond to patients with a CR or PR on two consecutive occasions >= 4 weeks apart per RECIST v1.1
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Table 32. Intercurrent events for investigator-assessed progression-free survival in study WO5144

Intercurrent Events for Progression-Free Survival, Full Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)
Patients without Intercurrent events	151 (93.8%)	157 (95.7%)
Patients with a PFS event	75 (46.6%)	106 (64.6%)
Patients with at least one Intercurrent event before PFS event/censoring (ICE 1 or ICE2)	10 (6.2%)	7 (4.3%)
Patients with a PFS event	7 (4.3%)	7 (4.3%)
Patients who discontinued from study treatment prior to PFS event/censoring (ICE 1)	8 (5%)	6 (3.7%)
Patients with a PFS event	5 (3.1%)	6 (3.7%)
Patients who started non-protocol anticancer therapy prior to PFS event/censoring (ICE 2)	5 (3.1%)	3 (1.8%)
Patients with a PFS event	4 (2.5%)	3 (1.8%)

Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Secondary endpoint overall survival (OS)

At CCOD of the final OS analysis, the OS HR was 0.67 (95% CI 0.48, 0.94) with 2-sided p-value 0.0190 crossing the pre-specified final OS significance boundary of p<0.0469. The overall OS maturity rate was 47.4% (n=154 events).

Table 33. Time to event summary for OS, FAS (CCOD 15 Nov 2024)

Protocol: WO41554, CCOD: 15NOV2024, Data Snapshot: 10JAN2025

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)
Patients with event (%)	72 (44.7%)	82 (50%)
Earliest contributing event		
Death	72 (100%)	82 (100%)
Patients without event (%)	89 (55.3%)	82 (50%)
Time to Event (months)		
Median	34.0	27.0
95% CI	(28.4, 44.8)	(22.8, 38.7)
25% and 75%-ile	17.8, 50.9	13.0, 50.0
Range (censored)	0.0 to 52.3	2.1 to 53.9
Range (event)	0.1 to 50.9	0.1 to 50.0
Stratified Analysis		
p-value (log-rank)	0.0190	
Hazard Ratio	0.67	
95% CI	(0.48, 0.94)	
Unstratified Analysis		
p-value (log-rank)	0.0846	
Hazard Ratio	0.76	
95% CI	(0.55, 1.04)	
6 months		
Patients remaining at risk	149	142
Event Free Rate (%)	96.84	90.11
95% CI	(92.58, 98.67)	(84.37, 93.82)
Difference in Event Free Rate	6.73	
95% CI	(1.38, 12.08)	
p-value (Z-test)	0.0136	
12 months		
Patients remaining at risk	131	119
Event Free Rate (%)	86.98	76.71
95% CI	(80.54, 91.40)	(69.32, 82.55)
Difference in Event Free Rate	10.27	
95% CI	(1.80, 18.73)	
p-value (Z-test)	0.0175	
18 months		
Patients remaining at risk	99	90
Event Free Rate (%)	74.33	67.18
95% CI	(66.44, 80.64)	(59.15, 73.99)
Difference in Event Free Rate	7.15	
95% CI	(-3.11, 17.40)	
p-value (Z-test)	0.1718	
24 months		
Patients remaining at risk	78	63
Event Free Rate (%)	65.78	56.25
95% CI	(57.28, 72.99)	(47.58, 64.05)
Difference in Event Free Rate	9.52	
95% CI	(-1.89, 20.93)	
p-value (Z-test)	0.1020	
30 months		
Patients remaining at risk	54	42
Event Free Rate (%)	56.54	46.29
95% CI	(47.49, 64.63)	(37.27, 54.82)
Difference in Event Free Rate	10.25	
95% CI	(-2.09, 22.59)	
p-value (Z-test)	0.1034	

Summaries of OS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Hazard ratios and log-rank p-values are using stratified methods by stratifying Visceral Disease, Endocrine Resistance, and Region. One patient was not included in the Overall Survival (OS) events due to an incomplete death date.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Git repository: https://code.roche.com/studies/clinicalreporting/WO41554_Overall_Survival_Reporting_Event_8219953
Git hash: 142631781fc0b756fa9e2423146b60eb622e69aa
03 FEB 2025 14:30 GMT
Output:/ocean/harbour/CDT70123/WO41554/CSRInterim_Ovrl_Surv/prod_srep_v1/output/t_ef_tte_OS_FAS_15NOV2024_41554.out Page 2 of 2

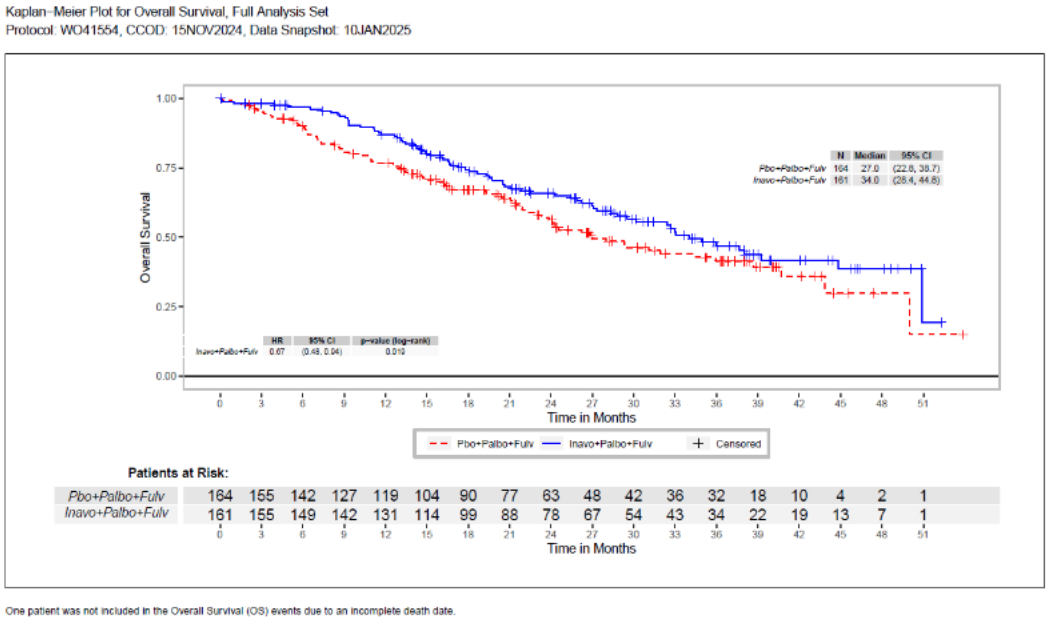


Figure 12. Kaplan-Meier plot for OS, FAS (CCOD 15 Nov 2024)

Table 34. Intercurrent events for overall survival in study WO41554 (CCOD 23 Sep 2023)

Intercurrent Events for Overall Survival, Full Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Inavo+Palbo+Fulv (N=161)	Pbo+Palbo+Fulv (N=164)
Patients without Intercurrent events	87 (54%)	80 (48.8%)
Patients with a OS event	11 (6.8%)	16 (9.8%)
Patients with at least one Intercurrent event before OS event/censoring (ICE 1 or ICE2)	74 (46%)	84 (51.2%)
Patients with a OS event	31 (19.3%)	39 (23.8%)
Patients who discontinued from study treatment prior to OS event/censoring (ICE 1)	20 (12.4%)	10 (6.1%)
Patients with a OS event	7 (4.3%)	5 (3%)
Patients who started non-protocol anticancer therapy prior to OS event/censoring (ICE 2)	64 (39.8%)	77 (47%)
Patients with a OS event	30 (18.6%)	36 (22%)

Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Other secondary endpoints

The final OS analysis was statistically significant, crossing the significance boundary $p \leq 0.0469$, and the hierarchical statistical testing therefore continued with the secondary endpoints ORR, BOR, and CBR. A summary of the results from the additional secondary endpoints is provided below.

Table 35. Overview of secondary endpoint results, FAS (CCOD 15 Nov 2024) – amended by the assessment team

	Final OS Analysis (CCOD: 15-Nov-2024)	
	Inavo + Palbo + Fulv N = 161	Pbo + Palbo + Fulv N = 164
Secondary Efficacy Endpoints		
Objective Response Rate (Investigator)		
Responders (n) (%)	101 (62.7%)	46 (28.0%)
95% CI	54.8, 70.2	21.3, 35.6
Difference (%) (95% CI)	34.7 (24.5, 44.8)	
p-value (CMH)	<0.0001	
Best Overall Response Rate (Investigator)		
Responders (n) (%)	109 (67.7%)	53 (32.3%)
95% CI	59.9, 74.8	25.2, 40.1
Difference (%) (95% CI)	35.4 (25.2, 45.6)	
p-value (CMH)	< 0.0001	
Clinical Benefit Rate (Investigator)		
Responders (n) (%)	131 (81.4%)	85 (51.8%)
95% CI	74.5, 87.1	43.9, 59.7
Difference (%) (95% CI)	29.5 (19.8, 39.3)	
p-value (CMH)	< 0.0001	
Duration of Response (Investigator)		
Number of evaluable patients	101	46
Patients with event (%)	58 (57.4%)	33 (71.7%)
Median (months) (95% CI)	19.2 (14.7, 28.3)	11.1 (8.5, 20.2)
Stratified HR (95% CI)	0.60 (0.37, 0.97)	
Primary Efficacy Endpoint		
Progression-Free Survival (Investigator) per RECIST v1.1		
Patients with event (%)	103 (64.0%)	141 (86.0%)
Median (months) (95% CI)	17.2 (11.6, 22.2)	7.3 (5.9, 9.2)
Stratified HR (95% CI)	0.42 (0.32, 0.55)	

CMH= Cochran-Mantel-Haenszel test; CCOD = clinical cutoff date; CI = confidence interval; GHS = global health status; HR = hazard ratio

[a]The pre-specified two-sided alpha boundary for OS at final analysis was 0.0469.

Patient reported outcomes (PROs)

The PRO variable time to confirmed deterioration (TTCD) in worst pain severity was assessed in the FAS using the BPI-DF worst pain item. The PRO variables TTCD in physical functioning, in role functioning, and in global health status/health related quality of life (GHS/HRQoL) were all assessed in the FAS using the EORTC QLQ-C30 questionnaire.

Questionnaire completion rates were comparable between the study arms for all questionnaires at all time-points.

There were no statistically significant differences in the PRO variable outcomes between the study arms.

Table 36. Overview of patient-reported outcome analyses, FAS (CCOD 15 Nov 2024)

	Inavo + Palbo + Fulv N = 161	Pbo + Palbo + Fulv N = 164
Secondary Efficacy Patient-Reported Outcome Endpoints		
TTCD in Worst Pain Severity		
Patients with event (%)	52 (32.3%)	53 (32.3%)
Median (months) (95% CI)	NE (20.3, NE)	19.6 (15.0, NE)
Stratified HR (95% CI)	0.74 (0.49, 1.10)	
P-value (log-rank)	0.1296	
TTCD in Physical Functioning[a]		
Patients with event (%)	60 (37.3%)	49 (29.9%)
Median (months) (95% CI)	26.1 (22.3, NE)	23.9 (15.0, NE)
Stratified HR (95% CI)	0.98 (0.66, 1.45)	
TTCD in Role Functioning[a]		
Patients with event (%)	64 (39.8%)	61 (37.2%)
Median (months) (95% CI)	28.4 (16.3, NE)	24.2 (9.7, NE)
Stratified HR (95% CI)	0.85 (0.59, 1.22)	
TTCD in GHS/HRQoL[a]		
Patients with event (%)	59 (36.6%)	56 (34.1%)
Median (months) (95% CI)	31.1 (25.7, 40.3)	19.4 (15.0, NE)
Stratified HR (95% CI)	0.81 (0.56, 1.19)	

CCOD = clinical cutoff date; CI = confidence interval; GHS = global health status; HR = hazard ratio; HRQoL = health-related quality of life; NE = not estimable; OS = overall survival; TTCD = time to confirmed deterioration.

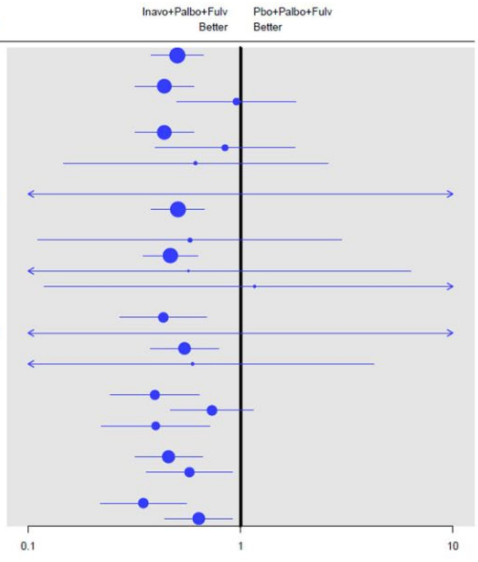
a. TTCD in worst pain severity did not cross the statistical boundary, therefore subsequent PRO endpoints were not formally tested.

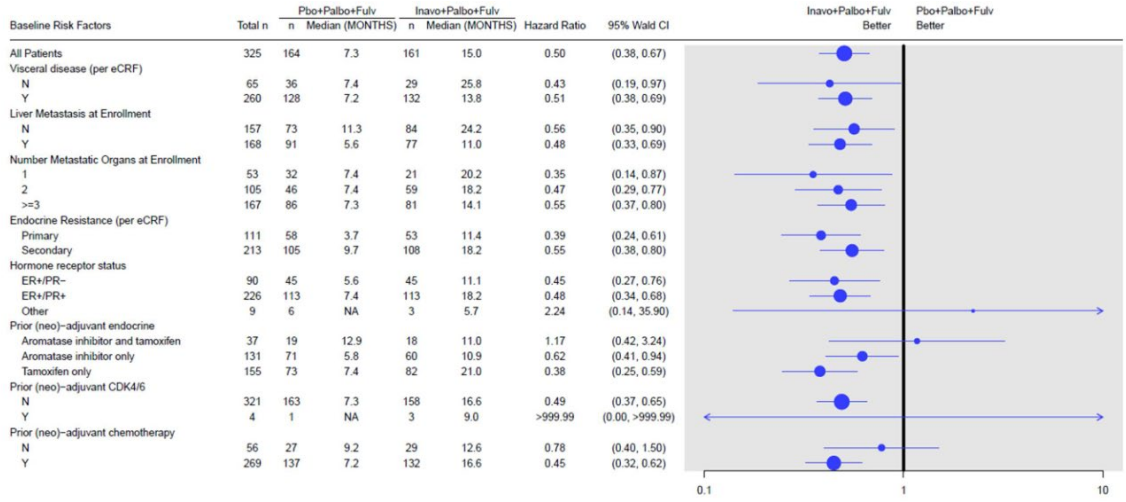
- **Ancillary analyses**

<u>Pre-defined subgroup analyses</u>

Figure 13. Forest plot of hazard ratio for PFS in key subgroups in baseline demographics and disease characteristics, FAS (CCOD 29 Sep 2023)

Baseline Risk Factors	Total n	Pbo+Palbo+Fulv n	Pbo+Palbo+Fulv Median (MONTHS)	Inavo+Palbo+Fulv n	Inavo+Palbo+Fulv Median (MONTHS)	Hazard Ratio	95% Wald CI
All Patients	325	164	7.3	161	15.0	0.50	(0.38, 0.67)
Age group 1 (years)							
< 65	266	130	7.2	136	16.6	0.44	(0.32, 0.60)
>= 65	59	34	10.7	25	9.3	0.96	(0.50, 1.83)
Age group 2 (years)							
< 65	266	130	7.2	136	16.6	0.44	(0.32, 0.60)
65 – 74	47	28	11.3	19	20.2	0.85	(0.40, 1.80)
>= 75	12	6	2.5	6	9.1	0.61	(0.15, 2.57)
Sex							
Male	6	1	NA	5	24.2	>999.99	(0.00, >999.99)
Female	319	163	7.3	156	14.6	0.51	(0.38, 0.68)
Ethnicity							
HISPANIC OR LATINO	20	10	20.3	10	24.2	0.58	(0.11, 3.00)
NOT HISPANIC OR LATINO	294	149	7.3	145	15.0	0.47	(0.35, 0.63)
NOT REPORTED	5	3	7.2	2	9.0	0.57	(0.05, 6.33)
UNKNOWN	6	2	1.6	4	6.8	1.16	(0.12, 11.39)
Race							
Asian	124	63	5.8	61	18.2	0.43	(0.27, 0.69)
Black or African American	2	1	16.8	1	9.0	>999.99	(0.00, >999.99)
White	191	97	7.5	94	16.6	0.54	(0.38, 0.79)
Unknown	8	3	7.2	5	11.0	0.59	(0.08, 4.25)
Region							
ASIA	114	58	5.8	56	14.6	0.40	(0.24, 0.64)
NORTH AMERICA/WESTERN EUROPE	127	64	9.3	63	13.8	0.73	(0.47, 1.15)
OTHER	84	42	5.6	42	21.0	0.40	(0.22, 0.72)
ECOG Performance Status at Baseline							
0	206	106	7.4	100	16.6	0.46	(0.32, 0.66)
1	118	58	5.6	60	11.4	0.58	(0.36, 0.92)
Menopausal status at randomization							
NOT POST-MENOPAUSAL	124	59	6.5	65	20.1	0.35	(0.22, 0.56)
POST-MENOPAUSAL	195	104	7.5	91	13.4	0.64	(0.44, 0.92)

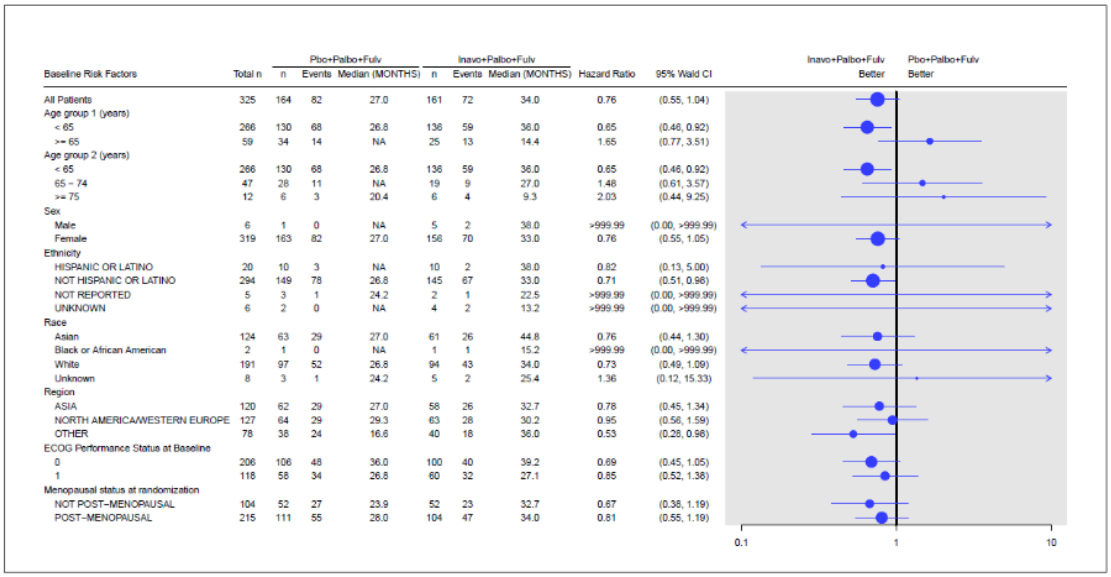




Post-hoc subgroup analyses

Figure 14. Forest plot of hazard ratio for OS in key subgroups in baseline demographics, FAS (CCOD 15 Nov 2024)

Forest Plot of Hazard Ratio for Overall Survival in Key Subgroups in Baseline Demographics, Full Analysis Set
Protocol: WO41554, CCOD: 15NOV2024, Data Snapshot: 10JAN2025

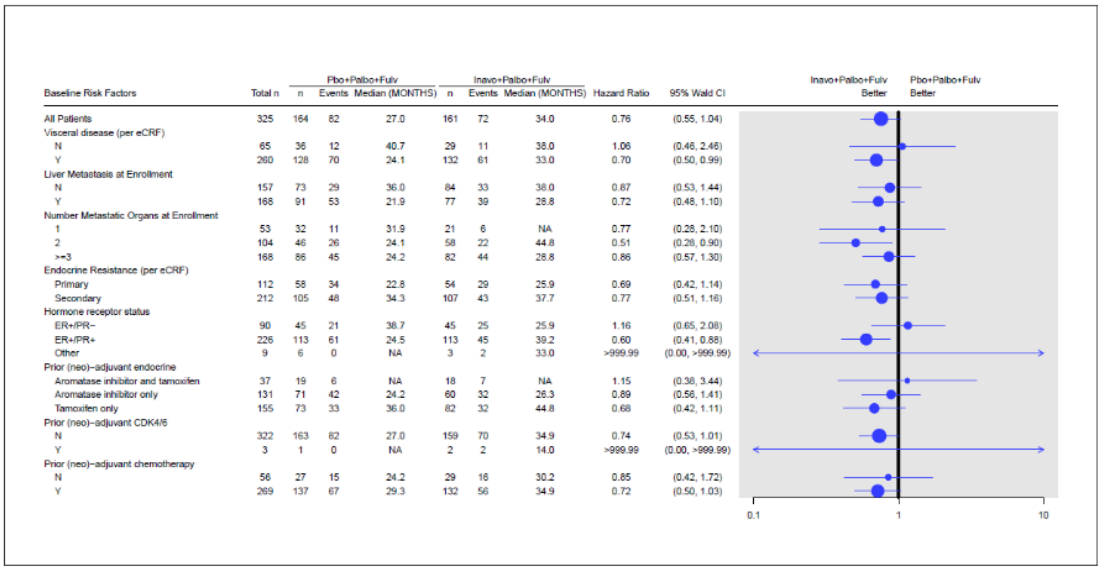


Unstratified hazard ratios are provided. One patient was not included in the Overall Survival (OS) events due to an incomplete death date.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant
Git repository: https://code.roche.com/studies/clinicalreporting/WO41554_Overall_Survival_Reporting_Event_8219953
Git hash: 142631781fc0b756fa9e2423146b60eb622e69aa
03 FEB 2025 14:22 GMT
Output:/ocean/harbour/CDT70123/WO41554/CSRInterim Ovrl Surv/prod sreo v1/output/o ef fo subd OS FAS 15NOV2024 41554.pdf

Note: Minor numerical updates to given baseline characteristics such as menopausal status and region were reported at the update analysis, as a result of ongoing data cleaning and updated definition of the menopausal status to include bilateral salpingo-oophorectomy.

Figure 15. Forest plot of hazard ratio for OS in key subgroups in baseline disease characteristics, FAS (CCOD 15 Nov 2024)

Forest Plot of Hazard Ratio for Overall Survival in Key Subgroups in Baseline Disease Characteristics, Full Analysis Set
Protocol: WO41554, CCOD: 15NOV2024, Data Snapshot: 10JAN2025



Unstratified hazard ratios are provided. One patient was not included in the Overall Survival (OS) events due to an incomplete death date.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant
Git repository: https://code.roche.com/studies/clinicalreporting/WO41554_Overall_Survival_Reporting_Event_8219953
Git hash: 142631781fc0b756fa9e2423146b60eb622e69aa
03 FEB 2025 14:23 GMT
Output:/ocean/harbour/CDT70123/WO41554/CSRInterim_Ovrl_Surv/prod_srep_v1/output/g_ef_fp_subc_OS_FAS_15NOV2024_41554.pdf

Note: Minor numerical updates to given baseline characteristics such as menopausal status and region were reported at the update analysis, as a result of ongoing data cleaning and updated definition of the menopausal status to include bilateral salpingo-oophorectomy.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of efficacy for trial WO41554 (INAVO120)

Title: WO41554 (INAVO120) – a phase III, randomised, double-blind, placebo-controlled study of inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant in patients with *PIK3CA*-mutant, HR+, HER2- locally advanced or metastatic breast cancer	
Study identifier	WO41554 (INAVO120) EudraCT Number: 2019-002455-42 ClinicalTrials.gov Identifier: NCT04191499
Design	Randomised, double-blind, placebo-controlled, multi-centre, phase III study. Regards patients with *PIK3CA*-mutated, HR+, HER2-, locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease. Patients were randomised 1:1 to inavo + palbo + fulv or pbo + palbo + fulv. Patients were stratified for: • visceral disease (yes or no) • endocrine resistance (primary or secondary according to ESMO ABC4 guidelines) • geographic region (North America/Western Europe, Asia, other)

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		29 January 2020 (first patient in) to 29 September 2023 (clinical cut-off date) not applicable not applicable
Hypothesis	<u>Superiority</u> The statistical hypothesis of this study is as follows: • H0: PFS inavo + palbo + fulv = PFS pbo + palbo + fulv • H1: PFS inavo + palbo + fulv ≠ PFS pbo + palbo + fulv The null and alternative hypotheses will be tested at a two-sided stratified log-rank test at a 0.05 significance level. The primary trial objective is to demonstrate superiority of the experimental over the control treatment.		
Treatments groups	Inavo + palbo + fulv (investigational arm)		Inavolisib: 9 mg PO QD on Days 1-28 of each 28-day cycle Palbociclib: 125 mg PO QD on Days 1-21 of each 28-day cycle Fulvestrant: 500 mg IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle (or approximately every 4 weeks) Treatment until unequivocal disease progression as determined by the Investigator, unacceptable toxicity, patient withdrawal of consent, loss to follow-up, death, or study termination. N=161 randomised patients
	Pbo + palbo + fulv (control arm)		Placebo: PO QD on Days 1-28 of each 28-day cycle Palbociclib: as for the investigational arm above Fulvestrant: as for the investigational arm above Treatment duration: as for the investigational arm above N=164 randomised patients
Endpoints and definitions	**Primary endpoint**	**PFS (Investigator)**	Time from randomisation to the first occurrence of disease progression as determined by the Investigator according to RECIST v1.1 or death from any cause (whichever occurred first).
	Secondary endpoint	Overall survival (OS)	Time from randomisation to death from any cause
	Secondary endpoint	Objective response rate (ORR) (Investigator)	Proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the Investigator according to RECIST v1.1
	Secondary endpoint	Best overall response (BOR) rate (Investigator)	Proportion of patients with a CR or PR, as determined by the Investigator according to RECIST v1.1

	Secondary endpoint	Duration of response (DOR) (Investigator)	Time from the first occurrence of a CR or PR to the first occurrence of disease progression as determined by the Investigator according to RECIST v1.1 or death from any cause (whichever occurred first)	
	Secondary endpoint	Clinical benefit rate (CBR) (Investigator)	Proportion of patients with a CR, PR, and/or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1	
	Secondary endpoint	Time to confirmed deterioration (TTCD) in worst pain severity	Time from randomisation to the first documentation of a ≥2-point increase from baseline on the "worst pain" item from the BPI-SF held for at least two consecutive cycles, or an initial increase followed by death or treatment discontinuation within three weeks from the last assessment	
	Secondary endpoint	TTCD in physical function (PF)	Time from randomisation to the first documentation of a ≥10-point decrease from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (EORTC QLQ-C30) Physical Function scale (items 1-5), held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment	
	Secondary endpoint	TTCD in role function (RF)	Time from randomisation to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 role function scale (items 6 and 7), held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment	
	Secondary endpoint	TTCD in health-related quality of life (HRQoL)	Time from randomisation to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-30 GHS/QoL scale (items 29 and 30), held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment	

Database lock	Database lock has not yet occurred; the study is ongoing. The PFS results are from the CCOD of the primary analysis as of 29 September 2023.			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set: All randomised participants; participants were included in the analyses according to the treatment they were assigned. Primary analysis (final PFS analysis) CCOD: 29 September 2023 Final OS analysis CCOD: 15Nov 2024			
Descriptive statistics and estimate variability	Treatment group	Inavo + palbo + fulv	Pbo + palbo + fulv	Effect estimates per comparison
	Number of subjects	161	164	
	PFS* (CCOD 29Sep 2023)			

	Median (months) (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)	HR 0.43 (0.32, 0.59) 2-sided p-value (log-rank) <0.0001
	OS** (CCOD 15Nov 2024)			
	Median (months) (95% CI)	34.0 (28.4, 44.8)	27.0 (22.8, 38.7)	HR 0.67 (0.48, 0.94) 2-sided p-value (log-rank) 0.0190 (stopping boundary p≤0.0469)
	ORR			
	Responders (n) (%) (95% CI, Clopper-Pearson)	101 (62.7%) (54.8, 70.2)	46 (28.0%) (21.3, 35.6)	Difference in response rate 34.7% (24.5, 44.8) p-value (CMH) <0.0001
	BOR rate			
	Responders (n) (%) (95% CI, Clopper-Pearson)	109 (67.7%) (59.9, 74.8)	53 (32.3%) (25.2, 40.1)	Difference in response rate 35.4% (25.2, 45.6) p-value (CMH) <0.0001
	CBR			
	Responders (n) (%) (95% CI, Clopper-Pearson)	131 (81.4%) (74.5, 87.1)	85 (51.8%) (43.9, 59.7)	Difference in response rate 29.5% (19.8, 39.3) p-value (CMH) <0.0001
	DOR			
	No. of evaluable patients Patients with event (%) Median (months) (95% CI)	101 58 (57.4%) 19.2 (14.7, 28.3)	46 33 (71.7%) 11.1 (8.5, 20.2)	HR 0.60 (0.37, 0.97)
	TTCD in worst pain severity			
	No. with event (%) Median (months) (95% CI)	52 (32.3%) NE (20.3, NE)	53 (32.3%) 19.6 (15.0, NE)	HR 0.74 (0.49, 1.10) p-value (log rank) 0.1296
	TTCD in PF			
	No. with event (%) Median (months) (95% CI)	60 (37.3%) 26.1 (22.3, NE)	49 (29.9%) 23.9 (15.0, NE)	HR 0.98 (0.66, 1.45)

	TTCD in RF			
	No. with event (%) Median (months) (95% CI)	64 (39.8%) 28.4 (16.3, NE)	61 (37.2%) 24.2 (9.7, NE)	HR 0.85 (0.59, 1.22)
	TTCD in HRQoL			
	No. with event (%) Median (months) (95% CI)	59 (36.6%) 31.1 (25.7, 40.3)	56 (34.1%) 19.4 (15.0, NE)	HR 0.81 (0.56, 1.19)
Notes	*The Type I error-controlled secondary endpoints were to be tested hierarchically according to the following pre-specified and fixed order of endpoints, only if the primary endpoint, PFS, was statistically significant at the primary PFS analysis: 1) OS; 2) ORR; 3) BOR rate; 4) CBR; 5) TTCD in worst pain severity; 6) TTCD in PF; 7) TTCD in RF; 8) TTCD in HRQoL. ** Results of all secondary endpoints are presented as of CCOD of the final OS analysis.			
CMH = Cochran-Mantel-Haenzel test BPI-SF = Brief Pain Inventory-Short Form				

2.6.5.3. *Clinical studies in special populations*

Table 38. Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	WO41554: 0/324	GO39374: 0/190
Hepatic impairment** patients (Subjects number /total number)	WO41554: 0/324	GO39374: 1/190
Paediatric patients <18 years (Subjects number /total number)	WO41554: 0/324	GO39374: 0/190
Age 65-74 (Subjects number /total number)	WO41554: Inavo+Palbo+Fulv: 19/162 Pbo+Palbo+Fulv: 28/162	GO39374: 55/190
Age 75-84 (Subjects number /total number)	WO41554: Inavo+Palbo+Fulv: 5/162 Pbo+Palbo+Fulv: 6/162	GO39374: 8/190
Age 85+ (Subjects number /total number)	WO41554: 0/324	GO39374: 1/190
Other (Subjects number /total number)	Not applicable	Not applicable

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C
Controlled trials included data from Study WO41554. Non-controlled trials included Study GP39374. For each study, total number of patients and patients number by subgroup are presented according to safety analysis set.

2.6.5.4. *In vitro biomarker test for patient selection for efficacy*

Clinical performance

In the pivotal study WO41554, the applicant used an in vitro diagnostic (IVD) biomarker test for identifying patients with study-eligible *PIK3CA* mutations. *PIK3CA* mutations were determined using the next generation sequencing (NGS) FoundationOne® Liquid CDx (F1LCDx) assay from Foundation Medicine, Inc (FMI), USA. Hence, F1LCDx is a co-developed companion diagnostic (CDx). The cut-point

was determined by the reliable determination of the presence of the relevant mutations. This is standard procedure with NGS diagnostics.

The technical information presented below is retrieved from the publicly available FDA SSED and Technical label.

Background information about the CDx

PIK3CA mutation status was prospectively determined through testing of blood plasma-derived circulating tumour DNA (ctDNA) using F1LCDx, performed at the sponsor-designated central laboratory. *PIK3CA* mutation status could also be determined through site-directed local testing of ctDNA or tumour tissue with a validated PCR or NGS assay. For patients enrolled by local tests, ctDNA was collected for confirmation of biomarker status with the central test, but for these patients, the results of central retesting did not influence their enrolment status.

In study WO41554, most of the patients (284/325 [87.4%]) were enrolled based on central ctDNA testing.

Table 39. Enrolment by central and local PIK3CA mutation tests, study WO41554

	Countries Other than Mainland China	Mainland China
Total Enrollment	N=282	N=43
Enrollment by Central Test	n=243	n=41
Liquid-based	n=243 (F1LCDx NGS)	n=41 (PredicineCARE NGS)
Enrollment by Local Test	n=39	n=2
Liquid-based	n=17 PCR-based: 3 NGS-based: 14	n=1 NGS-based: 1
Tumor tissue-based	n=22 PCR-based: 11 NGS-based: 8 Sanger sequencing*: 1 Unknown: 2	n=1 NGS-based: 1

NGS = next-generation sequencing; PCR = polymerase chain reaction
*Includes a PCR step

Pre-treatment tumour tissue specimens (fresh or archival) were also collected for retrospective testing on the FoundationOne® CDx (F1CDx) assay.

Study WO41554 was initiated prior to 26 May 2022, i.e., prior to the implementation of In Vitro Diagnostic Regulations (IVDR; 2017/746) in the European Union. An IVD clinical performance study application for F1LCDx (PLAN- 00023) was submitted in October 2022 and approved in August 2023 and October 2023 by the German BfArM and other ethics committees in accordance with IVDR.

The FMI platform is currently under review in the EU. Therefore, no summary of safety & performance (SSP) is available.

F1LCDx is currently approved as a *PIK3CA* companion diagnostic for alpelisib by the FDA (as of 26 Oct 2020). The analytical data below are summarised from publicly available FDA and applicant documents.

Scientific validity

Mutations in the oncogene *PIK3CA* occur in approximately 35-40% of HR+ breast cancers. The driver mutations initiate activity of the PI3K/AKT pathway, leading to modulation of downstream proteins promoting uncontrolled cellular and tumour growth.

Study eligible *PIK3CA* mutations were:

H1047D/I/L/N/P/Q/R/T/Y, E545A/D/G/K/L/Q/R/V, E542A/D/G/K/Q/R/V, Q546E/H/K/L/P/R, N345D/H/I/K/S/T/Y, C420R, M1043I/T/V, G1049A/C/D/R/S, E453A/D/G/K/Q/V, K111N/R/E, G106A/D/R/S/V, G118D, and R88Q.

These 62 mutations are included in the FDA approved companion diagnostic claim on F1LCDx for inavolisib.

The genomic regions of the *PIK3CA* gene in which variants are reported by F1LCDx are exons 2, 3, 5-8, 10, 14, 19, and 21; coding exons 1, 2, 4-7, 9, 13, 18, and 20.

Patients who are negative for the above-mentioned mutations should be reflexed to routine biopsy and their tumour mutation status confirmed using an approved tumour tissue test, if feasible.

For performance characteristics validation of PIK3CA mutations, >700 breast cancer samples were analysed in two studies. Additional details can be found in the F1LCDx Technical Information label (link: https://www.foundationmedicine.com/sites/default/files/media/documents/2025-04/v16_RAL-0035_P190032_S024_F1LCDx_Technical_Clean%20Label_10DEC2024.pdf)

Analytical process

F1LCDx is a qualitative NGS based IVD test that uses targeted high throughput hybridisation-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, rearrangements in eight (8) genes, and copy number alterations in three (3) genes.

F1LCDx utilises circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of patients with solid malignant neoplasms.

Sequence data are analysed using mainly proprietary software developed by Foundation Medicine.

Analytical performance

The detection of short variants and rearrangements by the F1LCDx assay was compared to that of an externally validated cfDNA NGS assay in 74 genes common to both assays across 278 samples that represented an array of tumour types (>50 unique disease ontologies across 23 cancer types).

For *PIK3CA*, the concordance data are summarised below:

Table 40. Concordance of CDx alterations called between the F1LCDx and the comparator assay

Targeted Alteration	*n*	PPA [95% CI]	NPA [95% CI]	PPV [95% CI]	NPV [95% CI]
PIK3CA base substitutions*	49	100% [92.7%-100%]	100% [99.9%-100%]	100% [92.7%-100%]	100% [99.9%-100%]

Source: FoundationOne Liquid® CDx, technical information, table 7

Of the 18 locally tested ctDNA samples in study WO41554, 17 were from other countries than China. Of these, 16/17 could be re-tested with F1LCDx, resulting in a concordant result among 15/16 (93.8%).

Of the 23 locally tested tissue samples in study WO41554, 22 were from other countries than China. Of these, 21/22 could be re-tested with F1LCDx, with concordant results among 12/21 (57.1%).

The two locally tested samples from China were re-tested using the PredicineCARE, with concordant results for both (100.0%).

Concordance analyses between local and central test results were descriptive only, without sufficient power for formal concordance testing.

Biomarker threshold

The biomarker definition for Study WO41554 consists of *PIK3CA* short variants.

According to the applicant, the F1LCDx assay does not apply a Variant Allele Frequency (VAF) cut-off for *PIK3CA* mutations. Reporting of variants by the FMI analysis pipeline are not determined by a singular threshold, but rather a number of thresholds and quality metrics that are set by the variant class (i.e., short variants, rearrangements, copy number amplifications and losses). The supporting reads for each identified candidate variant are analysed and several metrics are calculated and used to evaluate the quality of the variant call. Quality control (QC) filtering is applied based on a series of quality control filters which will reject a candidate call based on intrinsic sample noise, the expected noise level for the variant and other known error modes such as sequence homology. If a sample passes all QC metrics and a variant is detected, it will be reported as biomarker positive.

There remains a level of uncertainty regarding the in-vitro diagnostic used for definition of PIK3CA mutational status in pivotal study INAVO120 (FoundationOne®CDx (F1CDx)):

The justification for the definition of biomarker-positivity (i.e., *PIK3CA* alterations as specified) is following a scientific rationale mainly based on preclinical data. The exploratory clinical data from the INAVO120 study suggest that the definition applied may indeed be predictive. However, there is no final confirmation of clinical validity for all individual genetic alterations included.

No clinical thresholding for the cut-point defining a tumour as biomarker positive or negative was performed. Due to this, it cannot be excluded that in the threshold definition of biomarker-positivity being applied in study INAVO120 patients are included that do not relevantly benefit.

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

Not applicable

2.6.5.6. *Supportive study(ies)*

Please refer to 2.6.5.1 Dose-response study GO30374.

2.6.6. Discussion on clinical efficacy

The proposed indication is:

Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, hormone receptor (HR)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

In pre- or perimenopausal women, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

The sought indication for inavolisib is supported by the pivotal study WO41554 (INAVO120). In addition, supportive efficacy data from the ongoing, phase I, dose-escalation and dose-expansion study GO39374 were submitted.

Design and conduct of clinical studies

Study WO41554 is a randomised, double-blind, placebo-controlled, multi-centre, multinational study of inavolisib + palbociclib + fulvestrant (inavo + palbo + fulv) vs. placebo + palbociclib + fulvestrant (pbo + palbo + fulv) in patients with PIK3CA-mutated, hormone receptor (HR)+, HER2-, locally advanced (LA) or metastatic breast cancer (mBC) whose disease progressed during or <12 months of completing adjuvant endocrine therapy (ET). Prior (neo-)adjuvant treatment was allowed, but no prior systemic therapy for LA/mBC.

The study is ongoing, but enrolment is completed (last patient enrolled on 14 September 2023).

The study design was discussed at a scientific advice in 2019 and considered acceptable by the CHMP.

PIKC3A mutations are present in 35-40% of all patients with HR+ BC. Only patients with verified study-eligible *PIK3CA* mutations were included in the study and *PIK3CA* mutation status was determined at a central laboratory using the co-developed NGS FoundationOne® Liquid CDx (F1LCDx) assay. Testing could also be performed locally on ctDNA or tumour tissue using a validated PCR or NGS assay. The list of study eligible PIK3CA mutations corresponded to the recently updated FDA approved CDx claims on F1LCDx for inavolisib.

Most of the patients (87.4%) were enrolled based on central ctDNA testing. The concordance between local and central ctDNA testing was high (93.8%), whereas the concordance between local and central tissue-based testing was significantly lower (57.1%). It is noted, though, that these analyses were performed post-hoc, without sufficient power for formal concordance testing. Information about PIK3CA mutation testing for selection of treatment eligible patients is presented in the SmPC section 4.2.

At least one mutation from each codon of *PIK3CA* was present in the specimen from one or more enrolled patients. Based on results from the central FoundationOne® Liquid CDx assay, the most common *PIK3CA* alterations were short variants at amino acids H1047 (n=115, 42.6%), E545 (n=58, 21.5%), and E542 (n=39, 14.4%). There were 25 patients whose specimens harboured more than one *PIK3CA* alterations (i.e., multiple *PIK3CA* mutations), and 33 with less common *PIK3CA* alterations.

In total, 590 patients were screened and 325 were randomised 1:1 to either inavo + palbo + fulv (n=161) or pbo + palbo + fulv (n=164). Patients were stratified for presence of visceral disease, primary or secondary resistance, and geographic region.

The clinical cut-off date (CCOD) of the primary analysis was 29 September 2023. The CCOD of the final OS analysis was 15 November 2024.

All inavolisib exposed patients received the recommended inavolisib dose of 9 mg orally QD on days 1-28 of each 28-day cycle. Palbociclib and fulvestrant were administered in line with the approved Ibrance indication. Treatment was continued until disease progression or intolerable toxicity.

The primary endpoint was PFS by investigator assessment. The choice of PFS as primary endpoint and OS as secondary endpoint is acceptable given regulatory precedent in this treatment niche.

The type I error-controlled endpoints were tested hierarchically in the following pre-specified and fixed order: PFS, OS, ORR, BOR, CBR, and the PRO variables time to confirmed deterioration (TTCD) in worst pain severity, TTCD in physical functioning, TTCD in role functioning, and TTCD in HRQoL. All endpoints were investigator-assessed. The testing strategy is acceptable and the inclusion of PRO variables in the testing hierarchy is acknowledged.

Discussion on statistical methods

Efficacy analyses were performed on the Full Analysis Set including all randomised subjects included in the analyses according to the treatment they were assigned.

The primary estimand for PFS and OS handled ICEs (start of non-protocol anticancer therapy and early discontinuation from study treatment) with a treatment policy approach. Comparison between treatment arms used the two-sided stratified log-rank test at the 0.05 level of significance. The hazard ratio was estimated using a stratified Cox proportional hazards model. For each treatment arm, the Kaplan-Meier methodology was used to estimate the median. The analysis methods are standard and appropriate.

Several sensitivity analyses were performed for the primary endpoint (see below). Unstratified analysis and PFS assessed by BICR among others. The sensitivity and supplementary analyses are considered appropriate.

According to the disposition table the proportion of informatively censored patients is small (around 9%) and equally distributed between treatment arms. This is not considered to have any impact on interpretation of results.

The applicant introduced late changes to the study design approximately six months before CCOD. In protocol version 8, the sample size was reduced from 400 to 320 and the number of PFS events to trigger primary readout was reduced from 227 to 194 (resulting in a change in power for PFS from 90% to 80%). These changes were made due to an unexpected slow recruitment during the COVID-19 pandemic and to preserve the integrity of OS. This is considered acceptable, noting that the study is double blinded.

In protocol version 8, an OS interim analysis was also added. According to the original protocol, the OS endpoint was to be analysed at the time of final PFS analysis. It was also stated that: *"additional analyses of OS will be conducted after the primary analysis at timepoints defined through study milestones such as Health Authority interactions"*. However, no type I error-control was specified and hence it is interpreted as the only inferential analysis for OS was planned at the time point of PFS analysis. Although no sample size calculation was provided for OS in the original protocol, it is assumed that power would be low at this time point. In a late amendment to the protocol (about 6 months prior to the CCOD) an interim analysis for OS was added at the time of final PFS analysis and a final OS analysis at 153 events was added. Although this post hoc formalisation of an OS analysis at a later time point was made very late during the study it is accepted since the study was fully blinded and the change is considered reasonable.

Efficacy data and additional analyses

The full analysis set (FAS) used for efficacy analyses consisted of all 325 randomised patients, i.e., equals the intention to treat (ITT) population. Of these, all but one patient in the inavo + palbo + fulv arm received the intended study treatments (patient withdrew consent). In addition, two patients in the control group received inavolisib, and were included in the efficacy analysis per their assigned treatment (pbo arm) but in the safety analysis per received treatment (inavo arm).

Overall, the study population reflected the intended indication, and the study arms were well balanced as regards baseline demographic and disease characteristics.

The participants in the inavolisib arm were somewhat younger (84.5% <65 years) and, consequently, somewhat more pre/perimenopausal (40.4%) than in the placebo arm (79.3% <65 years, 36.0% not postmenopausal). There were six male participants randomised in the pivotal study.

At CCOD of the primary analysis, 58.4% (94/161) of the patients in the inavo triplet arm compared to 70.1% (115/164) in the pbo arm had discontinued any study treatment, mainly due to progressive disease (44.1% vs. 62.2% for inavo vs. pbo arms, respectively). At CCOD of the final OS analysis, 56.9% (185/325) of the patients had discontinued the study (53.4% [86] in the inavo triplet arm vs. 60.4% [99] in the placebo arm).

The number of patients with intercurrent events as described in the definition of estimands were provided during the procedure. This information does not cause concern and is not considered to affect the study outcome. Likewise, only five patients (1.5%) were reported lost to follow-up and are not considered to affect the study outcome. The reasons for censoring in the primary PFS analysis and the OS analysis were also provided. This information does not cause concern.

The HR for PFS was 0.43 (95% CI 0.32, 0.59, 2-sided p-value <0.0001) at CCOD, in favour of the inavo + palbo + fulv arm. The overall PFS maturity rate was 60.0% (82 events [50.9%] in the inavo arm vs. 113 events [68.9%] in the pbo arm). Thus, the inferential analysis became the final PFS analysis.

As the clinical interpretation of the HR is generally not straightforward, the restricted mean survival time differences at 18 and 24 months, respectively, were provided upon request as additional effect measures. The estimated gain in PFS time was 4 months (95% CI 2.6,5.4) at 18 months and 5.3 months (95% CI 3.3,7.3) at 24 months.

The median PFS was 15.0 (11.3, 20.5) months in the inavo + palbo + fulv arm compared to 7.3 (5.6, 9.3) months in the pbo + palbo + fulv arm. The PFS increase with the addition of inavolisib is both statistically significant and clinically relevant by common standards.

The primary PFS analysis was supported by additional PFS analyses using hypothetical estimand strategies ([i] patients who started new anti-cancer therapy prior to disease progression were censored at last assessment before initiation of the new treatment and [ii] a composite strategy where start of new anti-cancer treatment prior to progression was considered a PFS event) as well as sensitivity analyses based on BICR-assessment, *PIK3CA* mutation-positive patients by central testing only, and for assessing the impact of missing data.

The HR for OS at the final OS analysis showed a statistically significant improvement in favour of the inavo + palbo + fulv arm (HR 0.67 [95% CI 0.48, 0.94], p-value 0.0190), crossing the stopping boundary of the final OS analysis ($p \leq 0.0469$). This corresponded to a median OS of 34.0 (95% CI 28.4, 44.8) months in the inavo + palbo + fulv arm and a median OS of 27.0 (95% CI 22.8, 38.7) months in the pbo + palbo + fulv arm, which is considered a clinically relevant difference. The overall OS maturity was 47.4% (72 events [44.7%] in the inavo arm vs. 82 events [50.0%] in the pbo arm).

Several subgroups of PFS on baseline factors (age, sex, ethnicity, race, region, hormone receptor status, prior (neo)-adjuvant endocrine therapy, prior (neo)-adjuvant CDK4/6i therapy, and prior (neo)-adjuvant chemotherapy) have very wide confidence intervals, crossing 1. For other subgroup analyses, although in favour of inavolisib treatment, the effect estimates also varied. All subgroup analyses were non-multiplicity-controlled which limits their interpretability. Overall, post hoc subgroup analyses on OS were consistent with the results of the PFS analyses.

Two subgroup analyses, on geographical regions and age <65 years vs. ≥65 years, were noted based on point estimates. Regarding the subgroup analysis on geographical regions, a smaller PFS effect was noted for region `North America/Western Europe´ (HR 0.73 [95% CI 0.47, 1.15]) vs. the comparably large region `Asia´ (HR 0.40 [95% CI 0.24, 0.64]). This numerical difference was maintained in a subgroup analysis of OS by region at the time of the final OS analysis (NA/WE HR 0.95 [95% CI 0.56, 1.59], 44.9% events; Asia HR 0.78 [95% 0.45, 1.34], 55.8% events) although both subgroups had upper CI limits >1. The only geographical region with an upper CI <1 in the subgroup analysis of OS

was the small region `Other´, with >50% events. As outlined above, the interpretability of these subgroup analyses is limited. There is no biological rationale for why the treatment effect would be less enhanced among NA/WE patients in this highly biomarker selected population.

The limited study size and eligibility criteria selecting for a study population without relevant comorbidities resulted in median age in INAVO120 that was lower than in other studies in ER+, HER2- aBC studies (e.g., EMERALD or CAPItello-291) and frail patients were not included. In the small subgroup of patients aged ≥65 years, the PFS result did not illustrate an add-on effect of inavolisib (HR 0.96 [95% CI 0.50, 1.83]). Moreover, the post-hoc OS subgroup result at the time of the final OS analysis favoured the placebo rather than the inavolisib arm (OS HR 1.65 [95% CI 0.77, 3.15]). This was discordant to the result for the numerically more than 4 times larger patient group aged <65 years in a study population without relevant co-morbidities. It is noted, though, that the number of events in this analysis was limited (13 among the 25 patients aged ≥65 years in the inavo + palbo + fulv arm vs. 14 events among the 34 patients in the pbo + palbo + fulv arm).

Apart from the limitation with these analyses outlined above, it is noted that calendar age *per se* is not an effect modifier but may correlate to efficacy and safety due to an association with e.g., reduced physical fitness, performance status, organ function, and comorbidities more commonly observed in older patients. Hence, frailer, rather than just older, patients, may be less able to benefit from anti tumoral effects due to the lower tolerability. This is in line with the incidences of AEs and SAEs leading to dose modifications of any study treatment being numerically higher in patients aged ≥65 years, which is also outlined in the SmPC 4.8.

Thus, ECOG performance status has a greater possibility to affect treatment tolerability than age itself. In this context it is noted that the OS subgroup analysis by ECOG 1 had HR 0.85 (95% CI 0.52, 1.38) with CIs largely overlapping those of the entire population and twice as many events as for patients aged ≥65 years (32 events among 60 patients with ECOG 1 in the inavo + palbo + fulv arm vs. 34 events among 58 patients in the pbo + palbo + fulv arm).

Although the subgroup results by age do not seem to give rise to any specific concerns, considering the small numbers, it was agreed to reflect in SmPC section 4.2 that there are limited data in patients ≥ 65 years of age.

Subgroup analyses of PFS and ORR for patients with *ESR1* mutations were in line with the results of the FAS.

The remaining secondary endpoints were hierarchically tested and both ORR, BOR, and CBR were statistically significantly in favour of the inavo + palbo + fulv arm. ORR at CCOD of the final OS analysis was 62.7% (95% CI 54.8, 70.2) in the inavo + palbo + fulv arm compared to 28.0% (95% CI 21.3, 35.6) in the pbo + palbo + fulv arm. There were no statistically significant differences in the PRO variable outcomes between the study arms.

ORR for the most common activating PIK3CA alterations identified at CCOD of the primary analysis was provided upon request and was in line with the overall result.

Hyperglycaemia is a known, reversible, on-target effect of PI3K inhibitors. Furthermore, insulin can drive resistance to PI3K inhibitors. In the pivotal study, patients with type 1 diabetes as well as patients with type 2 diabetes requiring ongoing systemic anti-diabetic treatment were excluded. This is acknowledged. Similarly, the study population differs significantly from the expected future patient population that may be considered for the current treatment. Descriptive subgroup analyses of ORR for patients who experienced hyperglycaemia events, and/or received metformin and insulin, showed ORR results in line with the FAS.

The current procedure was part of the EMA Raw data pilot. Within the framework of this project, the effect of inavo + palbo + fulv vs. pbo + palbo + fulv on mean percentage change in tumour size from baseline for patients with primary and secondary endocrine resistance respectively, was assessed. No differences related to type of endocrine resistance were found for any of the treatment arms (data not shown).

Indication wording

The initially sought indication covered patients with hormone receptor positive disease. As expected, the majority of included patients were ER+/PR+ or ER+/PR-. The subgroup with ER-/PR+ tumours in the overall BC population is rare and in the pivotal study only six patients with ER-/PR+ tumours were included (three in each arm). The applicant underlined that palbociclib + fulvestrant is approved in HR+ patients, which is acknowledged. According to current ESMO guidelines, though, fulvestrant treatment is not recommended for ER-/PR+ patients. Due to this, and in line with precedent procedures, the indication was updated to include patients being ER+.

During the study period the inclusion of CDK4/6i in adjuvant treatment for patients with a high risk of recurrence was approved. According to study inclusion criteria, prior (neo-)adjuvant CDK4/6i treatment was allowed if the progression event (and subsequent study inclusion) occurred >12 months after completion of the CDK4/6i portion of the (neo-)adjuvant treatment. Only 3 patients with prior CDK4/6i treatment were enrolled. This is outlined in the SmPC 5.1.

Supportive evidence from study GO39374 cohort F on CDK4/6i pre-treated patients who showed low response rates is limited. The common practice of re-treatment with other oncology products, somewhat conflicting clinical data indicating the potential importance of switching the CDK4/6i and ET components upon re-treatment, as well as the potential benefit of triple blockade of the PI3K, CDK4/6, and endocrine signalling pathway to prevent or reverse treatment resistance as support as support for re-treatment with a CDK4/6i were discussed.

It is acknowledged that the treatment landscape has changed since the current study was initiated, with adjuvant CDK4/6i treatment nowadays being approved for use in patients at high-risk of recurrence. According to data provided by the applicant (not shown), the current incidence of previously CDK4/6i treated patients receiving re-treatment with a CDK4/6i is approximately 5% in the USA. This number will likely increase over time, considering the recent approvals of adjuvant CDK4/6i treatment (adjuvant abemaciclib approved in the EU in April 2022, adjuvant ribociclib in November 2024).

The current ESMO guidelines on mBC (2021) states that `Although there is little data on use of CD4/6 inhibitors after progression on CDK4/6 inhibitors, rechallenge may be possible after a treatment-free interval of $\geq$12 months based on evidence regarding rechallenge with other therapies.´

Furthermore, new emerging data from e.g., the MAINTAIN, postMONARCH, and EMBER-3 studies support re-treatment with a (preferably other) CDK4/6i. There are, however, currently no data specifically in support of re-treatment with palbociclib after exposure to abemaciclib or ribociclib.

Although it remains a fact that only three patients were re-treated with a CDK4/6i in study INAVO120, the above-mentioned data on retreatment with CDK4/6 inhibitors as well as expert opinion indicative that at least one year is a reasonable time interval between drug pressure and detected disease progression to make it less likely that proliferating clones are resistant to the CDK4/6 drug class. It is considered reasonable to accept the use of palbociclib in combination with inavolisib treatment as proposed, despite prior use of abemaciclib or ribociclib and despite the lack of direct evidence to support this use.

It is, however, not sufficient to state that the CDK4/6i treatment-free interval should be at least 12 months before re-treatment, since it is the time between primary CDK4/6i discontinuation and progression/detection of recurrence that is of likely importance; not the time between prior treatment and re-treatment (though it is acknowledged that these might roughly coincide). Hence, the final indication was amended to specify that patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In addition, the applicant will conduct a US-based multi-institutional, multi-year real-world data (RWD) study harnessing data from at least two data vendors to generate descriptive data on outcomes in the relevant patient population (REC). This is acknowledged, even though the study is not anticipated to provide sufficient reassurance with respect to biases or confounding to consider its results confirmatory. The final study protocol will also be provided (PAM-REC).

SmPC section 4.4 was updated to inform prescribers that information on the efficacy of the combination is very limited in patients who previously received a CDK4/6 inhibitor, and that efficacy may be lower in such patients.

The finally agreed indication was:

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In pre/perimenopausal women and in men, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

2.6.7. Conclusions on the clinical efficacy

A statistically significant and clinically relevant PFS and OS gain has been shown for the addition of inavolisib to palbociclib and fulvestrant compared to the combination of placebo, palbociclib, and fulvestrant in patients with *PIK3CA* mutated, ER+, HER2- advanced BC as first systemic treatment following progression after (neo-)adjuvant endocrine treatment. Thus, efficacy has been established.

2.6.8. Clinical safety

The safety data of the combination of inavolisib plus palbociclib and fulvestrant are primarily derived from the pivotal Phase III **Study WO41554** (INAVO120; clinical cutoff date [CCOD] of 29 September 2023).

Supportive safety data from the Phase I **Study GO39374** Arm A-F (CCOD of 27 March 2023) are provided. Arm E and Arm F evaluated the same treatment regimen and doses as in Study WO41554. In Arm F, patients deemed to be at high risk for hyperglycaemia were included and the study treatment comprised metformin, in addition to inavolisib, palbociclib and fulvestrant.

Summary of the studies is presented in Table 20 Summary of studies contributing to the efficacy evaluation

At the CCOD, the median duration of follow-up in Study WO41554 was 21.3 months (range: 0-43.1 months) in the Inavo+Palbo+Fulv arm, and 21.5 months (range: 0.6-40.3 months) in the Pbo+Palbo+Fulv arm.

Pooling of safety data across studies WO41554 and GO39374 was not performed due to differences in the patient populations, hyperglycaemia related inclusion criteria, treatment regimens, the range of inavolisib dose levels, and also the differences in AE grading criteria for these two studies. In addition, the sample sizes in the different treatment arms of study GO39374 were limited. Therefore, data from the supportive Study GO39374 are not assessed in detail and will only be discussed in case of relevant safety data.

2.6.8.1. *Patient exposure*

Table 41. Patient exposure (Study WO41554 CCOD 29 September 2023, Study GO39374 CCOD of 27 March 2023)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range (Inavolisib 9 mg)	Patients with long term** safety data
Blinded studies: WO41554 (placebo-controlled)	325	162	162	110 (67.9%) (>6 months) 65 (40.1%) (>12 months)
Blinded studies (active -controlled)	N/A	N/A	N/A	N/A
Open studies: GO39374	191	190	166	101 (53.2%) (>6 months) 65 (34.2%) (>12 months)
Post marketing	N/A			
Compassionate use	CUP AG42509 up to 14 November 2024: Patients enrolled (n=18); Patients exposed (n=5); Patients with long-term safety data (n=2)			

* Received at least 1 dose of active treatment

** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

N/A=not applicable

Table 42. Study WO41554: Extent of exposure to inavolisib, placebo, palbociclib, and fulvestrant (safety analysis set), DCO 29-Sep-2023

	Inavo+Palbo+Fulv (N=162)			Pbo+Palbo+Fulv (N=162)		
	Inavolisib	Palbociclib	Fulvestrant	Placebo	Palbociclib	Fulvestrant
Treatment Duration (months)*	n=162	n=162	n=162	n=162	n=162	n=162
Mean (SD)	12.1 (9.6)	12.0 (9.5)	11.9 (9.5)	8.4 (8.0)	8.2 (8.0)	7.9 (8.2)
Median	9.2	9.1	8.6	5.6	5.6	5.6
Min-Max	0.0-38.8	0.0-38.8	0.0-38.3	0.1-40.3	0.1-40.2	0.0-39.6
Treatment Duration	n=162	n=162	n=162	n=162	n=162	n=162
0 to ≤3 months	31 (19.1%)	27 (16.7%)	32 (19.8%)	53 (32.7%)	53 (32.7%)	61 (37.7%)
>3 to ≤6 months	21 (13.0%)	27 (16.7%)	22 (13.6%)	33 (20.4%)	32 (19.8%)	24 (14.8%)
>6 to ≤12 months	45 (27.8%)	43 (26.5%)	43 (26.5%)	38 (23.5%)	41 (25.3%)	42 (25.9%)

	Inavo+Palbo+Fulv (N=162)			Pbo+Palbo+Fulv (N=162)		
	Inavolisib	Palbociclib	Fulvestrant	Placebo	Palbociclib	Fulvestrant
>12 to ≤18 months	25 (15.4%)	27 (16.7%)	25 (15.4%)	19 (11.7%)	18 (11.1%)	18 (11.1%)
>18 months	40 (24.7%)	38 (23.5%)	40 (24.7%)	19 (11.7%)	18 (11.1%)	17 (10.5%)
Relative Dose Intensity (%)	n=162	n=162	n=162	n=162	n=162	n=162
Mean (SD)	87.3 (17.2)	84.0 (15.0)	99.0 (4.5)	0.0 (0.0)	84.4 (15.5)	98.8 (5.1)
Median	95.8	87.3	100.0	0.0	88.4	100.0
Min–Max	26.4-100.0	16.7-104.5	75.0-125.0	0.0-0.0	33.3-112.3	60.0-122.2
Number of Doses	n=162	n=162	n=162	n=162	n=162	n=162
Mean (SD)	347.9 (283.6)	259.3 (206.3)	14.4 (10.1)	246.8 (238.5)	176.8 (168.8)	10.2 (8.6)
Median	256.5	192.5	11.0	170.0	126.0	8.0
Min–Max	1.0-1180.0	1.0-877.0	1.0-43.0	2.0-1227.0	2.0-884.0	1.0-45.0
Total Cumulative Dose (mg)	n=162	n=162	n=162	n=162	n=162	n=162
Mean (SD)	2903.5 (2478.0)	29386.6 (23933.3)	7199.1 (5032.6)	0.0 (0.0)	19465.4 (17131.4)	5120.4 (4304.6)
Median	2127.0	23312.5	5500.0	0.0	13712.5	4000.0
Min–Max	9.0-10620.0	125.0-109625.0	500.0-21500.0	0.0-0.0	250.0-76250.0	500.0-22500.0

NE=not estimable.

* The calculation of treatment duration for fulvestrant does not include the 4-week period post last injection.

In the safety analysis set population, the median duration of treatment was longer in the Inavo+Palbo+Fulv arm compared with the Pbo+Palbo+Fulv arm (*inavolisib/placebo* [9.2 months Inavo+Palbo+Fulv arm vs. 5.6 months Pbo+Palbo+Fulv arm], *palbociclib* [9.1 months vs. 5.6 months], and *fulvestran*t [8.6 months vs. 5.6 months]).

2.6.8.2. *Adverse events*

Table 43. Overview of adverse events and deaths, safety analysis set, study WO41554

	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one AE	160 (98.8%)	162 (100%)
Total number of AEs	3298	2058
Total number of deaths	43 (26.5%)	54 (33.3%)
Total number of patients with at least one treatment-related AE		
Inavolisib/Placebo	142 (87.7%)	116 (71.6%)
Palbociclib	152 (93.8%)	153 (94.4%)
Fulvestrant	84 (51.9%)	72 (44.4%)
Any Treatment	158 (97.5%)	153 (94.4%)
Total number of patients with at least one		
AE with fatal outcome	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
Grade 3-4 AE	143 (88.3%)	133 (82.1%)
AE leading to withdrawal from treatment		
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
Any Treatment	11 (6.8%)	1 (0.6%)
AE leading to dose modification/interruption		
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)
Any Treatment	134 (82.7%)	121 (74.7%)

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

The frequency of patients with at least one AE was similar across study arms, 98.8% in the Inavo+Palbo+Fulv arm and 100% in the Pbo+Palbo+Fulv arm.

The frequency of SAEs and also AEs leading to discontinuation was higher in the Inavo+Palbo+Fulv arm (24.1% and 6.8%, respectively) compared with Pbo+Palbo+Fulv (10.5% and 0.6%, respectively).

Six AEs (3.7%) with fatal outcome were reported in the Inavo+Palbo+Fulv arm vs. 2 (1.2%) in the Pbo+Palbo+Fulv arm.

The overall frequency of AEs leading to dose modifications/interruption were higher in the Inavo+Palbo+Fulv arm (82.7%) vs. the Pbo+Palbo+Fulv arm (74.7%).

Safety data from the supportive Study GO39374 (all Patients, Arms A-F, n=190, with diverse treatment combinations and different patient populations) were overall consistent with those for Study WO41554.

Common AEs

Table 44. Adverse events with an incidence rate of at least 5% in any treatment arm, by MedDRA preferred term, safety analysis set, study WO41554

MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Neutropenia	88 (54.3%)	89 (54.9%)
Hyperglycaemia	87 (53.7%)	12 (7.4%)
Diarrhoea	78 (48.1%)	26 (16.0%)
Neutrophil count decreased	63 (38.9%)	64 (39.5%)
Anaemia	59 (36.4%)	59 (36.4%)
Stomatitis	53 (32.7%)	27 (16.7%)
Nausea	45 (27.8%)	27 (16.7%)
Platelet count decreased	42 (25.9%)	36 (22.2%)
Decreased appetite	38 (23.5%)	14 (8.6%)
Fatigue	38 (23.5%)	21 (13.0%)
COVID-19	37 (22.8%)	17 (10.5%)
Thrombocytopenia	36 (22.2%)	41 (25.3%)
White blood cell count decreased	35 (21.6%)	35 (21.6%)
Headache	34 (21.0%)	22 (13.6%)
Alopecia	30 (18.5%)	9 (5.6%)
Mucosal inflammation	30 (18.5%)	16 (9.9%)
Alanine aminotransferase increased	28 (17.3%)	21 (13.0%)
Aspartate aminotransferase increased	28 (17.3%)	26 (16.0%)
Leukopenia	28 (17.3%)	40 (24.7%)
Weight decreased	28 (17.3%)	1 (0.6%)
Hypokalaemia	26 (16.0%)	10 (6.2%)
Rash	26 (16.0%)	21 (13.0%)
Asthenia	25 (15.4%)	22 (13.6%)
Constipation	24 (14.8%)	23 (14.2%)
Vomiting	24 (14.8%)	8 (4.9%)
Urinary tract infection	21 (13.0%)	12 (7.4%)
Back pain	18 (11.1%)	16 (9.9%)
Cough	18 (11.1%)	12 (7.4%)
Dry skin	18 (11.1%)	7 (4.3%)
Abdominal pain	16 (9.9%)	10 (6.2%)
Arthralgia	16 (9.9%)	20 (12.3%)
Insomnia	16 (9.9%)	13 (8.0%)
Muscle spasms	16 (9.9%)	5 (3.1%)
Pyrexia	15 (9.3%)	13 (8.0%)
Abdominal pain upper	14 (8.6%)	11 (6.8%)
Dry eye	14 (8.6%)	5 (3.1%)
Hypocalcaemia	14 (8.6%)	4 (2.5%)
Upper respiratory tract infection	14 (8.6%)	7 (4.3%)
Dysgeusia	13 (8.0%)	6 (3.7%)
Dyspepsia	13 (8.0%)	4 (2.5%)
Gastrooesophageal reflux disease	13 (8.0%)	2 (1.2%)
Glycosylated haemoglobin increased	13 (8.0%)	2 (1.2%)
Dyspnoea	12 (7.4%)	9 (5.6%)
Pruritus	12 (7.4%)	12 (7.4%)
Blood insulin increased	10 (6.2%)	1 (0.6%)
Dizziness	10 (6.2%)	13 (8.0%)
Blood creatinine increased	9 (5.6%)	12 (7.4%)
Dry mouth	9 (5.6%)	5 (3.1%)
Oropharyngeal pain	9 (5.6%)	4 (2.5%)
Pain in extremity	9 (5.6%)	9 (5.6%)
Toothache	9 (5.6%)	4 (2.5%)
Lymphocyte count decreased	5 (3.1%)	10 (6.2%)

Investigator text for AEs encoded using MedDRA version 26.1.

Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

The most common AEs (≥ 50% of patients in either arm) by MedDRA SOC were (Inavo+Palbo+Fulv and Pbo+Palbo+Fulv, respectively):

- Blood and Lymphatic System Disorders (68.5% vs. 72.8%)
- Investigations (69.1% vs. 63.6%)
- Gastrointestinal Disorders (77.2% vs. 50.0%)
- General Disorders and Administration Site Conditions (53.7% vs. 50.0%)
- Metabolism and Nutrition Disorders (69.8% vs. 32.7%)
- Infections and Infestations (54.3% vs. 32.1%).

Table 45. Adverse events with a difference of at least 5% between treatment arms, safety analysis set, study WO41554

MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Hyperglycaemia	87 (53.7%)	12 (7.4%)
Diarrhoea	78 (48.1%)	26 (16.0%)
Stomatitis	53 (32.7%)	27 (16.7%)
Nausea	45 (27.8%)	27 (16.7%)
Fatigue	38 (23.5%)	21 (13.0%)
Decreased appetite	38 (23.5%)	14 (8.6%)
COVID-19	37 (22.8%)	17 (10.5%)
Headache	34 (21.0%)	22 (13.6%)
Mucosal inflammation	30 (18.5%)	16 (9.9%)
Alopecia	30 (18.5%)	9 (5.6%)
Leukopenia	28 (17.3%)	40 (24.7%)
Weight decreased	28 (17.3%)	1 (0.6%)
Hypokalaemia	26 (16.0%)	10 (6.2%)
Vomiting	24 (14.8%)	8 (4.9%)
Urinary tract infection	21 (13.0%)	12 (7.4%)
Dry skin	18 (11.1%)	7 (4.3%)
Muscle spasms	16 (9.9%)	5 (3.1%)
Dry eye	14 (8.6%)	5 (3.1%)
Hypocalcaemia	14 (8.6%)	4 (2.5%)
Dyspepsia	13 (8.0%)	4 (2.5%)
Gastrooesophageal reflux disease	13 (8.0%)	2 (1.2%)
Glycosylated haemoglobin increased	13 (8.0%)	2 (1.2%)
Blood insulin increased	10 (6.2%)	1 (0.6%)

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

The majority of the AEs which occurred at a higher frequency in the Inavo+Palbo+Fulv arm were associated with the identified safety profile of inavolisib (hyperglycaemia, stomatitis, gastrointestinal toxicity, and skin disorders).

AEs (all grades) associated with myelosuppression (neutropenia, neutrophil count decreased, anaemia, platelet count decreased, thrombocytopenia, and white blood cell count decreased) were similar between the treatment arms.

Adverse events of hyperglycaemia and rash had the highest AEs per patient-month for the first 2 months of treatment and diarrhoea, stomatitis and mucositis for the first 3 months of treatment.

AEs of grade 3-4

Table 46. NCI CTCAE Grade 3-4 adverse events with an incidence rate of at least 2% in any treatment arm, safety analysis set, study WO41554

MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Neutropenia	77 (47.5%)	78 (48.1%)
Neutrophil count decreased	56 (34.6%)	53 (32.7%)
White blood cell count decreased	23 (14.2%)	17 (10.5%)
Platelet count decreased	15 (9.3%)	4 (2.5%)
Leukopenia	11 (6.8%)	17 (10.5%)
Anaemia	10 (6.2%)	3 (1.9%)
Hyperglycaemia	9 (5.6%)	0
Thrombocytopenia	8 (4.9%)	3 (1.9%)
Alanine aminotransferase increased	6 (3.7%)	2 (1.2%)
Diarrhoea	6 (3.7%)	0
Weight decreased	6 (3.7%)	0
Stomatitis	5 (3.1%)	0
Febrile neutropenia	4 (2.5%)	1 (0.6%)
Hypokalaemia	4 (2.5%)	0

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Table 47. NCI-CTCAE Grade 3-4 adverse events with a difference of at least 2% between treatment arms, safety analysis set, study WO41554

MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
White blood cell count decreased	23 (14.2%)	17 (10.5%)
Platelet count decreased	15 (9.3%)	4 (2.5%)
Leukopenia	11 (6.8%)	17 (10.5%)
Anaemia	10 (6.2%)	3 (1.9%)
Hyperglycaemia	9 (5.6%)	0
Thrombocytopenia	8 (4.9%)	3 (1.9%)
Alanine aminotransferase increased	6 (3.7%)	2 (1.2%)
Diarrhoea	6 (3.7%)	0
Weight decreased	6 (3.7%)	0
Stomatitis	5 (3.1%)	0
Hypokalaemia	4 (2.5%)	0

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

The majority of Grade 3-4 AEs in both treatment arms were associated with myelosuppression.

Other common Grade 3-4 AEs (by PTs) were hyperglycaemia (Inavo+Palbo+Fulv: 5.6% and Pbo+Palbo+Fulv: 0%), diarrhoea (3.7% vs 0%), and stomatitis/oral mucositis (3.1% vs. 0%).

The frequency of Grade 3-4 platelet count decreased, anaemia, and thrombocytopenia was higher in the Inavo+Palbo+Fulv arm (9.3%, 6.2% and 4.9%, respectively) compared with Pbo+Palbo+Fulv (2.5%, 1.9% and 1.9%, respectively).

2.6.8.3. *Serious adverse event/deaths/other significant events*

Deaths

Table 48. Deaths, safety analysis set, study WO41554, CCOD 29SEP2023

	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)	All Patients (N=324)
Total number of deaths	43 (26.5%)	54 (33.3%)	97 (29.9%)
Primary Cause of Death			
n	43	54	97
Adverse Event	6 (14.0%)	2 (3.7%)	8 (8.2%)
Progressive Disease	32 (74.4%)	47 (87.0%)	79 (81.4%)
Other	5 (11.6%)	5 (9.3%)	10 (10.3%)

Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Table 49. Adverse events resulting in death, safety analysis set, study WO41554, CCOD 29SEP2023

MedDRA System Organ Class / MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one adverse event	6 (3.7%)	2 (1.2%)
Overall total number of events	6	2
Cardiac disorders		
Total number of patients with at least one adverse event	1 (0.6%)	1 (0.6%)
Total number of events	1	1
Acute coronary syndrome	1 (0.6%)	0
Cardiac arrest	0	1 (0.6%)
Infections and infestations		
Total number of patients with at least one adverse event	1 (0.6%)	1 (0.6%)
Total number of events	1	1
COVID-19	1 (0.6%)	0
COVID-19 pneumonia	0	1 (0.6%)
Nervous system disorders		
Total number of patients with at least one adverse event	2 (1.2%)	0
Total number of events	2	0
Cerebral haemorrhage	1 (0.6%)	0
Cerebrovascular accident	1 (0.6%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	1	0
Gastrointestinal haemorrhage	1 (0.6%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	1	0
Death	1 (0.6%)	0

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

The most common cause of death in both treatment arms was progressive disease (Inavo+Palbo+Fulv: 32 out of 43 patients [74.4%] vs. Pbo+Palbo+Fulv: 47 out of 54 patients [87.0%]).

Fatal AEs were reported in 6 patients (3.7%) in the Inavo+Palbo+Fulv arm and 2 patients (1.2%) in the Pbo+Palbo+Fulv arm. No event by PT resulting in death was reported in more than one patient in either arm. None of the Grade 5 AEs were reported as related to any study drug by the investigator.

The Grade 5 AEs (by PT) reported in the Inavo+Palbo+Fulv were: cerebral haemorrhage, cerebrovascular accident, gastrointestinal haemorrhage, acute coronary syndrome, death, and COVID-19. Grade 5 AEs reported in the Pbo+Palbo+Fulv arm were COVID-19 pneumonia and cardiac arrest.

SAEs

Table 50. Serious Adverse Events, Safety Analysis Set, Study WO41554

Total number of patients with at least one adverse event	39 (24.1%)	17 (10.5%)
Overall total number of events	59	21
Infections and infestations		
Total number of patients with at least one adverse event	11 (6.8%)	3 (1.9%)
Total number of events	14	3
COVID-19	4 (2.5%)	1 (0.6%)
Pneumonia	3 (1.9%)	0
Urinary tract infection	2 (1.2%)	0
Anal abscess	1 (0.6%)	0
Cellulitis	1 (0.6%)	0
Clostridium difficile colitis	0	1 (0.6%)
COVID-19 pneumonia	0	1 (0.6%)
Device related infection	1 (0.6%)	0
Lung abscess	1 (0.6%)	0
Upper respiratory tract infection	1 (0.6%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	7 (4.3%)	4 (2.5%)
Total number of events	9	5
Vomiting	1 (0.6%)	2 (1.2%)
Diarrhoea	2 (1.2%)	0
Abdominal pain	1 (0.6%)	0
Anal fistula	1 (0.6%)	0
Dysphagia	0	1 (0.6%)
Gastrointestinal haemorrhage	1 (0.6%)	0
Intestinal obstruction	0	1 (0.6%)
Intestinal perforation	1 (0.6%)	0
Nausea	1 (0.6%)	0
Oesophageal stenosis	0	1 (0.6%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	7 (4.3%)	1 (0.6%)
Total number of events	8	1
Anaemia	3 (1.9%)	0
Febrile neutropenia	3 (1.9%)	0
Neutropenia	0	1 (0.6%)
Thrombocytopenia	1 (0.6%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	4 (2.5%)	1 (0.6%)
Total number of events	4	1
Pyrexia	2 (1.2%)	0
Chest pain	0	1 (0.6%)
Death	1 (0.6%)	0
Malaise	1 (0.6%)	0
Nervous system disorders		
Total number of patients with at least one adverse event	4 (2.5%)	1 (0.6%)
Total number of events	4	1
Syncope	1 (0.6%)	1 (0.6%)
Cerebral haemorrhage	1 (0.6%)	0
Cerebrovascular accident	1 (0.6%)	0
Haemorrhage intracranial	1 (0.6%)	0

MedDRA System Organ Class MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Cardiac disorders		
Total number of patients with at least one adverse event	2 (1.2%)	2 (1.2%)
Total number of events	2	2
Acute coronary syndrome	2 (1.2%)	0
Atrial fibrillation	0	1 (0.6%)
Cardiac arrest	0	1 (0.6%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	3 (1.9%)	1 (0.6%)
Total number of events	5	1
Ankle fracture	1 (0.6%)	0
Femur fracture	0	1 (0.6%)
Post procedural fistula	1 (0.6%)	0
Procedural headache	1 (0.6%)	0
Snake bite	1 (0.6%)	0
Investigations		
Total number of patients with at least one adverse event	1 (0.6%)	2 (1.2%)
Total number of events	2	2
Alanine aminotransferase increased	1 (0.6%)	0
Aspartate aminotransferase increased	1 (0.6%)	0
Platelet count decreased	0	1 (0.6%)
White blood cell count decreased	0	1 (0.6%)
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one adverse event	2 (1.2%)	1 (0.6%)
Total number of events	2	1
Flank pain	1 (0.6%)	0
Muscular weakness	0	1 (0.6%)
Osteonecrosis of jaw	1 (0.6%)	0
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.6%)	2 (1.2%)
Total number of events	1	2
Pulmonary embolism	0	2 (1.2%)
Dyspnoea	1 (0.6%)	0
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	2 (1.2%)	0
Total number of events	4	0
Hypocalcaemia	1 (0.6%)	0
Hypokalaemia	1 (0.6%)	0
Tetany	1 (0.6%)	0
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	1 (0.6%)	1 (0.6%)
Total number of events	1	1
Skin ulcer	1 (0.6%)	1 (0.6%)
Product issues		
Total number of patients with at least one adverse event	0	1 (0.6%)
Total number of events	0	1
Device dislocation	0	1 (0.6%)
Renal and urinary disorders		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	1	0
Acute kidney injury	1 (0.6%)	0
Vascular disorders		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	2	0
Embolism	1 (0.6%)	0

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Only treatment emergent SAEs are displayed. For frequency counts by preferred term, multiple occurrences of the same SAE in an individual are counted only once. For frequency counts of""Total number of event"" rows, multiple occurrences of the same AE in an individual are counted separately.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

A higher proportion of patients experienced SAEs in the Inavo+Palbo+Fulv arm (24.1%) compared with the Pbo+Palbo+Fulv arm (10.5%). The SAEs were distributed across multiple PTs and no SAE was reported with a $\geq$ 2% difference between treatment arms.

The higher incidence of SAEs (any grade) in the Infections and Infestations SOC in the Inavo+Palbo+Fulv arm (11 patient [6.8%]) compared with the Pbo+Palbo+Fulv arm (3 patients [1.9%]) was primarily driven by PTs of COVID-19 (4 patients [2.5%] vs. 1 patient [0.6%]), pneumonia (3 patients [1.9%] vs. no patient [0%]) and urinary tract infection (2 patients [1.2%] vs. no patient [0%]).

One patient int the Inavo+Palbo+Fulv arm had osteonecrosis of jaw (ONJ) as SAE. Overall, 3 events of ONJ in the experimental arm vs. none in the comparator arm are noted.

AEs of special interest

The 7 protocol-defined AESIs are summarised by (i) Medical concept category and (ii) Group term, MedDRA Preferred term in tables below, together with 7 additional Selected AEs.

Further analysis of **AESI** and other **Selected AE**s are provided in the sections below.

Table 51. Summary of selected adverse events by medical concept category (safety analysis set) study WO41554

Medical Concept Category	Arm	All Grades	Grade 3-4	Fatal	Serious (All Grades)	Leading to Any Treatment Withdrawal	Leading to Any Treatment Reduction	Leading to Any Treatment Interruption	Requiring Treatment for Selected AEs (All Grades)
Total number of patients with at least one AE	Inavo+ palbo+Fulv	157 (96.9%)	137 (84.6%)	0 (0%)	8 (4.9%)	5 (3.1%)	63 (38.9%)	118 (72.8%)	131 (80.9%)
	Pbo+ Palbo+Ful	156 (96.3%)	130 (80.2%)	0 (0%)	4 (2.5%)	0 (0%)	50 (30.9%)	92 (56.8%)	85 (52.5%)
Hyperglycemia	Inavo+ palbo+Fulv	95 (58.6%)	9 (5.6%)	0 (0%)	0 (0%)	2 (1.2%)	4 (2.5%)	45 (27.8%)	66 (40.7%)
	Pbo+ Palbo+Ful	14 (8.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)
Diarrhea	Inavo+ palbo+Fulv	78 (48.1%)	6 (3.7%)	0 (0%)	2 (1.2%)	0 (0%)	2 (1.2%)	12 (7.4%)	46 (28.4%)
	Pbo+ Palbo+Ful	26 (16.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	6 (3.7%)
Rash	Inavo+ palbo+Fulv	41 (25.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	3 (1.9%)	24 (14.8%)
	Pbo+ Palbo+Ful	28 (17.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.2%)	2 (1.2%)	19 (11.7%)
Stomatitis and mucosal inflammation	Inavo+ palbo+Fulv	83 (51.2%)	9 (5.6%)	0 (0%)	0 (0%)	1 (0.6%)	6 (3.7%)	19 (11.7%)	69 (42.6%)
	Pbo+ Palbo+Ful	43 (26.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	3 (1.9%)	27 (16.7%)
Nausea	Inavo+ palbo+Fulv	45 (27.8%)	1 (0.6%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.6%)	4 (2.5%)	20 (12.3%)
	Pbo+ Palbo+Ful	27 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	12 (7.4%)
Vomiting	Inavo+ palbo+Fulv	24 (14.8%)	1 (0.6%)	0 (0%)	1 (0.6%)	0 (0%)	2 (1.2%)	3 (1.9%)	8 (4.9%)
	Pbo+ Palbo+Ful	8 (4.9%)	2 (1.2%)	0 (0%)	2 (1.2%)	0 (0%)	0 (0%)	1 (0.6%)	2 (1.2%)
Colitis	Inavo+ palbo+Fulv	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Pbo+ Palbo+Ful	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ocular Toxicities	Inavo+ palbo+Fulv	36 (22.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	16 (9.9%)
	Pbo+ Palbo+Ful	21 (13.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (4.9%)

Medical Concept Category	Arm	All Grades	Grade 3-4	Fatal	Serious (All Grades)	Leading to Any Treatment Withdrawal	Leading to Any Treatment Reduction	Leading to Any Treatment Interruption	Requiring Treatment for Selected AEs (All Grades)
Pneumonitis	Inavo+ palbo+Fulv	3 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)
	Pbo+ Palbo+Ful	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)
Neutropenia	Inavo+ palbo+Fulv	144 (88.9%)	130 (80.2%)	0 (0%)	0 (0%)	1 (0.6%)	50 (30.9%)	92 (56.8%)	28 (17.3%)
	Pbo+ Palbo+Ful	147 (90.7%)	127 (78.4%)	0 (0%)	1 (0.6%)	0 (0%)	47 (29.0%)	85 (52.5%)	37 (22.8%)
Thrombocytopenia	Inavo+ palbo+Fulv	78 (48.1%)	23 (14.2%)	0 (0%)	1 (0.6%)	0 (0%)	8 (4.9%)	12 (7.4%)	18 (11.1%)
	Pbo+ Palbo+Ful	73 (45.1%)	7 (4.3%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.6%)	9 (5.6%)	7 (4.3%)
ALT/AST elevation	Inavo+ palbo+Fulv	31 (19.1%)	6 (3.7%)	0 (0%)	1 (0.6%)	1 (0.6%)	0 (0%)	5 (3.1%)	12 (7.4%)
	Pbo+ Palbo+Ful	30 (18.5%)	3 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	8 (4.9%)
Anemia	Inavo+ palbo+Fulv	60 (37.0%)	10 (6.2%)	0 (0%)	3 (1.9%)	0 (0%)	1 (0.6%)	10 (6.2%)	16 (9.9%)
	Pbo+ Palbo+Ful	59(36.4%)	3 (1.9%)	0 (0%)	0 (0%)	0 (0%)	2 (1.2%)	3 (1.9%)	13 (8.0%)
Lymphopenia	Inavo+ palbo+Fulv	6 (3.7%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	2 (1.2%)	1 (0.6%)
	Pbo+ Palbo+Ful	15 (9.3%)	3 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; Inavo=Inavolisib; Palbo=Palbociclib; Fulv=Fulvestrant

Table 52. Summary of selected adverse events by group term, safety analysis set, study WO41554

Selected Adverse Event Category MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one adverse event	157 (96.9%)	156 (96.3%)
Overall total number of events	1668	1019
Neutropenia		
Total number of patients with at least one adverse event	144 (88.9%)	147 (90.7%)
Total number of events	502	426
Neutropenia	88 (54.3%)	89 (54.9%)
Neutrophil count decreased	63 (38.9%)	64 (39.5%)
Thrombocytopenia		
Total number of patients with at least one adverse event	78 (48.1%)	73 (45.1%)
Total number of events	187	134
Platelet count decreased	42 (25.9%)	36 (22.2%)
Thrombocytopenia	36 (22.2%)	41 (25.3%)
Stomatitis and mucosal inflammation		
Total number of patients with at least one adverse event	83 (51.2%)	43 (26.5%)
Total number of events	163	65
Stomatitis	53 (32.7%)	27 (16.7%)
Mucosal inflammation	30 (18.5%)	16 (9.9%)
Aphthous ulcer	8 (4.9%)	3 (1.9%)
Mouth ulceration	4 (2.5%)	2 (1.2%)
Glossitis	1 (0.6%)	0
Glossodynia	1 (0.6%)	0
Lip ulceration	1 (0.6%)	0
Anemia		
Total number of patients with at least one adverse event	60 (37.0%)	59 (36.4%)
Total number of events	106	104
Anaemia	59 (36.4%)	59 (36.4%)
Haemoglobin decreased	1 (0.6%)	0
Hyperglycemia		
Total number of patients with at least one adverse event	95 (58.6%)	14 (8.6%)
Total number of events	218	51
Hyperglycaemia	87 (53.7%)	12 (7.4%)
Blood glucose increased	8 (4.9%)	2 (1.2%)
Diarrhea		
Total number of patients with at least one adverse event	78 (48.1%)	26 (16.0%)
Total number of events	158	35
Diarrhoea	78 (48.1%)	26 (16.0%)
Nausea		
Total number of patients with at least one adverse event	45 (27.8%)	27 (16.7%)
Total number of events	59	39
Nausea	45 (27.8%)	27 (16.7%)
Rash		
Total number of patients with at least one adverse event	41 (25.3%)	28 (17.3%)
Total number of events	78	42
Rash	26 (16.0%)	21 (13.0%)
Rash maculo-papular	7 (4.3%)	4 (2.5%)
Rash pruritic	4 (2.5%)	1 (0.6%)
Dermatitis acneiform	2 (1.2%)	1 (0.6%)
Folliculitis	2 (1.2%)	0
Rash erythematous	2 (1.2%)	0

Selected Adverse Event Category MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Rash papular	1 (0.6%)	1 (0.6%)
Dermatitis	1 (0.6%)	0
Dermatitis bullous	1 (0.6%)	0
Erythema	0	1 (0.6%)
Rash pustular	1 (0.6%)	0
ALT/AST elevation		
Total number of patients with at least one adverse event	31 (19.1%)	30 (18.5%)
Total number of events	77	65
Aspartate aminotransferase increased	28 (17.3%)	26 (16.0%)
Alanine aminotransferase increased	28 (17.3%)	21 (13.0%)
Ocular Toxicities		
Total number of patients with at least one adverse event	36 (22.2%)	21 (13.0%)
Total number of events	55	24
Dry eye	14 (8.6%)	5 (3.1%)
Vision blurred	6 (3.7%)	2 (1.2%)
Lacrimation increased	4 (2.5%)	1 (0.6%)
Cataract	3 (1.9%)	1 (0.6%)
Eye pruritus	3 (1.9%)	0
Visual acuity reduced	1 (0.6%)	2 (1.2%)
Xerophthalmia	3 (1.9%)	0
Myopia	1 (0.6%)	1 (0.6%)
Photophobia	1 (0.6%)	1 (0.6%)
Photopsia	2 (1.2%)	0
Punctate keratitis	1 (0.6%)	1 (0.6%)
Retinal vascular disorder	2 (1.2%)	0
Visual impairment	1 (0.6%)	1 (0.6%)
Vitreous floaters	2 (1.2%)	0
Blepharitis	0	1 (0.6%)
Chalazion	0	1 (0.6%)
Conjunctival haemorrhage	0	1 (0.6%)
Conjunctivitis allergic	1 (0.6%)	0
Dacryoadenitis acquired	0	1 (0.6%)
Diplopia	0	1 (0.6%)
Epiretinal membrane	1 (0.6%)	0
Eye discharge	0	1 (0.6%)
Eye haemorrhage	1 (0.6%)	0
Eye irritation	0	1 (0.6%)
Eye swelling	1 (0.6%)	0
Eyelid oedema	0	1 (0.6%)
Eyelid pain	1 (0.6%)	0
Hypoaesthesia eye	1 (0.6%)	0
Keratitis	1 (0.6%)	0
Keratopathy	1 (0.6%)	0
Ocular hyperaemia	1 (0.6%)	0
Ocular toxicity	1 (0.6%)	0
Periorbital oedema	0	1 (0.6%)
Retinal haemorrhage	1 (0.6%)	0

Selected Adverse Event Category MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Vomiting		
Total number of patients with at least one adverse event	24 (14.8%)	8 (4.9%)
Total number of events	48	9
Vomiting	24 (14.8%)	8 (4.9%)
Lymphopenia		
Total number of patients with at least one adverse event	6 (3.7%)	15 (9.3%)
Total number of events	14	24
Lymphocyte count decreased	5 (3.1%)	10 (6.2%)
Lymphopenia	1 (0.6%)	5 (3.1%)
Pneumonitis		
Total number of patients with at least one adverse event	3 (1.9%)	1 (0.6%)
Total number of events	3	1
Pneumonitis	3 (1.9%)	1 (0.6%)

Investigator text for AEs is coded using MedDRA version 26.1.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Multiple AEs for one individual that meet the specified criteria are counted only once
Percentages are based on N in the column headings
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Hyperglycaemia

Table 53. Overview of deaths and selected adverse events, hyperglycaemia, safety analysis set

	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one AE	95 (58.6%)	14 (8.6%)
Total number of AEs	218	51
Total number of deaths	26 (16.0%)	4 (2.5%)
Total number of patients with at least one treatment-related AE		
Inavolisib/Placebo	89 (54.9%)	12 (7.4%)
Palbociclib	12 (7.4%)	0
Fulvestrant	7 (4.3%)	0
Any Treatment	90 (55.6%)	12 (7.4%)
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	0	0
Grade 3-4 AE	9 (5.6%)	0
AE leading to withdrawal from treatment		
Inavolisib/Placebo	1 (0.6%)	0
Palbociclib	1 (0.6%)	0
Fulvestrant	1 (0.6%)	0
Any Treatment	2 (1.2%)	0
AE leading to dose modification/interruption		
Inavolisib/Placebo	46 (28.4%)	1 (0.6%)
Palbociclib	5 (3.1%)	0
Fulvestrant	4 (2.5%)	0
Any Treatment	46 (28.4%)	1 (0.6%)

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

For inclusion in Study WO41551, HbA1C <6.0% (<42 mmol/mol) and fasting glucose <126 mg/dL (<7.0 mmol/L) was required. Type 2 diabetes requiring ongoing systemic treatment at the time of study entry, or any history of Type 1 diabetes, were exclusion criteria.

The overall proportion of patients with hyperglycaemia was 58.6% in the Inavo+Palbo+Fulv arm (n=95) vs. 8.6% in the Pbo+Palbo+Fulv arm (n=14).

The majority of patients who experienced hyperglycaemia had Grade 1 (Inavo+Palbo+Fulv: 16.0% and Pbo+Palbo+Fulv: 8.0%) or Grade 2 events (37.0% and 0.6%). Grade 3 hyperglycaemia events were only reported in the Inavo+Palbo+Fulv arm (9 patients [5.6%]).

No Grade 4 or 5 hyperglycaemia events were reported in either arm, and no serious cases of hyperglycaemia. No cases of diabetic ketoacidosis were reported in Study WO41551.

Hyperglycaemia events led to withdrawal of inavolisib in 1 patient (0.6%), dose reduction of inavolisib in 4 patients (2.5%), and dose interruption of inavolisib in 44 patients (27.2%) in the Inavo+Palbo+Fulv arm.

The median time to first onset of hyperglycaemia was 7 days (range: 2.0 to 955.0 days).

Among patients with at least one hyperglycaemia event reported, all hyperglycaemia events had resolved in 67 of 95 patients (70.5%) at the primary analysis CCOD of 29 September 2023.

Of the 97 patients in the Inavo+Palbo+Fulv arm who experienced an ADR of hyperglycaemia, 72 patients (74.2%) received metformin and/or other anti-diabetic agents as either hyperglycaemia prophylaxis or hyperglycaemia treatment.

Metformin was reported in 28.0% and 3.7%, and metformin hydrochloride in 19.9% and 1.2% in Inavo+Palbo+Fulv arm and Pbo+Palbo+Fulv arm, respectively, as "Concomitant medications initiated during study treatment".

Overall, 11 of the 97 patients (11.3%) in the Inavo+Palbo+Fulv arm that experienced an ADR of hyperglycaemia received treatment with insulin during study with the median duration of insulin use of 5 days (range: 1-539 days). According to the protocol, short-term insulin was allowed to control blood glucose levels, but goal should be to maintain on oral agents once acute episode resolved.

Exploratory analyses of Hyperglycaemia by Baseline Risk Factors indicated that risk factors of Fasting glucose ≥ 100 mg/dL at baseline and BMI ≥ 30 kg/m2 at baseline contributed to higher incidence of hyperglycaemia.

Pneumonitis

The proportion of patients with AEs of pneumonitis was 3 patients [1.9%] in the Inavo+Palbo+Fulv arm vs. 1 patient [0.6%]) in the Pbo+Palbo+Fulv arm.

There were no Grade 3 or Grade 4 events, SAEs, or events leading to withdrawal or dose reduction of any study drug in either of the arms due to pneumonitis.

Pneumonitis events led to dose interruption of inavolisib/placebo in 1 patient (0.6%) in the Inavo+Palbo+Fulv arm and 1 patient (0.6%) in the Pbo+Palbo+Fulv arm.

In the Inavo+Palbo+Fulv arm, 1 patient had pneumonitis reported not recovered/not resolved at the CCOD.

Stomatitis or mucosal inflammation

The overall proportion of patients with AEs of stomatitis and mucosal inflammation was 51.2% in the Inavo+Palbo+Fulv arm vs. 26.5% Pbo+Palbo+Fulv arm. The majority had Grade 1 events (Inavo+Palbo+Fulv: 32.1% and Pbo+Palbo+Fulv: 21.0%) or Grade 2 events (13.6% and 5.6%). Grade 3 events were only reported in the Inavo+Palbo+Fulv arm (5.6% of patients). No Grade 4 or 5 events were reported in either arm, and no serious cases of stomatitis were reported.

Stomatitis events led to withdrawal of inavolisib in 1 patient (0.6%), dose reduction of inavolisib in 3.7% of patients, and dose interruption of inavolisib in 9.9% of patients in the Inavo+Palbo+Fulv arm.

There were 42.6% of patients who received treatment for stomatitis and mucosal inflammation AEs in the Inavo+Palbo+Fulv arm, most commonly dexamethasone mouthwash.

According to the protocol, corticosteroid mouthwash was recommended for (i) prophylaxis or (ii) treatment of stomatitis/mucositis. Among patients who received inavolisib, prophylaxis containing dexamethasone was used in 19.1%.

Rash

The overall proportion of patients with AEs of rash was 25.3% in the Inavo+Palbo+Fulv vs. 17.3% in the Pbo+Palbo+Fulv arm

There were no Grade 3 or 4 events, and no patient experienced an SAE of a rash event during the study in either arm.

No rash event led to withdrawal of any study drug in both arms. Dose reduction of inavolisib due to rash was reported in 1 patient (0.6%) and dose interruption of inavolisib in 2 patients (1.2%).

There were 16.0% of patients who received treatment for rash AEs in the Inavo+Palbo+Fulv arm, most common topical formulations.

Diarrhoea

The overall proportion of patients with AEs of diarrhoea was 48.1% in the Inavo+Palbo+Fulv arm vs. 16.0% in the Pbo+Palbo+Fulv arm. The majority had Grade 1 (Inavo+Palbo+Fulv: 27.8% and Pbo+Palbo+Fulv: 13.6%) or Grade 2 events (16.7% and 2.5%). Grade 3 diarrhoea events were only reported in the Inavo+Palbo+Fulv arm (6 patients [3.7%]). No Grade 4 or 5 diarrhoea events were reported in either arm.

Two patients (1.2%) in the Inavo+Palbo+Fulv arm experienced SAEs of diarrhoea, both of which were Grade 3 in severity and reported recovered/resolved at the CCOD.

No diarrhoea event led to withdrawal of any study drug in either arm. Diarrhoea events led to dose reduction of inavolisib in 2 patients (1.2%), and dose interruption of inavolisib in 11 patients (6.8%).

There were 28.4% patients who received treatment for diarrhoea AEs in the Inavo+Palbo+Fulv arm, most commonly loperamide.

Colitis or enterocolitis

No cases of treatment-emergent colitis were reported in study WO41554.

In supportive study GO39374, 1 patient (Arm D: Inavo+Fulv) experienced a colitis event which was Grade 3 non-serious colitis and resolved within a day with the administration of steroids.

Grade $\geq$ 3 ALT or AST elevation

The overall proportion of patients with AEs of ALT/AST elevation was 19.1% in Inavo+Palbo+Fulv vs. 18.5% in the Pbo+Palbo+Fulv arm.

The proportion of patients with Grade 3 (Inavo+Palbo+Fulv: 3.1% and Pbo+Palbo+Fulv: 1.9%) and Grade 4 (1 patient [0.6%] and no patient [0%]) ALT/AST elevation events was numerically higher in the Inavo+Palbo+Fulv arm. No patient experienced a Grade 5 AST/ALT elevation event in either arm.

ALT/AST elevation events led to withdrawal of inavolisib/placebo in 1 patient (0.6%) in the Inavo+Palbo+Fulv arm and no patients (0%) in the Pbo+Palbo+Fulv arm.

ALT/AST elevation events led to dose interruption of inavolisib in 4 patients (2.5%) in the Inavo+Palbo+Fulv arm and 1 patient (0.6%) in the Pbo+Palbo+Fulv arm.

Potential cases of DILI were evaluated using Hy's law algorithm. All potential Hy's Law cases (1 patient in the Inavo+Palbo+Fulv arm and 3 patients in the Pbo+Palbo+Fulv arm) were confounded by progress and worsening of disease involvement in the liver, and did not qualify as DILI.

Adverse drug reactions in SmPC

Study WO41554

To identify the adverse drug reactions (ADRs) for inavolisib, any AE (PT) with incidence ≥ 10% (all grades) or ≥ 2% for Grades 3-4 in the Inavo+Palbo+Fulv arm of Study WO41554 were reviewed.

Furthermore, all grade AEs with ≥ 5% difference and or Grade 3-4 AEs with ≥ 2% difference between treatment arms were reviewed.

In addition, all Grade 3-5 events were reviewed for Designated Medical Events and AEs that are known class effects/known effects from the perspective of mechanism of action.

Furthermore, the following general criteria were applied:

a) Events whose incidence was lower than 10% (all grades) could be included if there was a medical rationale supporting the assessment such as a known class effect/known effect from mechanism of action and at least one of the observed AE reports was assessed by the Sponsor as related to inavolisib.

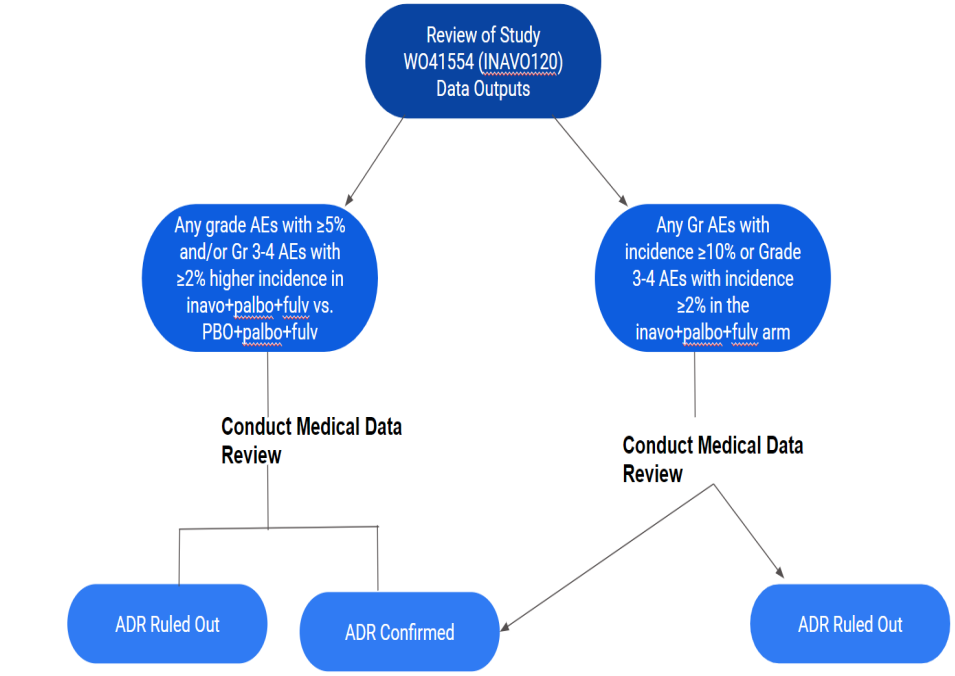
b) Medical judgment would be further applied to a potential ADR, taking into consideration the extent to which the AE was consistent with the pharmacology of the drug, apparent dose-response trend, re-challenge response, temporality and the consistency of the pattern of symptoms across studies/indications, confounders and quality of information.

In the SmPC, frequency categories were defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). These translated to the following frequency categories:

- Very common ≥ 10%
- Common ≥ 1% to <10%
- Uncommon ≥ 0.1% to <1%
- Rare ≥ 0.01% to <0.1%
- Very rare <0.01%

The methodology to identify the ADRs is presented in figure below.

Figure 16. Algorithm for ADR evaluation from Inavo+Palbo+Fulv arm of study WO41554



Based on medical judgement, a decision may be made to include terms that have not met any of the pre-defined criteria, or not to include terms that have met one or more numerical criteria. Medical judgement includes knowledge of biological plausibility, experience with similar-in-class agents, exclusion of alternative causes and general medical knowledge of human pathophysiology.

Adverse drug reactions with ≥ 5% (all grades) or ≥ 2% (Grade 3-4) higher incidence in the Inavo+Palbo+Fulv arm versus the Pbo+Palbo+Fulv arm of Study WO41554 are summarised in table below.

Table 54. Adverse drug reactions with ≥5% (all grades) or ≥2% (grade 3-4) higher incidence in the Inavo+Palbo+Fulv arm of study WO41554

System Organ Class Adverse Reaction	Inavolisib + Palbociclib + Fulvestrant N=162			Placebo + Palbociclib + Fulvestrant N=162	
	Frequency Category (All Grades)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Infections and Infestations					
Urinary Tract Infection	Very Common	13	1.2*	7.4	0
Blood and Lymphatic System Disorders					
Thrombocytopenia[a]	Very Common	48.1	14.2	45.1	4.3
Anaemia[b]	Very Common	37	6.2*	36.4	1.9*
Metabolism and Nutrition Disorders					
Hyperglycaemi[a]	Very Common	59.9	5.6*	9.9	0
Decreased appetite	Very Common	23.5	0	8.6	0
Hypokalaemia	Very Common	16	2.5	6.2	0
Hypocalcaemia	Common	8.6	1.2*	2.5	0.6*
Nervous System Disorders					
Headache	Very Common	21	0	13.6	0
Eye Disorders					
Dry eye	Common	8.6	0	3.1	0
Gastrointestinal Disorders					

Stomatitis[d]	Very Common	51.2	5.6*	26.5	0
Diarrhoea	Very Common	48.1	3.7*	16	0
Nausea	Very Common	27.8	0.6*	16.7	0
Vomiting	Very Common	14.8	0.6*	4.9	1.2*
Dyspepsia	Common	8	0	2.5	0
Skin and Subcutaneous Tissue Disorders					
Rash[e]	Very Common	25.3	0	17.3	0
Alopecia	Very Common	18.5	0	5.6	0
Dry skin[f]	Very Common	13	0	4.3	0
General Disorders and Administration Site Conditions					
Fatigue	Very Common	37.7	1.9*	25.3	1.2*
Investigations					
Alanine aminotransferase increased	Very Common	17.3	3.7*	13	1.2*
Weight decreased	Very Common	17.3	3.7*	0.6	0
Blood insulin increased	Common	6.2	0	0.6	0

Grading according to CTCAE version 5.0.

* No Grade 4 events were observed.

[a] Includes the preferred terms (PTs) of platelet count decreased and thrombocytopenia.

[b] Includes the PTs of anaemia and haemoglobin decreased.

[c] Includes the PTs of hyperglycaemia, blood glucose increased, hyperglycaemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated haemoglobin increased.

[d] Includes the PTs of aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.

[e] Includes the PTs of rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

[f] Includes the PTs of dry skin, skin fissures, xerosis, and xeroderma.

Other adverse reactions that were considered with <5% (all grades) or <2% (Grade 3-4) in patients in the inavolisib arm are presented below:

- **Gastrointestinal Disorders:** Abdominal pain, including the PTs of abdominal pain, abdominal pain upper, abdominal pain lower (all grades: 15.4%; Grade 3: 0.6%; no Grade 4 events); dysgeusia, including the PTs of dysgeusia, ageusia, and hypogeusia (all grades: 8.6%; Grade 3-4: 0%).
- **Skin and subcutaneous tissue disorders:** Dermatitis, including the PTs of dermatitis, dermatitis acneiform, and dermatitis bullous (all grades: 2.5%; Grade 3-4: 0%); folliculitis (all grades: 1.2%; Grade 3-4: 0%)

These ADRs have been included in the relevant table of section 4.8 of the SmPC.

2.6.8.4. *Laboratory findings*

Haematology

Commonly occurring haematology shifts from baseline included low total absolute neutrophils (81.7% Inavo+Palbo+Fulv vs. 78.5% Pbo+Palbo+Fulv), low total leukocyte count (42.5% vs. 49.7%), low platelet count (15.6% vs. 3.7%), low haemoglobin (7.5% vs. 2.5%), and low absolute lymphocytes (7.3% vs. 14.8%).

Clinical chemistry

Commonly occurring shifts from baseline included high triglycerides (6.7% Inavo+Palbo+Fulv vs. 0% Pbo+Palbo+Fulv), low potassium (6.3% vs. 0.6%), and high cholesterol and high triacylglycerol lipase (6.2% vs. 0% each).

Hypocalcaemia is listed as an ADR in SmPC section 4.8 and reported in 8.6% of inavolisib treated patients (1.2% Grade 3 event), vs. a frequency of 2.5% (0.6% Grade 3 event) in the Pbo+Palbo+Fulv arm. One patient in the Inavo+Palbo+Fulv arm had a SAE of both Hypocalcaemia grade 3 and Tetany Grade 3, and the investigator considered hypocalcaemia to be related to concomitant use of pamidronate.

Vital signs

There were no clinically relevant differences between the treatment arms with respect to vital sign parameters during the course of the study.

ECG

Inavolisib is not expected to cause clinically relevant QT prolongation based on the totality of evidence including pre-clinical data and the clinical (cardiovascular) safety database, in addition to the concentration-QT analysis.

2.6.8.5. *In vitro biomarker test for patient selection for safety*

Not applicable

2.6.8.6. *Safety in special populations*

Table 55. AEs by age for study WO41554

	Active (Inavo+Palbo+Fulv)				Comparator (Pbo+Palbo+Fulv)			
MedDRA Terms	Age <65 N=138 (%)	Age 65-74 N=19 (%)	Age 75-84 N=5 (%)	Age 85+ n (%)	Age <65 N=128 (%)	Age 65-74 N=28 (%)	Age 75-84 N=6 (%)	Age 85+ n (%)
Total AEs	2916	295	87	0	1654	359	45	0
Serious AEs – Total	29 (21.0%)	7 (36.8%)	3 (60.0%)	0	12 (9.4%)	4 (14.3%)	1 (16.7%)	0
- Fatal	2 (1.4%)	2 (10.5%)	2 (40.0%)	0	2 (1.6%)	0	0	0
- Hospitalisation/prolong existing hospitalisation	25 (18.1%)	6 (31.6%)	1 (20.0%)	0	10 (7.8%)	3 (10.7%)	1 (16.7%)	0
- Life-threatening	2 (1.4%)	3 (15.8%)	0	0	1 (0.8%)	1 (3.6%)	0	0
- Disability/incapacity	0	0	0	0	1 (0.8%)	0	0	0
- Other (medically significant)	0	1 (5.3%)	0	0	1 (0.8%)	0	0	0
AE leading to discontinuation of any study drug	8 (5.8%)	3 (15.8%)	0	0	1 (0.8%)	0	0	0
Psychiatric disorders	23 (16.7%)	2 (10.5%)	0	0	18 (14.1%)	1 (3.6%)	0	0
Nervous system disorders	56 (40.6%)	3 (15.8%)	1 (20.0%)	0	29 (22.7%)	14 (50.0%)	0	0
Accidents and injuries	13 (9.4%)	2 (10.5%)	0	0	4 (3.1%)	0	0	0
Cardiac disorders	12 (8.7%)	1 (5.3%)	0	0	9 (7.0%)	4 (14.3%)	0	0
Vascular disorders	22 (15.9%)	3 (15.8%)	0	0	11 (8.6%)	1 (3.6%)	0	0
Central nervous system haemorrhages and cerebrovascular conditions (SMQ)	3 (2.2%	0	1 (20.0%)	0	0	1 (3.6%)	0	0
Infections and infestations	78 (56.5%)	10 (52.6%)	0	0	39 (30.5%)	11 (39.3%)	2 (33.3%)	0

	Active (Inavo+Palbo+Fulv)				Comparator (Pbo+Palbo+Fulv)			
MedDRA Terms	Age <65 N=138 (%)	Age 65-74 N=19 (%)	Age 75-84 N=5 (%)	Age 85+ n (%)	Age <65 N=128 (%)	Age 65-74 N=28 (%)	Age 75-84 N=6 (%)	Age 85+ n (%)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	15 (10.9%)	0	0	0	10 (7.8%)	6 (21.4%)	0	0
Other AE appearing more frequently in older patients								
Blood and Lymphatic System Disorders	95 (68.8%)	13 (68.4%)	3 (60.0%)	0	92 (71.9%)	21 (75.0%)	5 (83.3%)	0
Neutropenia	75 (54.3%)	11 (57.9%)	2 (40.0%)	0	65 (50.8%)	19 (67.9%)	5 (83.3%)	0
Thrombocytopenia	28 (20.3%)	6 (31.6%)	2 (40.0%)	0	29 (22.7%)	9 (32.1%)	3 (50.0%)	0
Febrile neutropenia	2 (1.4%)	1 (5.3%)	1 (20.0%)	0	1 (0.8%)	0	0	0
Investigations	96 (69.6%)	13 (68.4%)	3 (60.0%)	0	83 (64.8%)	17 (60.7%)	3 (50.0%)	0
Platelet count decreased	35 (25.4%)	6 (31.6%)	1 (20.0%)	0	30 (23.4%)	5 (17.9%)	1 (16.7%)	0
Aspartate aminotransferase increased	22 (15.9%)	4 (21.1%)	2 (40.0%)	0	23 (18.0%)	2 (7.1%)	1 (16.7%)	0
Alanine aminotransferase increased	22 (15.9%)	4 (21.1%)	2 (40.0%)	0	21 (16.4%)	0	0	0
Weight decreased	21 (15.2%)	5 (26.3%)	2 (40.0%)	0	1 (0.8%)	0	0	0
Blood creatinine increased	7 (5.1%)	2 (10.5%)	0	0	10 (7.8%)	1 (3.6%)	1 (16.7%)	0
Metabolism and Nutrition Disorders	97 (70.3%)	12 (63.2%)	4 (80.0%)	0	44 (34.4%)	9 (32.1%)	0	0
Decreased appetite	29 (21.0%)	6 (31.6%)	3 (60.0%)	0	10 (7.8%)	4 (14.3%)	0	0
Hyponatremia	5 (3.6%)	2 (10.5%)	1 (20.0%)	0	4 (3.1%)	1 (3.6%)	0	0
Infections and Infestations	78 (56.5%)	10 (52.6%)	0	0	39 (30.5%)	11 (39.3%)	2 (33.3%)	0
COVID-19	32 (23.2%)	5 (26.3%)	0	0	13 (10.2%)	3 (10.7%)	1 (16.7%)	0
Upper respiratory tract infection	11 (8.0%)	3 (15.8%)	0	0	6 (4.7%)	1 (3.6%)	0	0
Skin and Subcutaneous Tissue Disorders	67 (48.6%)	9 (47.4%)	0	0	42 (32.8%)	10 (35.7%)	1 (16.7%)	0
Dry skin	15 (10.9%)	3 (15.8%)	0	0	5 (3.9%)	2 (7.1%)	0	0
Respiratory, Thoracic and Mediastinal Disorders	41 (29.7%)	6 (31.6%)	2 (40.0%)	0	24 (18.8%)	8 (28.6%)	0	0
Dyspnoea	9 (6.5%)	2 (10.5%)	1 (20.0%)	0	8 (6.2%)	1 (3.6%)	0	0

Age

Overall, the incidences of SAEs and AEs leading to dose modification/interruption of any study treatment was numerically higher in elderly patients (i.e. in patients in 65-74 years and ≥ 75 years age groups compared to those in < 65 years age group) which could be due to higher prevalence of comorbidities in elderly patients and/or reduction in the reserve capacity of the organs in general. For

AEs with fatal outcomes, the number of patients in each of the age categories was low (i.e., 2 patients in each of the age categories). Analysis of the safety of inavolisib comparing patients ≥ 65 years of age (14.8%) to younger patients (85.2%) shows a numerically higher incidence of inavolisib dose modification/interruptions (79.2% versus 68.1%).

Gender

Consistent with the disease demographics for breast cancer, the vast majority of patients treated with Inavo+Palbo+Fulv were female (n=157) compared with male (n=5).

Renal impairment

A dedicated renal impairment study (GP44944) in subjects with moderate or severe renal impairment is ongoing. Please refer to PK section for further details on renal impairment.

Hepatic impairment

Based on the absorption, distribution, metabolism, and excretion (ADME) properties of inavolisib, hepatic impairment is unlikely to have a clinically significant impact on the PK of inavolisib. Please refer to PK section for further details on hepatic impairment.

Race

A majority of 162 patients treated with Inavo+Palbo+Fulv were White (n=94, 58.0%) followed by Asian (n=62, 38.3%), Unknown (n=5, 3.1%), and Black or African American (n=1, 0.6%).

The overall incidence of AEs (97.9% vs. 100.0%), AEs leading to withdrawal of any study treatment (8.5% vs. 4.8%), and AEs leading to dose modification/interruption of inavolisib (68.1% vs. 71.0%) were comparable between White and Asian racial subgroups, respectively.

The incidence of AEs with fatal outcome were low in both racial subgroups (4.3% and 3.2%).

The incidences of the following selected AEs were higher in White compared to the Asian racial subgroup: diarrhoea (52.1% vs. 43.5%) and ocular toxicities (25.5% vs. 16.1%).

The incidences of the following selected AEs were higher in Asian compared to the White racial subgroup: neutropenia (93.5% vs. 85.1%), thrombocytopenia (71.0% vs. 35.1%), stomatitis and mucosal inflammation (64.5% vs. 42.6%), hyperglycaemia (62.9% vs. 56.4%), anaemia (45.2% vs. 31.9%), and ALT/AST elevation (27.4% vs. 13.8%).

AEs leading to withdrawal from any study treatment or dose modification/interruption of inavolisib between the White and Asian racial subgroups were comparable.

2.6.8.7. *Immunological events*

Not applicable

2.6.8.8. *Safety related to drug-drug interactions and other interactions*

Please refer to PK section.

2.6.8.9. *Discontinuation due to adverse events*

Table 56. Adverse events leading to withdrawal of any study drug, safety analysis set, study WO41554

MedDRA System Organ Class MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one adverse event	11 (6.8%)	1 (0.6%)
Overall total number of events	14	1
Investigations		
Total number of patients with at least one adverse event	3 (1.9%)	1 (0.6%)
Total number of events	3	1
Alanine aminotransferase increased	1 (0.6%)	0
Blood creatinine increased	0	1 (0.6%)
Neutrophil count decreased	1 (0.6%)	0
Weight decreased	1 (0.6%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	2 (1.2%)	0
Total number of events	3	0
Gastric ulcer	1 (0.6%)	0
Intestinal perforation	1 (0.6%)	0
Stomatitis	1 (0.6%)	0
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	2 (1.2%)	0
Total number of events	3	0
Hyperglycaemia	2 (1.2%)	0
Type 2 diabetes mellitus	1 (0.6%)	0
Infections and infestations		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	1	0
Anal abscess	1 (0.6%)	0
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	2	0
Bone pain	1 (0.6%)	0
Musculoskeletal pain	1 (0.6%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	1	0
Transitional cell carcinoma	1 (0.6%)	0
Renal and urinary disorders		
Total number of patients with at least one adverse event	1 (0.6%)	0
Total number of events	1	0
Acute kidney injury	1 (0.6%)	0

Investigator text for AEs encoded using MedDRA version 26.1.
Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed where the study medication adjustment CRF question is answered as "Drug withdrawn". For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

Table 57. Adverse events leading to dose reduction of any study drug, safety analysis set, study WO41554

MedDRA System Organ Class MedDRA Preferred Term	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one adverse event	71 (43.8%)	51 (31.5%)
Overall total number of events	112	74
Investigations		
Total number of patients with at least one adverse event	33 (20.4%)	23 (14.2%)
Total number of events	50	29
Neutrophil count decreased	28 (17.3%)	23 (14.2%)
White blood cell count decreased	7 (4.3%)	3 (1.9%)
Platelet count decreased	5 (3.1%)	0
Blood creatinine increased	1 (0.6%)	0
Electrocardiogram QT prolonged	1 (0.6%)	0
Lymphocyte count decreased	1 (0.6%)	0
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	27 (16.7%)	25 (15.4%)
Total number of events	37	40
Neutropenia	22 (13.6%)	24 (14.8%)
Leukopenia	3 (1.9%)	4 (2.5%)
Thrombocytopenia	3 (1.9%)	1 (0.6%)
Anaemia	1 (0.6%)	2 (1.2%)
Febrile neutropenia	2 (1.2%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	9 (5.6%)	1 (0.6%)
Total number of events	10	2
Stomatitis	3 (1.9%)	1 (0.6%)
Diarrhoea	2 (1.2%)	0
Vomiting	2 (1.2%)	0
Aphthous ulcer	1 (0.6%)	0
Nausea	1 (0.6%)	0
Proctalgia	1 (0.6%)	0
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	6 (3.7%)	1 (0.6%)
Total number of events	6	1
Hyperglycaemia	4 (2.5%)	0
Hypokalaemia	1 (0.6%)	1 (0.6%)
Hypocalcaemia	1 (0.6%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	4 (2.5%)	0
Total number of events	7	0
Asthenia	3 (1.9%)	0
Mucosal inflammation	2 (1.2%)	0
Oedema	1 (0.6%)	0
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	2 (1.2%)	2 (1.2%)
Total number of events	2	2
Rash	1 (0.6%)	2 (1.2%)
Papulopustular rosacea	1 (0.6%)	0

AEs by PT leading to Dose interruption of inavolisib/placebo in ≥ 3% of patients in either arm are listed below (Inavo+Palbo+Fulv and Pbo+Palbo+Fulv, respectively):

- Hyperglycaemia (24.7% vs. 0.6%)
- COVID-19 (16.0% vs. 4.9%)
- Neutropenia (12.3% vs. 9.9%) and Neutrophil count decreased (10.5% vs. 4.9%)
- Diarrhoea (6.8% vs. 0.6%)
- Mucosal inflammation (4.9% vs. 0%) and Stomatitis (3.7% vs. 1.9%)
- Upper respiratory tract infection (4.3% vs. 0.6%)
- Anaemia (4.3% vs. 0.6%)

2.6.8.10. *Post marketing experience*

Inavolisib was approved in the US in October 2024. As of 01 March 2025, two cases of diabetic ketoacidosis were reported in the safety database from the post-marketing setting:

- One event of diabetic ketoacidosis was observed in a patient with Type 2 diabetes on insulin who were hospitalised due to diabetic ketoacidosis 6 days after initiation of inavolisib. It was reported that her glucometer was broken and did not get glucometer readings. The event of diabetic ketoacidosis resolved on an unreported date. Inavolisib was permanently discontinued.
- The other event of diabetic ketoacidosis was observed in a patient with suspected poorly controlled Type 2 diabetes mellitus. Blood glucose was not normalised prior to inavolisib use and was prescribed a higher inavolisib dose than recommended in the label based on renal insufficiency. There was no indication of monitoring for fasting plasma glucose prior to symptomatic hyperglycaemia. The patient was hospitalised 5 days after initiation of inavolisib and diagnosed with diabetic ketoacidosis, and did not respond to verbal or physical stimuli. The patient was further diagnosed with MSSA pneumonia/aspiration pneumonia, septic shock, acute hypoxemic respiratory failure, and lactic acidosis before dying 14 days after initiation of inavolisib.

2.6.9. Discussion on clinical safety

The safety database in the sought indication and at the proposed posology is based on the randomised, double blinded, placebo-controlled Study WO41554 (INAVO120) in which 162 participants were treated with inavolisib + palbociclib + fulvestrant and 162 participants were treated with placebo+ palbociclib + fulvestrant.

Supportive safety data are derived from the first-in-human Study GO39374 Arms E (n=20) and F (n=20) in which the same treatment regimen and doses as in Study WO41554 were given.

The relatively limited size of the safety database from the pivotal study WO41554 is acceptable considering that the sought indication concerns a restricted patient population with "recurrence on or within 12 months of completing adjuvant endocrine treatment", and the fact that the observed safety data are in line with known safety profiles of PI3K and CDK4/6 inhibitors.

The median duration of treatment with inavolisib was 9.2 months (range 0-38.8) vs 5.6 months (range 0.1-40.3) with placebo.

The median duration of follow-up had reached 21.3 months (range 0-43.1) in the Inavo+Palbo+Fulv arm at the CCOD 29 September 2023.

In the Inavo+Palbo+Fulv arm, the median relative dose intensity was 95.8% (range: 26.4%-100.0%) for inavolisib, 87.3% (range: 16.7% 104.5%) for palbociclib and 100.0% (range: 75.0%-125.0%) for fulvestrant. Thus, adequate doses of palbociclib and fulvestrant was maintained in the combination with inavolisib.

As of the CCOD, 64.6% of patients in the Inavo+Palbo+Fulv arm and 59.1% of patients in the Pbo+Palbo+Fulv arm were continuing the study, either on study treatment or in follow-up. Death was the main reason for study discontinuation in both treatment arms, 26.1% of patients in the Inavo+Palbo+Fulv arm and 33.5% of patients in the Pbo+Palbo+Fulv arm.

The most **common AEs** in either arm by PT included (Inavo+Palbo+Fulv and Pbo+Palbo+Fulv, respectively): Neutropenia (54.3% vs. 54.9%), Hyperglycaemia (53.7% vs. 7.4%), Diarrhoea (48.1% vs. 16.0%), Anaemia (36.4% vs. 36.4%), and Stomatitis (32.7% vs. 16.7%).

Overall, the proportion of patients with Grade 3-4 AEs was comparable between the Inavo+Palbo+Fulv (85.8%) and the Pbo+Palbo+Fulv (82.1%) arms.

The majority of Grade 3-4 AEs in both treatment arms were associated with myelosuppression, which is in line with observed safety profiles for both palbociclib and inavolisib.

Other common Grade 3-4 AEs (by PTs) were hyperglycaemia (Inavo+Palbo+Fulv: 5.6% and Pbo+Palbo+Fulv: 0%), diarrhoea (3.7% vs 0%), and stomatitis (3.1% vs. 0%). Hyperglycaemia and GI related adverse effects are common mechanistic side effects of inavolisib.

SAEs were reported at a higher frequency in the Inavo+Palbo+Fulv arm (24.1%) compared with the Pbo+Palbo+Fulv arm (10.5%). The SAEs were distributed across multiple PTs and no SAE was reported with a $\geq$ 2% difference between treatment arms.

The SAEs occurring in > 2 patients in either arm included COVID-19 (4 patients [2.5%] Inavo+Palbo+Fulv vs. 1 patient [0.6%] Pbo+Palbo+Fulv), and pneumonia, anaemia, febrile neutropenia (3 patients [1.9%] vs no patient [0%] each).

Three events of Osteonecrosis of jaw (ONJ) are noted in the experimental arm (of which one was reported as an SAE) vs none in the comparator arm. The two additional non-serious events of ONJ reported in the Inavo+Palbo+Fulv arm were Grade 1-2. In the supportive study GO39374, ONJ was reported in 5 patients (2.6%), all Grade 2 in severity. Notably, ONJ is an ADR in the SmPC of similar product alpelisib (addressed in section 4.4 and 4.8) and also listed as an Important identified risk for alpelisib. Based on available data, with incidence of ONJ in the WO41554 study being comparable with the background prevalence of ONJ in breast cancer patients (Rugani et al. 2016) and all three cases of ONJ in the WO41554 study being confounded by concomitant bisphosphate/denosumab use, continued monitoring of ONJ by routine pharmacovigilance measures is considered sufficient.

Fatal AEs were reported in 6 patients (3.7%) in the Inavo+Palbo+Fulv arm and 2 patients (1.2%) in the Pbo+Palbo+Fulv arm. The Grade 5 AEs (by PT) reported in the Inavo+Palbo+Fulv arm were: cerebral haemorrhage, cerebrovascular accident, gastrointestinal haemorrhage, acute coronary syndrome, death, and COVID-19. These 6 deaths due to AEs in the Inavo+Palbo+Fulv arm do not raise any specific concern.

A higher proportion of patients in the Inavo+Palbo+Fulv arm (11 patients [6.8%]) compared with the Pbo+Palbo+Fulv arm (1 patient [0.6%]) experienced AEs leading to discontinuation of any study drug. However, the discontinuation rates due to AEs are relatively low in the Inavo+Palbo+Fulv arm, indicating that AEs are manageable with the risk minimisation measures as laid out in the SmPC. This is also reflected by a high relative dose intensity in Inavo+Palbo+Fulv arm. The only PT leading to withdrawal of any study drug in $\geq$ 2 patients in either arm was hyperglycaemia in the Inavo+Palbo+Fulv arm (2 patients [1.2%]).

A higher proportion of patients in the Inavo+Palbo+Fulv arm (43.8%) compared with the Pbo+Palbo+Fulv arm (31.5%) experienced AEs leading to the dose reduction of any study drug. This was mainly driven by neutrophil count decreased (17.3% Inavo+Palbo+Fulv vs. 14.2% Pbo+Palbo+Fulv), platelet count decreased (3.1% vs. 0%), and hyperglycaemia (2.5% vs. 0%).

A higher proportion of patients in the Inavo+Palbo+Fulv arm (80.9%) compared with the Pbo+Palbo+Fulv arm (65.4%) experienced AEs leading to the dose interruption of any study drug. This was mainly driven by differences in hyperglycaemia (25.3% Inavo+Palbo+Fulv vs. 0.6% Pbo+Palbo+Fulv), COVID-19 (16.0% vs. 7.4%) and diarrhoea (7.4% vs. 0.6%).

Safety data from the supportive first-in-human Study GO39374 (all Patients, Arms A-F, n=190) were overall consistent with those for Study WO41554. However, data from the Study GO39374 are not

assessed in detail due to differences in the patient populations, treatment regimens, inavolisib dose levels, and differences in AE grading criteria for these two studies.

Adverse events of Special Interest and Other selected AEs

Hyperglycaemia is an expected on-target toxicity associated with PI3K inhibitors and constitutes a major safety issue during treatment with inavolisib, and relevant dose modifications and warnings are included in the SmPC sections 4.2 and 4.4 respectively.

In study WO41544, patients with Type 1 diabetes or Type 2 diabetes requiring ongoing systemic therapy were excluded as were patients with fasting glucose >126 mg/dL (>7.0 mmol/L) and HbA1C >6.0% (>42 mmol/mol). In addition, patients with >1 risk factor for hyperglycaemia (including pre-diabetes, HbA1C ≥ 5.7%, BMI ≥ 30 kg/m2, ≥ 45 years, history of gestational diabetes, or family history of diabetes mellitus) should be considered for prophylactic treatment with metformin on Cycle 1 Day 1.

The overall proportion of patients with hyperglycaemia was 58.6% in the Inavo+Palbo+Fulv arm vs. 8.6% in the Pbo+Palbo+Fulv arm. The majority had Grade 1 (Inavo+Palbo+Fulv: 16.0% and Pbo+Palbo+Fulv: 8.0%) or Grade 2 events (37.0% and 0.6%). Grade 3 events were only reported in the Inavo+Palbo+Fulv arm (9 patients [5.6%]). No Grade 4-5 events, and no serious cases, were reported in either arm.

In the pivotal Study WO41554, hyperglycaemia led to withdrawal of inavolisib in 1 patient (0.6%), dose reduction of inavolisib in 4 patients (2.5%), and dose interruption of inavolisib in 44 patients (27.2%) in the Inavo+Palbo+Fulv arm. Thus, hyperglycaemia was mainly managed by dose interruptions but rarely required withdrawal of inavolisib.

The rate of new onset of hyperglycaemia was highest during the first 2 months of treatment, with a median time to first onset of 7 days (range: 2 to 955 days) in inavolisib-treated patients.

Of the 97 patients in the Inavo+Palbo+Fulv arm who experienced an ADR of hyperglycaemia 72 patients (74.2%) received metformin and/or other anti-diabetic agents as either hyperglycaemia prophylaxis or hyperglycaemia treatment.

Eleven patients in the Inavo+Palbo+Fulv arm received insulin with a median duration of insulin of 5 days (range: 1-539 days). Thus, there is limited experience in patients receiving insulin when being treated with inavolisib. The potential risk for hypoglycaemia in patients treated with insulin or sulfonylureas during periods of inavolisib interruption is highlighted in the SmPC section 4.4.

Of the 54 patients in the Inavo+Palbo+Fulv arm who experienced a Grade $\geq$ 2 worst fasting glucose, 52 patients (96.3%) had an improvement by at least one grade in a median of 8 days (range 2 to 43 days). Among patients with at least one hyperglycaemia event reported, all hyperglycaemia events had resolved in 67 of 95 patients (70.5%) at the primary analysis CCOD of 29 September 2023.

Only a limited number of Type 2 diabetic patients were enrolled in pivotal Study WO41554 (n=1) and in the Supportive study GO39374 Arms A-F (n=12). The majority of these patients with pre-existing type 2 diabetes reported hyperglycaemia events, which were not serious, but Grade 2/3 and required anti-hyperglycaemic treatment.

No cases of diabetic ketoacidosis were reported in the pivotal Study WO41554 or supportive Study GO39374. Further, according to the applicant´s review of the inavolisib safety database, no events of diabetic ketoacidosis were reported in any of the studies across the inavolisib developmental programme up to 30-September-2024. Two postmarketing events of diabetic ketoacidosis were considered to be related to inavolisib and they occurred within one week after initiation of inavolisib. As outlined in section 2.6.8.10, one of the cases had concurrent severe conditions and fatal outcome. Of

note, diabetic ketoacidosis including fatal events have previously been reported for other medicines targeting PI3K pathway. Recent observations indicate that patients with pre-existing type 2 diabetes are at higher risk for developing diabetic ketoacidosis during treatment with similar products targeting the PI3K/AKT/PTEN pathway (Cheung et al. 2022; Dilawari et al. 2024). Consequently, ketoacidosis was included in SmPC 4.8 with frequency uncommon, which was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed.

The substantial risk of hyperglycaemia is considered the main safety issue during inavolisib treatment. The pivotal trial indicates that these risks can be managed in patients that are normoglycemic at baseline, and do not require antidiabetic therapy for this, by means of extensive precautionary measures described in the SmPC. However, there is a concern that the impact of inavolisib on blood sugar control may be less manageable in patients with diabetes type 2 or type 1, especially when used in routine clinical care without a detailed study protocol to follow.

The complete lack of safety and efficacy data in any patients with Type 2 diabetes requiring systemic therapy, or in patients with Type 1 diabetes, is notable, and reflected in SmPC section 4.4. Moreover, only 1 patient with Type 2 diabetes (not requiring systemic therapy) was included in the Inavo+Palbo+Fulv arm.

With the proposed indication, all patients with Type 2 diabetes and Type 1 diabetes (regardless of ongoing anti-hyperglycaemic therapy) are included in the target population, despite the absence of safety and efficacy data as described above. In line with the previous CHMP evaluations of products in the same class, this lack of data is not considered prohibitive for use in diabetes type 2 or type 1 patients, given that blood sugar can readily be monitored and carefully managed. This concern is adequately addressed in the RMP. Section 4.4 of the SmPC reflects the requirement for optimised glucose levels before treatment, and for intensified anti-hyperglycaemic treatment and more frequent fasting glucose testing during treatment.

The following SmPC statements have been agreed to inform prescribers:

"*The safety and efficacy of Itovebi in patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycaemic therapy have not been studied as these patients were excluded from the phase III clinical study. Moreover, only 1 patient with Type 2 diabetes was included in the Inavo+Palbo+Fulv arm of the phase III clinical study. This should be considered if inavolisib is prescribed to patients with diabetes mellitus."*

"*Hyperglycaemia has been frequently reported in patients treated with Itovebi. Severe cases of hyperglycaemia including ketoacidosis with fatal outcome have occurred*". "*Hyperglycaemia and Associated Complications (including Diabetic Ketoacidosis*)" is listed as an Important identified risk. "*Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment)*" and also "*Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)*" are listed as Missing information in the RMP.

The applicant will conduct a PASS (study GO45322) to prospectively study patients (n=40) with Type 2 diabetes mellitus on anti-hyperglycaemic medicine excluding insulin, and *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who are suitable for inavolisib and fulvestrant (with or without palbociclib) treatment. The primary objective is to assess safety. Secondary objectives comprise the assessment of efficacy including ORR, BoR, DOR, PFS, and OS (see RMP).

In addition, the applicant will conduct a post-authorisation non-interventional database study of inavolisib and fulvestrant treatment with or without a CDK inhibitor in patients with *PIK3CA*-mutated breast cancer and Type 1 or Type 2 Diabetes (requiring insulin treatment) (see RMP).

Pneumonitis was reported in 3 patients [1.9%] in the Inavo+Palbo+Fulv arm vs. 1 patient [0.6%]) in the Pbo+Palbo+Fulv arm. There were no Grade 3-4 events, no SAEs, and no events leading to withdrawal or dose reduction of any study drug in either of the arms. Pneumonitis events led to dose interruption of inavolisib in 1 patient (0.6%) in the Inavo+Palbo+Fulv arm and 1 patient (0.6%) in the Pbo+Palbo+Fulv arm.

In palbociclib SmPC, pneumonitis is an ADR addressed in section 4.2, 4.4, and 4.8.

Based on available data, with all the pneumonitis events being reported with the palbociclib combination, and an incidence of pneumonitis in the WO41554 study being comparable with the reported incidence in palbociclib clinical studies, continued monitoring of pneumonitis by routine pharmacovigilance measures is sufficient.

The overall proportion of patients with stomatitis was 51.2% in the Inavo+Palbo+Fulv vs. 26.5% in the Pbo+Palbo+Fulv arm. Grade 3 stomatitis were only reported in the Inavo+Palbo+Fulv arm (5.6% of patients). No Grade 4-5, and no serious cases were reported.

In study WO41544, corticosteroid mouthwash was recommended for (i) prophylaxis or (ii) treatment of stomatitis/mucositis. Prophylaxis containing dexamethasone or triamcinolone was used in 19.1% and 42.6% received treatment for stomatitis in the Inavo+Palbo+Fulv arm.

The frequency and severity of stomatitis in inavolisib treated patients appear to be higher than reported for similar products alpelisib and capivasertib. Patients should be advised to start alcohol free corticosteroid mouthwash at the first sign of stomatitis and to avoid alcohol or peroxide containing mouthwashes as they may exacerbate the condition. Dietary modifications (e.g., avoiding spicy foods) should be considered.

The risk of stomatitis is adequately addressed in the SmPC section 4.2, 4.4, and 4.8.

ALT is listed as an ADR in section 4.8 of the inavolisib SmPC (17% any Grade and 3.7% had Grade 3).In palbociclib SmPC section 4.8 ADR table, it is stated that ALT (any grade) was increased in 10.6% of patients treated with palbociclib plus endocrine treatment, with Grade 3 in 2.1% and Grade 4 in 0.1%.

Nausea, vomiting, ocular toxicity, neutropenia, thrombocytopenia, lymphopenia, and anaemia were also subjected to increased supervision as Other Selected AEs, but no concerns were observed. These risks are reflected in the SmPC as needed (Nausea, Vomiting, Dry eye, Thrombocytopenia, Anaemia are reflected in the SmPC section 4.8, ADR table).

Proposal for adverse reactions

The methodology for selection of ADRs appears overall acceptable. It is noted that AEs (all grades) associated with myelosuppression (including neutropenia, anaemia, and thrombocytopenia) were similar between the treatment arms, which is in line with the known safety profile of palbociclib. However, the frequency of Grade 3-4 platelet count decreased, anaemia, and thrombocytopenia was higher in the Inavo+Palbo+Fulv arm (9.3%, 6.2% and 4.9%, respectively) compared with Pbo+Palbo+Fulv (2.5%, 1.9% and 1.9%, respectively). These data indicate that the combination of inavolisib and palbociclib causes a deeper suppression of platelets and haemoglobin than only palbociclib and motivates the inclusion of Thrombocytopenia and Anaemia as ADRs. However, Neutropenia and related events are not selected as ADRs, and not addressed in the SmPC. This is supported given that the frequency of both Any grade neutropenia, and Grade 3-4 neutropenia, were comparable between the Inavo+Palbo+Fulv arm and Pbo+Palbo+Fulv arm. Neutropenia is addressed in palbociclib SmPC sections 4.2, 4.4, and 4.8.

Laboratory findings

Hypocalcaemia is listed as an ADR in SmPC section 4.8 and reported in 8.6% of inavolisib treated patients (1.2% Grade 3 event), vs. a frequency of 2.5% (0.6% Grade 3 event) in the Pbo+Palbo+Fulv arm. One patient in the Inavo+Palbo+Fulv arm had a SAE of both Hypocalcaemia grade 3 and Tetany Grade 3, and the investigator considered hypocalcaemia to be related to concomitant use of pamidronate. Of note, hypocalcaemia is also an ADR for similar product alpelisib. Eleven out of 14 patients who developed hypocalcaemia in the Inavo+Palbo+Fulv arm of Study WO41554 were confounded by concomitant use of bisphosphonates or denosumab and several patients had confounding conditions in their medical history including osteopenia. The events of hypocalcaemia were generally low grade, non-serious, recovered/resolved and did not require dose modifications. Based on available data, it is sufficient to include Hypocalcaemia in the ADR table in SmPC section 4.8.

Shifts from baseline included high triglycerides (6.7% Inavo+Palbo+Fulv vs. 0% Pbo+Palbo+Fulv) and high cholesterol and high triacylglycerol lipase (6.2% vs. 0% each). Such events are not addressed in the labelling for similar products. Since the mechanism of action of PI3K inhibitors is not directly linked with these lab elevations (Zhang et al. 2019), and the incidence is low in the respective fasting laboratory values without concurrent AEs, inavolisib treatment is not considered associated with these laboratory findings.

Safety in special populations

The small number of patients in the age groups of 65-74 years (n=19) and ≥ 75 years (n=5), hampers the assessment of safety per age category.

The number of male patients is too small to draw any firm conclusion on safety in this subgroup.

A dedicated renal impairment study (GP44944) in subjects with moderate or severe renal impairment is ongoing. The applicant will submit the results from study GP44944 when available in Q3 2025 (REC).

The applicant argues that a dedicated study is not warranted in patients with moderate or severe hepatic impairment because, based on the absorption, distribution, metabolism, and excretion (ADME) properties of inavolisib, hepatic impairment is unlikely to have a clinically significant impact on the PK of inavolisib. Please refer to PK assessment for further details on hepatic impairment.

2.6.10. Conclusions on the clinical safety

The safety profile of inavolisib as add-on to palbociclib and fulvestrant is mainly characterised by hyperglycaemia and GI adverse events such as stomatitis, nausea, vomiting, and diarrhoea. Moreover, the risk of urinary tract infections appears increased, as is the incidence of fatigue. Notwithstanding, the safety profile of inavolisib + palbociclib + fulvestrant is considered acceptable and manageable in the sought indication with appropriate risk minimisation measures laid out in the SmPC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 58. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hyperglycaemia and Associated Complications (including Diabetic Ketoacidosis)
Important potential risks	None

Missing information	Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)

2.7.2. Pharmacovigilance plan

Table 59. Summary of on-going and planned additional pharmacovigilance activities

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				
n/a				
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				
n/a				
Category 3 - Required additional pharmacovigilance activities				
A Phase II, Prospective, Multicentre, Open-Label, Safety Study of inavolisib and fulvestrant with or without palbociclib in patients with *PIK3CA*-Mutated, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer and Type 2 Diabetes *Planned*	To evaluate the safety and tolerability of the use of inavolisib and fulvestrant with or without palbociclib in well-controlled type 2 diabetic patients with *PIK3CA*-mutated, hormone receptor positive, HER2-negative advanced breast cancer treated with a combination of inavolisib plus palbociclib and endocrine therapy.	Missing Information: safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment).	*Final Study Report*	*TBD*
A non-interventional study of Inavolisib and Fulvestrant with or without a CDK inhibitor in patients with *PIK3CA*-mutated, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer and Type 1 or Type 2 Diabetes (requiring insulin treatment) *Planned*	To evaluate the safety of inavolisib and fulvestrant, with or without a CDK inhibitor in type 1 or type 2 diabetic patients (requiring insulin treatment) with *PIK3CA*-mutated hormone receptor-positive, HER2-negative advanced breast cancer	Missing Information: Safety in patients with type 1 or type 2 diabetes mellitus (requiring insulin treatment) Important Identified Risk: Hyperglycaemia and Associated complications (including diabetic ketoacidosis)	*Final report submission*	*TBD*

2.7.3. Risk minimisation measures

Table 60. Summary table of pharmacovigilance activities and risk minimisation measures by safety concern

Safety concern	Risk-minimisation measures	Pharmacovigilance activities
Hyperglycaemia and Associated Complications (including Diabetic Ketoacidosis)	**Routine risk-minimisation measures:** SmPC section 4.2, and 4.4, and 4.8 Dose modification and management advice for hyperglycaemia is included in SmPC section 4.2. Recommendations on monitoring and management of hyperglycaemia, including diabetic ketoacidosis is included in SmPC section 4.4. **Other routine risk-minimisation measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine **No additional risk-minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** Planned Studies to evaluate inavolisib-associated hyperglycaemia in Type 1 or Type 2 diabetic patients
1) Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) 2) Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)	**Routine risk-minimisation measures:** SmPC section 4.4 Information pertaining to the use of inavolisib in patients with Type 1 and Type 2 diabetes is included in Section 4.4. **Other routine risk-minimisation measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine **No additional risk-minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Planned Studies to evaluate inavolisib-associated hyperglycaemia in Type 1 or Type 2 diabetic patients

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of personal data (PD) and identification of commercially confidential information (CCI) in any updated RMP submitted throughout this procedure.

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 10.10.2024. 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, Itovebi (inavolisib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The finally approved indication was:

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In pre/perimenopausal women and in men, endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

3.1.2. Available therapies and unmet medical need

Breast cancer is the most common cancer in women, with a 5-year prevalence in Europe of 552.2 per 100,000 women in 2020. BC is also a molecularly diverse disease with several clearly defined molecular subgroups, with hormone receptor positive (HR+), HER2-negative (HER2-) BC being the most common, accounting for approximately 70% of all BCs. Patients with HR+ BC benefit from adjuvant ET, which reduces the risk of recurrence and, ultimately, cancer death. Resistance to ET, however, continues to be a clinical problem.

Despite adjuvant ET, approximately 30-60% of patients with stage II-III BC recur. The risk of recurrence in patients with HR+, HER2- early BC is highest during the first 5 years after diagnosis, but still more than half of those who recur experience late recurrences (≥5 years from diagnosis). The prognosis for HR+, HER2- BC with distant metastases is poor, with a 5-year survival of 34%. The indication focuses on a high-risk population with endocrine resistance and tumour recurrence on or within 12 months of completing adjuvant endocrine treatment.

Standard of care first- and second-line treatment for ER-positive HER2-negative LA/mBC is either an aromatase inhibitor (AI) or fulvestrant in combination with a CDK4/6 inhibitor. ET monotherapy may be appropriate for frail patients with endocrine sensitive tumours and comorbidities. The treatment approach for men with LA/mBC is the same as for women.

There are several treatment options for patients who relapse after ET plus a CDK4/6 inhibitor, with the options being tailored depending on several factors including e.g., presence of somatic *PIK3CA*, *AKT1*, *PTEN*, or *ESR1* mutations (ESMO 2023; NCCN 2024, Vasconcelos de Matos et al., 2023). According to current international treatment guidelines, a second-line CDK4/6 inhibitor + ET may also be used in some cases (ESMO 2023; NCCN 2024).

PIK3CA mutations occur in approximately 35-40% of all HR+ BCs. In 2022, the PI3Kα inhibitor alpelisib was indicated in combination with fulvestrant for *PIK3CA*-mutated LA/mBC, and in 2024 the AKT-inhibitor capivasertib was indicated in combination with fulvestrant for *PIK3CA/AKT/PTEN* altered LA/mBC. Both products are indicated in patients who have failed prior ET (see EPAR for Piqray and Truqap).

Although other available therapies, not directed against PI3Kα, are efficacious in patients with *PIK3CA* mutated LA/mBC, these patients may derive less benefit compared to patients with *PIK3CA* wildtype tumours. Furthermore, in this setting, disease is incurable and inevitably leads to death. Thus, there is a high unmet need for further treatment enhancements in this patient population.

3.1.3. Main clinical studies

Data to support the sought indication are derived from the randomised, double-blind, placebo-controlled, multi-centre, phase III study WO41554 (INAVO120) in patients with *PIK3CA*-mutated, HR+, HER2- LA/mBC with relapse on or <12 months of completion of adjuvant ET.

Key eligibility criteria included (a) verified *PIK3CA* mutation, (b) progression during or <12 months of completing adjuvant ET, (c) progression >12 months after completing (neo-)adjuvant CDK4/6i treatment, (d) ECOG performance status 0-1, (e) no prior systemic therapy for mBC, (f) no prior treatment with PI3K-AKT-mTOR inhibitors, (g) no type 2 diabetes requiring ongoing systemic treatment at the time of study entry, (h) no history of type 1 diabetes.

The primary endpoint was investigator-assessed PFS. Secondary endpoints to be tested hierarchically after a statistically significant PFS result were OS, ORR, BOR, CBR, DOR, and several PRO variables. All analyses except DOR were performed using the full analysis set (=ITT population).

3.2. Favourable effects

Results were derived from the primary PFS analysis as of CCOD 29 September 2023, with an overall PFS maturity rate of 60.0%. At the time of CCOD, 67/161 (41.6%) of the patients in the inavo + palbo + fulv arm were still on treatment compared to 49/164 (29.9%) in the pbo + palbo + fulv arm.

HR for PFS at the primary analysis was 0.43 (95% CI 0.32, 0.59) 2-sided p-value <0.0001 (tested at a two-sided 0.05 alpha level), in favour of inavo + palbo + fulv treatment. The median PFS for inavo + palbo + fulv was 15.0 months vs. 7.3 months for pbo + palbo + fulv.

The final OS analysis (CCOD 15 Nov 2024) was statistically significant with HR 0.67 (95% CI 0.48, 0.94) and p-value 0.0190 crossing the pre-specified final analysis OS stopping boundary of $p \leq 0.0469$. The median OS was 34.0 (95% CI 28.4, 44.8) months in the inavo + palbo + fulv arm vs. 27.0 (22.8, 38.7) months in the pbo + palbo + fulv arm.

The secondary endpoints ORR, BOR, and BCR were hierarchically tested after OS and were all statistically significant and in favour of the inavo + palbo + fulv arm.

3.3. Uncertainties and limitations about favourable effects

Uncertainties pertain to the activity of a CDK4/6i in patients who have received prior such treatment. The sought indication covers CDK4/6i re-challenge but only three patients who had received (neo-)adjuvant CDK4/6i were included in the study. Therefore, there is limited data showing that the regimen, in particular the combination partner palbociclib, is efficacious in patients that have progressed despite previous CDK4/6i treatment. In line with clinical guideline statements and the eligibility criteria it was added to the indication "Patients previously treated with a CDK4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK4/6 inhibitor treatment and the detection of recurrence" and a relevant warning was added in SmPC section 4.4 to inform prescribers that efficacy may be lower in such patients.

There remains a level of uncertainty regarding the in-vitro diagnostic used for definition of *PIK3CA* mutational status in pivotal study INAVO120 (FoundationOne®CDx (F1CDx)):

- The justification for the definition of biomarker-positivity (i.e., *PIK3CA* alterations as specified) is following a scientific rationale mainly based on preclinical data. The exploratory clinical data from the INAVO120 study suggest that the definition applied may indeed be predictive. However, there is no final confirmation of clinical validity for all individual genetic alterations included.
- No clinical thresholding for the cut-point defining a tumour as biomarker positive or negative was performed. Due to this, it cannot be excluded that in the threshold definition of biomarker-positivity being applied in study INAVO120 patients are included that do not relevantly benefit.

3.4. Unfavourable effects

The safety database in the sought indication and at the proposed posology is primarily based on Study WO41554 (INAVO120) in which 162 participants were treated with inavolisib + palbociclib + fulvestrant and 162 participants were treated with placebo+ palbociclib + fulvestrant.

The median duration of treatment with inavolisib was 9.2 months (range 0-38.8) vs 5.6 months (range 0.1-40.3) with placebo. The median duration of follow-up had reached 21.3 months (range 0-43.1) in the Inavo +Palbo + Fulv arm at the CCOD.

The most common AEs in either arm by PT included (Inavo + Palbo + Fulv and Pbo + Palbo + Fulv, respectively): Neutropenia (54.3% vs. 54.9%), Hyperglycaemia (53.7% vs. 7.4%), Diarrhoea (48.1% vs. 16.0%), Anaemia (36.4% vs. 36.4%), and Stomatitis (32.7 % vs. 16.7%), with a proportion of events attributed to the combination partners.

The majority of Grade 3-4 AEs in both treatment arms were related to myelosuppression with Grade 3-4 AEs of neutropenia (Inavo + Palbo + Fulv: 47.5% vs. Pbo + Palbo + Fulv: 48.1%). Other common Grade 3-4 AEs were hyperglycaemia (Inavo + Palbo + Fulv: 5.6% and Pbo + Palbo + Fulv: 0%), diarrhoea (3.7% vs 0%), and stomatitis (3.1% vs. 0%).

SAEs were reported for 24.1% of patients in the Inavo + Palbo + Fulv arm vs. 10.5% in the Pbo + Palbo + Fulv arm. The SAEs occurring in > 2 patients in either arm included COVID-19 (2.5% Inavo + Palbo + Fulv vs. 0.6% Pbo + Palbo + Fulv), and pneumonia, anaemia, febrile neutropenia (1.9% vs 0% each). Three events of osteonecrosis of the jaw (ONJ) are noted in the experimental arm (of which one was reported as an SAE) vs none in the comparator arm. All three events were associated with use of zoledronic acid as a concomitant medication.

Fatal AEs were reported in 6 patients (3.7%) in the Inavo + Palbo + Fulv arm and 2 patients (1.2%) in the Pbo + Palbo + Fulv arm.

Eleven patients [6.8%]) in the Inavo + Palbo + Fulv arm, vs 1 patient (0.6%) in the Pbo + Palbo + Fulv arm experienced AEs leading to discontinuation of any study drug. The only PT leading to withdrawal of any study drug in ≥ 2 patients in either arm was hyperglycaemia in the Inavo + Palbo + Fulv arm (2 patients [1.2%]).

In the Inavo + Palbo + Fulv arm, 43.8% of patients experienced AEs leading to the dose reduction of any study drug, vs. 31.5% in the Pbo + Palbo + Fulv arm. The dose reductions were mainly driven by events of neutrophil count decreased (17.3% Inavo + Palbo + Fulv vs. 14.2% Pbo + Palbo + Fulv), platelet count decreased (3.1% vs. 0%), and hyperglycaemia (2.5% vs. 0%).

AEs leading to the dose interruption of any study drug were reported in 80.9% of patients in the Inavo + Palbo + Fulv arm vs. 65.4% in the Pbo + Palbo + Fulv arm. This was mainly driven by events of hyperglycaemia (25.3% Inavo + Palbo + Fulv vs. 0.6% Pbo + Palbo + Fulv), COVID-19 (16.0% vs. 7.4%), and diarrhoea (7.4% vs. 0.6%).

The key safety issue during treatment with inavolisib is hyperglycaemia which was reported in 58.6% of patients in the Inavo + Palbo + Fulv arm vs. 8.6% in the Pbo + Palbo + Fulv arm, with Grade 3 events in 5.6% of patients the Inavo + Palbo + Fulv arm vs. none in the comparator arm. Hyperglycaemia led to withdrawal of inavolisib in 1 patient (0.6%), dose reduction of inavolisib in 4 patients (2.5%), and dose interruption of inavolisib in 44 patients (27.2%) in the Inavo + Palbo + Fulv arm.

Two cases of diabetic ketoacidosis are reported in the postmarketing setting, one of the cases had concurrent severe conditions and fatal outcome.

3.5. Uncertainties and limitations about unfavourable effects

There is a lack of safety data in any patients with Type 2 diabetes requiring systemic therapy, and in patients with Type 1 diabetes. Relevant warnings have been reflected in the PI, and two category 3 studies were agreed in the RMP: one in patients with well-controlled type 2 diabetes and one in patients with type 1 or type 2 diabetes requiring insulin treatment.

3.6. *Effects Table*

Table 61. Effects table for inavolisib in combination with palbociclib and fulvestrant, for *PIK3CA*-mutated, ER positive, HER2 negative, LA or metastatic BC, study WO41554 (INAVO120), CCOD 29 Sep 2023.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Full analysis set (FAS), n=325 participants						
			Inavolisib + palbociclib + fulvestrant N=161[1]	**Placebo + palbociclib + fulvestrant N=164[1]**		
PFS (primary endpoint)	Time from randomisation to first occurrence of disease progression or death, whichever comes first.	Median, months 95% CI	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)	Assessed by investigator. CCOD primary analysis 29 Sep 2023. HR 0.43 (95% CI 0.32, 0.59) 2-sided p-value <0.0001	
OS* (secondary endpoint)	Time from randomisation to death from any cause.	Median, months (95% CI)	34.0 (28.4, 44.8)	27.0 (22.8, 38.7)	CCOD final OS analysis 15 Nov 2024. HR 0.67 (0.48, 0.94) 2-sided p 0.0190**	
Unfavourable Effects						
			Inavolisib + palbociclib + fulvestrant (n=162)[2]	**Placebo + palbociclib + fulvestrant (n=162)[2]**		
AEs all Grade > 30% of patients in either arm	Any Hyperglycaemia Diarrhoea Anaemia Stomatitis	%	99 54 48 36 33	100 7 16 36 17		
AEs Grade 3-4	Any Platelet count decreased Anaemia Hyperglycaemia Diarrhoea Stomatitis	%	86 9 6 6 4 3	82 3 2 0 0 0		
SAEs in > 2 patients in either arm	Any Pneumonia Anaemia Febrile neutropenia Diarrhoea	%	24 2 2 2 1	11 0 0 0 0		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
AEs leading to discontinuation of any study drug in ≥ 2 patients in either arm	Any Hyperglycaemia	%	7 1	1 0		
AEs leading to dose reduction of any study drug	Any	%	44	32		
AEs leading to the dose interruption of any study drug	Any	%	81	65		

Notes: [1] FAS: Final Analysis Set (i.e. ITT), [2]SAS: Safety Analysis Set (all patients who received at least one dose of treatment) (of note, one patient withdrew consent after randomisation but before receiving inavo combo, two patients in the control group received inavo so are included in the efficacy analysis per their assigned treatment (pbo arm) but in the safety analysis per received treatment (inavo arm).
*The secondary endpoints OS, ORR, BOR, CBR, and PRO variables Time to confirmed deterioration (TTCD) in worst pain severity, TTCD in physical functioning, TTCD in role functioning, and TTCD in HRQoL were hierarchically tested in this order provided that the primary endpoint PFS was statistically significant at the interim analysis.
**Statistically significant. The final analysis stopping boundary for OS was p≤0.0469.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study WO41554 (INAVO120) met its primary endpoint of PFS showing a statistically significant improvement of PFS with inavolisib + palbociclib + fulvestrant (inavo + palbo + fulv) vs. placebo + palbociclib + fulvestrant (pbo + palbo + fulv). The median PFS for inavo + palbo + fulv was more than twice as long as for the comparator arm; median PFS 15.0 (95% CI 11.3, 20.5) months for inavo + palbo + fulv vs. 7.3 (5.6, 9.3) months for pbo + palbo + fulv. The effect size is clinically meaningful by accepted regulatory standards.

The final OS analysis also showed a statistically significant and clinically relevant improvement of OS for inavo + palbo + fulv over pbo + palbo + fulv, with median OS 34.0 (95% CI 28.4, 44.8) for inavo + palbo + fulv vs. 27.9 (22.8, 38.7) months for pbo + palbo + fulv.

Only three patients in the pivotal study had received prior CDK4/6i treatment. Notably, the treatment landscape has evolved since the pivotal study was initiated. Adjuvant CDK4/6i treatment with abemaciclib or ribociclib is now approved for patients at high-risk of recurrence. Emerging external data as well as international guidelines is understood to support the re-treatment with a CDK4/6i under certain circumstances. To reduce the likelihood of non-response on re-challenge, recurrence >12 months after termination of (neo)adjuvant CDK4/6i is a prerequisite, under the assumption that selection of a drug-resistant tumour phenotype would then be reasonably unlikely (see also Discussion of Clinical Efficacy). This is clearly outlined in the indication stating that patients previously treated with a CDK4/6i should have an interval of at least 12 months between termination of previous CDK4/6i and the detection of recurrence.

The RWD study proposed by the applicant to generate descriptive data on outcomes in the CDK4/6i pre-treated patient population is listed as a recommendation.

Diverging results for the subgroup of elderly patients were described. In SmPC section 4.2. it is addressed that there are limited data in patients ≥ 65 years of age.

From a safety point of view, the key risks identified for inavolisib are hyperglycaemia and GI adverse events such as stomatitis, nausea, vomiting and diarrhoea. Moreover, the risk of urinary tract infections appears increased, as is the incidence of fatigue. The substantial risk of hyperglycaemia is considered the main safety issue to be managed. The pivotal trial indicates that these risks can be managed in patients that are normoglycemic at baseline, and do not require antidiabetic therapy for this. However, there is a concern that the impact of inavolisib on blood sugar control may be less manageable in patients with diabetes, with complications such as diabetic ketoacidosis which have been reported in the US post-marketing setting including one case with concurrent severe conditions and fatal outcome. The complete lack of safety and efficacy data in any patients with Type 2 diabetes requiring systemic therapy, or in patients with Type 1 diabetes, is notable. In line with the previous CHMP evaluations of products in the same class, this lack of data is not considered prohibitive for use in diabetes type 2 or type 1 patients, given that blood sugar can readily be monitored and carefully managed, and relevant information is reflected in the SmPC section 4.4 to guide prescribers. The lack of data to support this use is sufficiently addressed in the SmPC and in the RMP, where additional studies have been requested. In addition, proper guidance for the management of hyperglycaemia in all diabetic patients (both Type 1 and Type 2 diabetes mellitus regardless of ongoing anti-hyperglycaemic therapy) is given in section 4.4 of the SmPC.

3.7.2. Balance of benefits and risks

In study WO41554 (INAVO120), efficacy has been established for inavolisib + palbociclib + fulvestrant over placebo + palbociclib + fulvestrant with a median of seven months increase in both PFS and OS. Efficacy results are considered robust. Safety data indicate that the toxicity profile of the combination is manageable and acceptable in this treatment niche subject to appropriate risk minimisation measures in the SmPC. Patients with type 1 diabetes or type 2 diabetes requiring systemic therapy have not been studied, and this has been adequately addressed in the SmPC and in the RMP. It can be concluded that the benefit/risk balance of inavolisib is positive in the agreed indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Itovebi 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 majority decision that the benefit-risk balance of Itovebi is favourable in the following indication(s):

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic

breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In pre/perimenopausal women and in men, endocrine therapy 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.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that inavolisib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously

Divergent position(s)

Divergent positions to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITION DATED 22 May 2025

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Itovebi EMEA/H/C/006353/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Itovebi for the indication:

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER) positive, HER2 negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1).

Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

In pre/perimenopausal women and in men, endocrine therapy should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

More specifically, the undersigned members of the CHMP did not agree on the inclusion in the indication of patients previously treated with a CDK4/6 inhibitor.

The reason for divergent opinion was the following:

Insufficient data on re-treatment with palbociclib after prior CDK4/6 inhibitor treatment have been generated in the INAVO120 trial or elsewhere to ascertain efficacy in a population previously treated with a CDK4/6 inhibitor. There were only three patients re-treated with a CDK4/6i in the pivotal study INAVO120. Furthermore, convincing efficacy was not demonstrated in the dose response study GO39374, where the arm (F) including the majority of patients exposed to re-challenge with CDK4/6 inhibitor showed a response rate of 16.7% (3/18).

Presently, it remains uncertain whether previous treatment with a CDK4/6 inhibitor is an effect modifier for treatment with palbociclib. It cannot be excluded that the benefit risk ratio in a CDK4/6 inhibitor pre-treated population could be negative, especially in view of the notable toxicity with the inavolisib/palbociclib/fulvestrant regimen, e.g., high occurrence of hyperglycaemia and diarrhoea. The magnitude of benefit in the CDK4/6 inhibitor pre-treated population remains unknown and broadening the indication to pre-treated patients based on the INAVO120 study data is not supported, as there is insufficient data from only three patients generated from the trial itself and insufficient external data to conclude on the benefits and risks of treatment with the inavolisib/palbociclib/fulvestrant regimen in this subgroup.

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